Clinical practice guidelines: Type 1 diabetes in children and adolescents

Prepared by the Australasian Paediatric Endocrine Group for the Department of Health and Ageing

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These guidelines were approved by the National Health and Medical Research Council (NHMRC) at its 156th Session on 9 March 2005, under Section 14A of the National Health and Medical Research Council Act 1992. Approval for the guidelines by NHMRC is granted for a period not exceeding five years, at which date the approval expires. The NHMRC expects that all guidelines will be reviewed no less than once every five years. Readers should check with the Department of Health and Ageing for any reviews or updates of these guidelines.

Disclaimer
This document is a general guide to appropriate practice, to be followed subject to the clinician’s judgement and the patient’s preference in each individual case.

The guidelines are designed to provide information to assist decision-making and are based on the best evidence available at the time of compilation.

These guidelines can be downloaded from the National Health and Medical Research Council website: www.nhmrc.gov.au/publications.
# Table of Contents

Table of Contents .................................................................................................................. i
Tables ........................................................................................................................................ x
Figures ....................................................................................................................................... x

Introduction .............................................................................................................................. 1
  Background .............................................................................................................................. 1
  Rationale for the Guidelines ................................................................................................. 1
  Scope of the Guidelines ......................................................................................................... 1
    Areas beyond the remit of the guidelines ........................................................................... 1
  Target Audience ....................................................................................................................... 2
  Guidelines Development Process ........................................................................................... 2
    Guidelines writing committee ............................................................................................. 2
    Review of existing guidelines ............................................................................................ 2
  Formulation of Clinical Questions ......................................................................................... 2
  Locating the Evidence ............................................................................................................. 2
  Levels of Evidence and Critical Appraisal ............................................................................ 3
  Economic Considerations ....................................................................................................... 6
  Guidelines Review Date .......................................................................................................... 6
  Structure of the Guidelines .................................................................................................... 6
  Overview of the Guidelines ................................................................................................... 6
  Consultation and Peer-review Process .................................................................................. 7
  Dissemination ........................................................................................................................ 7
  Legal Considerations ............................................................................................................. 7
  Reference List ........................................................................................................................ 7

List of Abbreviations ............................................................................................................... 8

Acknowledgements ................................................................................................................... 9

Executive Summary of Recommendations and Principles .................................................. 10
  1. Definition, Epidemiology and Classification ................................................................. 10
  2. Phases of Diabetes .......................................................................................................... 10
  3. Medical Management ..................................................................................................... 11
  4. Insulin Preparations and Storage .................................................................................... 11
  5. Insulin Regimens and Delivery ....................................................................................... 12
  6. Glycaemic Control .......................................................................................................... 13
  7. Nutrition .......................................................................................................................... 13
  8. Physical Activity ............................................................................................................. 14
  9. Diabetic Ketoacidosis ..................................................................................................... 14
  10. Surgery and Fasting ....................................................................................................... 15
  11. Sick Day Management .................................................................................................. 15
  12. Hypoglycaemia ............................................................................................................. 16
  13. Psychosocial Aspects .................................................................................................... 17
  14. Diabetes Complications ............................................................................................... 17
  15. Other Complications and Associated Conditions ....................................................... 18
  16. Foot Care ...................................................................................................................... 18
  17. Dental Health ............................................................................................................... 18
  18. Adolescent Health Issues ............................................................................................. 18
  19. School .......................................................................................................................... 19
  20. Diabetes Camps for Children and Adolescents ............................................................ 20
  21. Travelling and Holidays ............................................................................................... 20
# Table of Contents

## Chapter 1: Definition, Epidemiology and Classification

- Definition ........................................................................................................... 26  
- Epidemiology .................................................................................................... 26  
- Classification .................................................................................................... 28  
- Clinical Staging of Diabetes ............................................................................... 28  
- Aetiologic Classification of Diabetes.................................................................... 29  
- Diagnostic Criteria for Diabetes in Childhood and Adolescence....................... 31  
- Oral Glucose Tolerance Test (OGTT) .................................................................. 32  
- Interpretation of OGTT ....................................................................................... 32  
- Intravenous Glucose Tolerance Test (IVGTT) ...................................................... 33  
- Metabolic Syndrome .......................................................................................... 33  
- Type 2 Diabetes .................................................................................................. 34  
- Screening for Type 2 Diabetes .......................................................................... 35  
- Other Types of Diabetes .................................................................................... 35  
- Maturity Onset Diabetes of the Young (MODY) .................................................. 35  
- DIDMOAD Syndrome (Wolfram Syndrome) ..................................................... 36  
- Mitochondrial Diabetes ..................................................................................... 36  
- Neonatal Diabetes ............................................................................................. 36  
- Cystic Fibrosis and Diabetes ............................................................................ 37  
- Drug Induced Diabetes ...................................................................................... 37  
- Stress Hyperglycaemia ...................................................................................... 37  
- The Evidence ..................................................................................................... 38  
- Recommendations and Principles ..................................................................... 38  
- Reference List .................................................................................................... 39

## Chapter 2: Phases of Diabetes

- Preclinical Diabetes ............................................................................................ 41  
  - Risks of progression to diabetes .......................................................................... 41  
- Presentation of Type 1 Diabetes .......................................................................... 42  
  - Non-emergency presentations ............................................................................ 42  
  - Emergency presentations ................................................................................... 42  
  - Diagnostic difficulties leading to late diagnosis ................................................. 43  
  - Differentiating between type 1 and type 2 diabetes at diagnosis ....................... 43  
- Partial Remission or Honeymoon Phase ................................................................ 43  
- Chronic Phase of Lifelong Dependence on Insulin ............................................. 43  
  - Transplantation ................................................................................................ 44  
- The Evidence ...................................................................................................... 44  
- Recommendations and Principles ..................................................................... 44  
- Reference List .................................................................................................... 45

## Chapter 3: Medical Management

- Aims of Diabetes Management .......................................................................... 46  
- Hospital versus Ambulatory Stabilisation ............................................................ 46  
- Foundations of Diabetes Management ................................................................. 47  
- Diabetes Education ............................................................................................. 47  
- Insulin Replacement Therapy ............................................................................. 48  
- Immunisation ...................................................................................................... 48  
- Outreach Services .............................................................................................. 49  
- Transition to Adult Services ............................................................................... 49  
- Cost Issues ......................................................................................................... 49
Table of Contents

Australian Clinical Practice Guidelines: Type 1 Diabetes in Children and Adolescents

Chapter 4: Insulin Preparations and Storage ................................................................. 53
  Insulin Action .............................................................................................................. 53
  Types of Insulin ......................................................................................................... 53
    Rapid-acting insulin ................................................................................................. 54
    Short-acting insulin .................................................................................................. 55
    Intermediate-acting insulin ....................................................................................... 55
    Long-acting insulins ................................................................................................. 55
    Basal insulin analogues ............................................................................................ 55
    Premixed insulin preparations ............................................................................... 56
  Local Reactions to Insulin ........................................................................................ 56
  Mixing Insulins .......................................................................................................... 56
  Insulin Concentrations .............................................................................................. 57
  Storage Conditions .................................................................................................... 57
  Adjunct Therapy with Oral Antidiabetic Drugs .......................................................... 57
  Cost Issues ................................................................................................................ 59
  The Evidence ............................................................................................................. 59
  Recommendations and Principles .......................................................................... 59
  Reference List ........................................................................................................... 60

Chapter 5: Insulin Regimens and Delivery .................................................................... 62
  Insulin Regimens ...................................................................................................... 62
  Use of Short-Acting Insulin ....................................................................................... 63
  Use of Intermediate and Long-Acting Insulins ......................................................... 64
  Regimens using Pre-mixed Insulins ......................................................................... 64
  Number of Injections per Day ................................................................................... 64
  Total Daily Insulin Dosage and Distribution ............................................................ 65
  Insulin Administration ............................................................................................... 65
    Insulin absorption .................................................................................................... 65
  Insulin Delivery Devices ............................................................................................ 67
    Insulin syringes and pens ......................................................................................... 67
    Automatic injection devices ..................................................................................... 68
    Jet injection devices ................................................................................................ 68
    Indwelling cannulas ............................................................................................... 68
    Insulin pumps (CSII) ............................................................................................ 68
  Practical Aspects of Insulin Administration .............................................................. 68
  Insulin Adjustment .................................................................................................... 69
    Adjusting usual doses of insulin based on blood glucose patterns over several days or
    longer ......................................................................................................................... 69
    Pro-active day to day adjustments to insulin based on activity and food intake ....... 70
    Adjustments to correct the current BG level when it is outside the desired range .... 70
    Insulin pump adjustments ....................................................................................... 70
  Cost Issues ................................................................................................................ 71
  The Evidence ............................................................................................................. 71
  Recommendations and Principles .......................................................................... 72
  Reference List ........................................................................................................... 72

Chapter 6: Glycaemic Control ....................................................................................... 75
  Intensive Diabetes Management .............................................................................. 75
  Risks and Side Effects of Intensive Diabetes Management ...................................... 75

The Evidence .............................................................................................................. 49
Recommendations and Principles .............................................................................. 50
Reference List ........................................................................................................... 51
# Table of Contents

- **Indicators of Poor Glycaemic Control** ................................................................. 75
- **Glycaemic Goals** ............................................................................................... 76
- **Parameters of Glycaemic Control** .................................................................... 77
- **Blood Glucose Monitoring** ................................................................................ 77
  - *Timing of blood glucose testing* ........................................................................ 77
  - *Techniques for blood glucose testing* ............................................................... 78
  - *Devices for blood glucose testing* ..................................................................... 78
  - *Record keeping and review of records* ............................................................... 79
- **HbA1c** .................................................................................................................. 80
- **Fructosamine** ...................................................................................................... 81
- **Urine Testing for Glucose** ................................................................................... 81
- **Testing for Ketones** ............................................................................................ 81
- **Blood ketones** ..................................................................................................... 81
- **Urine ketones** ....................................................................................................... 82
- **The Evidence** ....................................................................................................... 82
- **Recommendations and Principles** ....................................................................... 83
- **Reference List** ..................................................................................................... 84

## Chapter 7: Nutrition .................................................................................................. 86

- **Nutrition Therapy** ............................................................................................. 86
- **Nutritional Assessment** ...................................................................................... 86
- **Nutrition Review** ................................................................................................. 86
- **Dietary Recommendations** .................................................................................. 87
  - **Energy Intake** .................................................................................................. 87
  - **Dietary Carbohydrate** ...................................................................................... 88
  - **Glycaemic Index (GI)** ....................................................................................... 88
  - **Sugars** .............................................................................................................. 89
    - *Artificially sweetened products* ........................................................................ 89
  - **Fibre** .................................................................................................................. 90
  - **Dietary Fat Intake** ............................................................................................. 90
  - **Protein** .............................................................................................................. 91
- **Variations in Advised Meal Patterns and Insulin Regimens** ............................... 91
- **Age-group Specific Advice** ................................................................................ 92
  - **Infants** .............................................................................................................. 92
  - **Toddlers** .......................................................................................................... 92
  - **Primary school-aged children** ........................................................................ 92
  - **Adolescents** ..................................................................................................... 92
- **The Evidence** ...................................................................................................... 93
- **Recommendations and Principles** .................................................................... 93
- **Reference List** ................................................................................................... 96

## Chapter 8: Physical Activity .................................................................................... 98

- **Need for Physical Activity and General Recommendations** ......................... 98
- **Short-Term Effects** ............................................................................................ 98
- **Long-term Effects** ............................................................................................. 99
- **The Evidence** ..................................................................................................... 99
- **Recommendations and Principles** .................................................................... 100
- **Reference List** .................................................................................................. 100

## Chapter 9: Diabetic Ketoacidosis .......................................................................... 101

- **Definition and Aetiology** .................................................................................. 101
- **Epidemiology** .................................................................................................... 102
- **Management** ..................................................................................................... 103
## Table of Contents

**Chapter 11: Sick Day Management** .......................................................................... 122

- Diabetes and Infectious Illnesses ........................................................................ 122
- Impact of Illnesses on Diabetes .......................................................................... 122
- Infections Causing Little Effect on Blood Glucose Levels .................................. 122
- Infections Causing Low Blood Glucose levels ...................................................... 123
- Infections Causing High Blood Glucose Levels .................................................... 123
- General Principles of Sick Day Management ....................................................... 123
- Insulin Regimens in Infections associated with Hyperglycaemia and Ketosis ....... 125
  - Management in hospital .................................................................................. 125
  - Insulin Regimens in Infections Associated with Persistent Hypoglycaemia ... 127
  - Management at home ....................................................................................... 127
  - Management in hospital .................................................................................. 127
- Glucagon .............................................................................................................. 127
- Minidose Glucagon .............................................................................................. 127
- Insulin Pump Sick Day Management .................................................................. 128
- The Evidence ...................................................................................................... 129
- Recommendations and Principles ....................................................................... 129
- Reference List ....................................................................................................... 130
Chapter 12: Hypoglycaemia
Definition ..................................................................................................................... 131
Symptoms and Signs .................................................................................................. 131
Grading ....................................................................................................................... 133
Frequency ................................................................................................................... 133
Nocturnal Hypoglycaemia .......................................................................................... 133
Consequences ............................................................................................................. 134
Counter-Regulatory Responses to Hypoglycaemia and Hypoglycaemia Unawareness
Prevention .................................................................................................................... 135
Confirmation ................................................................................................................. 135
Treatment ..................................................................................................................... 135
  Mild to moderate hypoglycaemia .............................................................................. 135
  Severe hypoglycaemia ............................................................................................... 136
Follow-Up of Treatment of Hypoglycaemia .............................................................. 136
Hypoglycaemia and Physical Activity ......................................................................... 137
Somogyi Phenomenon .................................................................................................. 137
Hypoglycaemia in School ............................................................................................ 137
Foods for Management of Hypoglycaemia .................................................................. 138
The Evidence .............................................................................................................. 138
Recommendations and Principles ................................................................................ 139
Reference List .............................................................................................................. 139
Chapter 13: Psychosocial Aspects .............................................................................. 142
Impact on Child ............................................................................................................ 142
Impact on Family ......................................................................................................... 142
Psychosocial Factors and Metabolic Control .............................................................. 143
Adherence to Therapy ................................................................................................. 144
Risk Factors ................................................................................................................ 145
Treatments and Interventions ....................................................................................... 145
The Evidence .............................................................................................................. 146
Recommendations and Principles ................................................................................ 147
Reference List .............................................................................................................. 147
Chapter 14: Diabetes Complications ......................................................................... 150
Discussing Complications ......................................................................................... 150
Diabetic Retinopathy .................................................................................................. 150
  Prevalence and association studies of retinopathy .................................................... 151
  Screening for retinopathy ......................................................................................... 152
  Interventions to prevent or delay progression of diabetic retinopathy ...................... 153
Cataracts ...................................................................................................................... 153
Refractive Errors ........................................................................................................ 153
Diabetic Nephropathy ................................................................................................ 154
  Screening for nephropathy ....................................................................................... 154
  Interventions to prevent or delay progression of diabetic nephropathy .................... 155
Diabetic Neuropathy ................................................................................................... 156
  Screening for neuropathy ........................................................................................ 156
  Interventions to prevent or delay diabetic neuropathy ............................................. 157
Macrovacular Disease ................................................................................................. 157
Hypertension .............................................................................................................. 157
  Blood pressure assessment in children and adolescents ....................................... 157
  Method for BP measurement .................................................................................. 157
  Paediatric reference values ..................................................................................... 158
## Table of Contents

**Chapter 21: Travelling and Holidays**

- Preparation ......................................................... 207
- Supplies ............................................................... 207
- Management of Diabetes on Long Flights ................. 208
- The Evidence ......................................................... 208

**Chapter 20: Diabetes Camps**

- Background ......................................................... 203
- The Need for Diabetes Camps in Australia ................. 203
- Benefits .............................................................. 203
- Goals ................................................................. 204
- Other Benefits ..................................................... 204
- Prerequisites ......................................................... 204
- Medical Management .......................................... 205
- Conclusion ........................................................... 205
- Information on diabetes camps ................................. 205
- Recommendations and Principles ............................ 206
- Reference List ....................................................... 206

**Chapter 19: School**

- General Considerations in the Development of the Care Plan ........... 197
- Issues to be Considered in the Individual Care Plan ..................... 197
- Detentions ............................................................ 199
- Travel to and from School by Bus ................................ 199
- Emergencies at School ........................................... 199
- School Examinations .............................................. 199
- High School Examinations ...................................... 199
- School Camps ...................................................... 200
- Short-term Effects of Fluctuations in Glycaemia on Cognitive Function ................................................................. 200
- Long-term Effects of Fluctuations in Glycaemia on Cognitive Function ................................................................. 200
- The Evidence ......................................................... 201
- Recommendations and Principles ................................ 202
- Reference List ....................................................... 202

**Career Options** .................................................. 186

**Driving** ............................................................ 186

**Risk Taking Behaviour** ........................................ 187

- Smoking ............................................................. 187
- Alcohol ............................................................... 188
- Drugs ................................................................. 189

**Sexuality** .......................................................... 189

- Impotence ............................................................ 189
- Contraceptives ..................................................... 190
- Oral contraceptive pill (OCP) ................................... 190
- Intrauterine devices (IUDs) ..................................... 190
- Barrier methods (condom, diaphragm) ...................... 190
- Progestogen depot/implant ...................................... 190

**Diabetes and Pregnancy** ........................................ 191

**Eating Disorders** ................................................ 191

**The Evidence** ..................................................... 192

**Recommendations and Principles** .......................... 192

**Reference List** ..................................................... 193
Chapter 22: Complementary and Alternative Medicine

Complementary and Alternative Medicine use in Diabetes
Clinicians and Complementary and Alternative Medicine
Management of a Patient using Complementary and Alternative Medicine
The Evidence
Recommendations and Principles
Reference List

Resources

Appendix 1: Guidelines Writing Committee Members and Contributors

Appendix 2: Evidence Tables

Table of Contents
Australian Clinical Practice Guidelines: Type 1 Diabetes in Children and Adolescents
Tables

Table I: NHMRC Levels of Evidence........................................................................................................... 5
Table II: Recommendation Codes .................................................................................................................. 6
Table 1.1: Aetiological Classification of Disorders of Glycaemia................................................................. 29
Table 1.2: Other Specific Types of Diabetes.................................................................................................. 30
Table 1.3: WHO Criteria Values for Diagnosis of Diabetes Mellitus and Other Categories of Hyperglycaemia .................................................................................................................. 31
Table 4.1: Insulins Currently in Use in Australia .......................................................................................... 54
Table 5.1: Mean Cutis/Subcutis Thickness ................................................................................................... 66
Table 7.1: The Dietary Guidelines for Children and Adolescents in Australia ........................................... 87
Table 7.2: The Glycaemic Index of Some Foods (Glucose = 100) ................................................................ 89
Table 7.3: Summary of the Australian Dietary Guidelines for Dietary Fat Intake during Childhood ................................................................. 90
Table 10.1: Maintenance Fluid Volume for Different Age Groups ............................................................... 118
Table 11.1: Emergency Kit For Sick Day Management at Home ................................................................. 124
Table 11.2: Indicators for Patient to be Transferred to Hospital ................................................................. 125
Table 11.3: Sick Day Foods and Fluids ........................................................................................................ 125
Table 11.4: How to Calculate the Amount of Extra Insulin on Sick Day .................................................. 126
Table 11.5: Recommended Dose for Mini-dose Glucagon ......................................................................... 127
Table 11.6: Management of Sick Days with Insulin Pump ........................................................................ 128
Table 12.1: Symptoms of Hypoglycaemia in Diabetic Children and Recommendations for its Treatment .................................................................................................................. 132
Table 14.1: Blood Pressure Ranges for Height Centiles .............................................................................. 161

Figures

Figure 1.1: Annual Incidence Rates for Type 1 Diabetes (0-14 years age group) Comparing Different Countries in the World .................................................................................................................. 27
Figure 4.1: Schematic Action Profiles of Insulin Preparations ................................................................... 58
Figure 5.1: Recommended Injection Sites ................................................................................................... 66
Figure 7.1: Body Mass Index-for-age Percentiles: Girls, 2-20 Years ........................................................... 94
Figure 7.2: Body Mass Index-for-age Percentiles: Boys, 2-20 Years ............................................................ 95
Figure 12.1: Glucagon Kit for Treatment of Hypoglycaemia .................................................................... 136
Introduction

Background

The development of the Australian Clinical Practice Guidelines for the Management of Type 1 Diabetes in Children and Adolescents arose out of a recommendation by the National Diabetes Strategy Group to update the APEG Handbook on Childhood and Adolescent Diabetes published in 1996. In updating the guidelines, the decision was made to take an evidence-based approach in order to improve the usefulness of the guidelines for practising clinicians. The project was funded by the Australian Government Department of Health and Ageing and carried out by the Australasian Paediatric Endocrine Group in collaboration with Diabetes Australia and the Juvenile Diabetes Research Foundation. Consumer input was obtained from the latter two organisations and by nationwide public consultation.

The guidelines development process was coordinated by a national multidisciplinary writing committee, which met to determine the scope of the work and resolved that the new guidelines would be aimed at the practising health care professional involved in all aspects of the care of children and adolescents with type 1 diabetes. It was considered important that the guidelines were to retain the user-friendly format of the APEG handbook. The guidelines were developed in accordance with the NHMRC handbook series on preparing clinical practice guidelines.(1-7)

Rationale for the Guidelines

Type 1 diabetes is one of the most common chronic diseases of childhood and adolescence. It affects approximately 10,000 children and adolescents in Australia and its incidence is rising 2-4% per year. The disease impacts heavily on their lifestyle and that of their families. Lifelong insulin replacement and monitoring of blood glucose levels are needed. Children and adolescents with type 1 diabetes are liable to acute, subacute and chronic complications of diabetes. The development and progression of the chronic microvascular complications of diabetes are influenced by diabetes control. The transition process from paediatric to adult services has been highlighted as an area of need. People with type 1 diabetes are also at greater risk of developing cardiovascular disease. These risks can be decreased by control of high blood pressure and lipid disorders. Regular review of diabetes control and of the risk factors for the development of microvascular and macrovascular complications of diabetes need to form part of the long-term management of type 1 diabetes. The economic burden of diabetes is high for the individual, the family, the health care sector and society as a whole. In addition there is a high personal and family burden in growing up and living with type 1 diabetes.

Scope of the Guidelines

The guidelines address the diagnosis and all relevant aspects relating to the clinical management of type 1 diabetes in children of all ages, including adolescents up to the point of transition to adult care.

Areas beyond the remit of the guidelines

The guidelines do not address:

- The management of type 1 diabetes in adults.
- The management of gestational diabetes.
- The management of type 2 diabetes.
Target Audience

The guidelines are aimed at all health care professionals involved in the care of children and adolescents with type 1 diabetes.

Guidelines Development Process

Guidelines writing committee
A multidisciplinary writing committee was convened consisting of clinicians, diabetes educators, consumers, parents, and experts in guideline development. The members of the Writing Committee and other contributors are listed in Appendix 1.

Review of existing guidelines
Other guidelines, position papers and technical reports regarding the management of type 1 diabetes in children and adolescents were sought from the World Health Organization (WHO), International Diabetes Federation (IDF), American Diabetes Association (ADA), National Health and Medical Research Council (NHMRC), Australian Paediatric Endocrine Group (APEG) and International Society for Pediatric and Adolescent Diabetes (ISPAD). In addition, the Writing Group was privileged to have access to the UK National Health Services (NHS) National Institute of Clinical Excellence (NICE) guideline on type 1 diabetes: Diagnosis and Management of type 1 diabetes in children and young people to be released in 2004, and the findings of the Consensus Statement on Diabetic Ketoacidosis by the Lawson Wilkins Pediatric Endocrine Society (USA) and the European Society for Pediatric Endocrinology (ESPE), produced in September, 2003.

The above sources were considered for their usefulness in updating the 1996 APEG Handbook. The NICE guidelines and the Consensus Statement on Diabetic Ketoacidosis (DKA), in particular, were found to be evidence-based documents which could be adapted to inform the update of the 1996 APEG guidelines.

Formulation of Clinical Questions

The writing committee formulated clinical questions which needed to be addressed by the updated guidelines. Questions were formulated to cover areas of controversy or of particular concern within the Australian health care context. These questions are listed in Appendix 2.

Locating the Evidence

The relevant literature was systematically searched with the aim of identifying the clinical, epidemiological, psychosocial, research and diagnostic data relevant to type 1 diabetes in children and adolescents. Electronic databases (Medline, Embase, the Cochrane Database of Systematic Reviews and Central Register of Controlled Trials, and, where relevant to the topic, PsychINFO and CINAHL) were searched from inception to August 31, 2003. Search strategies were devised to address the clinical questions and incorporated key words, MeSH terms (Medical Index Subject Headings) and free text terms. All searches were restricted to English language and Human studies. The only animal study cited was a classic study on CSF pH changes in diabetic ketoacidosis in dogs which was published in the Journal of Pediatrics in 1980 (Bureau MA, Begin R, Berthiaume Y, Shapcott D, Khoury K, Gagnon N: Cerebral hypoxia from bicarbonate infusion in diabetic acidosis. Journal of Pediatrics 96:968-973, 1980). Studies available only as abstracts were excluded from the main analysis. No age limit was used in the searches (ie all paediatric and adult literature was considered). In considering
the search yield, the primary focus was on childhood studies. However, the adult literature was included when considered relevant to childhood and adolescent practice. As it was anticipated that for many important areas of type 1 diabetes management and care there would be a paucity of high quality evidence, studies of all types were included. Additional references were identified from the reference lists of relevant articles and by a ‘call for information’ from colleagues and experts involved in the writing process of the guidelines. Evidence tables are listed in Appendix 2.

Four additional references were added to the evidence tables as a result of the public consultation (Evidence Tables: Chapter 3, Srinivasan et al. 2004; Chapter 4, Sarnblad et al. 2003; Chapter 5, Diglas et al. 1999; Chapter 12, Schoenle et al. 2002). Additional references, provided by expert reviewers during the public consultation phase, not included in the evidence tables, but relevant to the background information of the document, were included after consideration by the writing committee (even if published after the 30th August 2003).

Levels of Evidence and Critical Appraisal

These guidelines searched for evidence for the following issues in detail:

- **Chapter 1: Definition, Epidemiology and Classification**
- **Chapter 2: Phases of Diabetes**
  - Intervention trials to delay or prevent the onset of type 1 diabetes.
- **Chapter 3: Medical Management**
  - Differences in glycaemic control between urban and rural children and adolescents with type 1 diabetes in the Australian health care system.
  - The effect of educational interventions on metabolic and psychological outcomes in children and adolescents with type 1 diabetes.
- **Chapter 4: Insulin Preparations and Storage**
  - Benefits of animal insulin over human insulin use in children and adolescents with type 1 diabetes.
  - Treatment of children with type 1 diabetes with insulin glargine.
  - Metformin as an adjunct therapy to insulin in the treatment of children and adolescents with type 1 diabetes.
- **Chapter 5: Insulin Regimens and delivery**
  - Relationship of number of daily insulin injections with glycaemic control.
  - The length of needle for the injection for insulin therapy in the treatment of children with type 1 diabetes.
  - Children and adolescents with type 1 diabetes and management with insulin pump therapy.
- **Chapter 6: Glycaemic Control**
  - Benefits of near patient testing of HbA1c at outpatient visits.
  - Benefits of improved glycaemic control on development of microvascular and macrovascular complications.
- **Chapter 7: Nutrition**
  - Low glycaemic index diets in the management of type 1 diabetes in children and adolescents.
  - Adjusting insulin dose for carbohydrate quantity in the management of type 1 diabetes in children and adolescents.
⇒ Effect of moderate use of sugars on glycaemic control in children and adolescents with type 1 diabetes.

- Chapter 8: Physical Activity
  ⇒ Longterm effects of physical activity in children and adolescents with type 1 diabetes.

- Chapter 9: Diabetic Ketoacidosis
  ⇒ Aetiology, epidemiology, risk factors, cerebral oedema and management of diabetic ketoacidosis.

- Chapter 10: Surgery and Fasting
  ⇒ Management of surgery and fasting in children and adolescents with diabetes.

- Chapter 11: Sick Day Management
  ⇒ Insulin adjustment during “sick days” /intercurrent illnesses in children and adolescents with type 1 diabetes.
  ⇒ Management of severe hypoglycaemia with intravenous glucose or intramuscular/intravenous glucagon.

- Chapter 12: Hypoglycaemia
  ⇒ Effect of intensive diabetes management on the incidence of hypoglycaemia.
  ⇒ Management of severe hypoglycaemia with intravenous glucose or intramuscular/intravenous glucagon.
  ⇒ Effects of hypoglycaemia on cognitive function in children and adolescents with type 1 diabetes.

- Chapter 13: Psychosocial Aspects
  ⇒ The incidence and risk factors for non-adherence with treatment regimens in children and adolescents with type 1 diabetes.
  ⇒ The effect of psychosocial interventions on metabolic and psychological outcomes in children and adolescents with type 1 diabetes.

- Chapter 14: Diabetes Complications
  ⇒ Effect of intensive diabetes management on microvascular and macrovascular complications in adolescents.
  ⇒ How frequently should children and adolescents with type 1 diabetes be screened for microvascular (retinopathy, nephropathy, neuropathy) complications?
  ⇒ How frequently should children and adolescents with type 1 diabetes be screened for macrovascular complications?

- Chapter 15: Other Complications and Associated Conditions
  ⇒ How frequently should children and adolescents with type 1 diabetes be screened for thyroid disease?
  ⇒ How frequently should children and adolescents with Type 1 diabetes be screened for coeliac disease?
  ⇒ Effect of a gluten free diet (GFD) in asymptomatic patients with type 1 diabetes found to have coeliac disease on routine screening.

- Chapter 16: Foot Care
  ⇒ The effect of type 1 diabetes on joint mobility in the feet of young people.
  ⇒ The management of high plantar pressure and callus in adolescents with type 1 diabetes.
  ⇒ How frequently should children and adolescents with type 1 diabetes be screened for foot complications?

- Chapter 17: Dental Health
  ⇒ How frequently should children and adolescents with type 1 diabetes have a dental review?
  ⇒ The effect of type 1 diabetes on dental health in children and adolescents.

- Chapter 18: Adolescent Health
• Glycaemic control in adolescents compared with adults.
• Current transition processes and outcomes for adolescents with type 1 diabetes moving to the adult care system
• The effect of type 1 diabetes on driving performance.
• Eating disorders in type 1 diabetes.

• Chapter 19: School
  • Effects of type 1 diabetes on cognitive function in children and adolescents.

• Chapter 20: Diabetes Camps
  • Benefits on glycaemic control of diabetes camps in children with type 1 diabetes.

• Chapter 21: Travelling and Holidays
  • Insulin regimens during travel when crossing time zones.

• Chapter 22: Complementary and Alternative Medicine
  • Do complementary and alternative medicine therapies cure or improve diabetes in children?

Identified studies were assigned a level of evidence according to the NHMRC Hierarchy of Evidence (NHMRC, 2001) (Table I) and are included in the Evidence tables. Those studies which were used to formulate recommendations (and thus provided the evidence-base for those recommendations) were critically appraised for their methodological quality. Other recommendations and principles of clinical practice in the guidelines have been based on Technical Reports or when no level I-IV information existed, on Consensus Statements based on expert opinion. Apart from outlining recommendations and principles of clinical practice the guidelines provide a wealth of highly referenced information for practicing clinicians and health care professionals.

Study quality was assessed on a number of parameters such as the quality of the study methodology reporting, methods of randomisation and allocation concealment (for Randomised Control Trials (RCT’s)), blinding of patients or outcomes assessors, attempts made to minimise bias, sample sizes and the ability of the study to measure ‘true effect’. The applicability of results outside the study sample was also examined as were the appropriateness of the statistical methods used to describe and evaluate the study data.

As the NHMRC levels of evidence are designed for application specifically to intervention studies, the population-based studies, cohort studies and case-control studies which were identified by the literature search are allocated a relatively low level of evidence. The highest level of evidence that can be allocated to these studies based upon NHMRC criteria is Level IV. This does not reflect the high level and quality of many of the population-based studies referenced in the guidelines and used to base recommendation upon.

Table I: NHMRC Levels of Evidence

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<th>Level</th>
<th>Description</th>
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<tr>
<td>I</td>
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<td>II</td>
<td>Level II</td>
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<td>Level III-2</td>
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<tr>
<td>III-3</td>
<td>Level III-3</td>
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<tr>
<td>IV</td>
<td>Level IV</td>
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</tbody>
</table>
Economic Considerations

A broad literature search was designed to find all economic studies relating to children and adolescents with type 1 diabetes. All studies addressing resource utilisation as well as studies comparing the costs of different alternatives (economic evaluations) were considered if they were generalisable to the Australian health care system. These were incorporated into the relevant chapters within the guidelines. It was agreed that a new economic evaluation would only be relevant if guidelines recommendations had major resource implications or represented a change in policy.

Guidelines Review Date

The recommendations in the guidelines incorporate the most recent published evidence, position papers, technical reports and consensus statements as of August 31, 2003. In view of the anticipated advances in diabetes research and management it is recommended that the guidelines should be reviewed after five years in 2008.

Structure of the Guidelines

In writing the guidelines, the writing committee aimed to retain the user-friendly format of the original 1996 APEG guidelines. For this reason it was decided to incorporate the available evidence and recommendations for care within the context of the overall discussion of the topic. At the end of each chapter the important evidence is summarised according to levels of evidence, and recommendations arising from the available evidence are made (with the corresponding level of evidence indicated using the NHMRC roman numeral system). Where no studies could be located recommendations were made based on state, national and international consensus statements, WHO technical reports, NICE technology appraisals and other relevant technical reports. Where this occurs it is clearly indicated in the text by the use of identifying codes as listed in Table II below:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>C</td>
<td>Consensus statement endorsed by professional organisations</td>
</tr>
<tr>
<td>T</td>
<td>WHO technical reports</td>
</tr>
<tr>
<td></td>
<td>Technical reports produced by expert panels convened by WHO</td>
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</tbody>
</table>

Evidence tables summarising the studies which constituted the evidence-base for the recommendations can be found in Appendix 2.

Overview of the Guidelines

The guidelines are comprehensively referenced and incorporate up-to-date evidence-based and expert consensus management recommendations. The initial chapters contain the most recent information on diagnosis, classification and epidemiology of type 1 diabetes, the phases of diabetes, the options for the initial management of diabetes, the currently available insulin preparations and regimens, and, the methods of monitoring metabolic control. A detailed description is provided of the international consensus management guidelines of diabetic ketoacidosis as well as the management of the child with diabetes undergoing minor and major surgery. The guidelines offer practical advice on the problems of hypoglycaemia, sick day management, travelling and holidays. The psychosocial issues of diabetes are detailed as well as school and adolescent health issues. Comprehensive guidance is provided...
on the screening for and the management of the chronic complications of diabetes. Other complications including thyroid disease, coeliac disease are also addressed as well as foot care and dental health. The challenges of transition from paediatric to adult care are reviewed and guidance how best to manage this difficult stage is offered.

**Consultation and Peer-review Process**

The consultation and peer-review process included a nationally advertised call for public comment, invitations for critical review by members of the Australasian Paediatric Endocrine Group, International Society for Pediatric and Adolescent Diabetes, International Diabetes Federation Consultative Section on Childhood and Adolescent Diabetes, Diabetes Australia, Australian Diabetes Society, Royal Australasian College of Physicians, Royal Australian College of General Practitioners, Dietitians Association of Australia, Australian Diabetes Educators Association and the Juvenile Diabetes Research Foundation. The comment were collated, de-identified, formally considered and addressed by the Guideline Writing Group.

**Dissemination**

The full text of the guidelines will be freely available as a pdf file on the NHMRC and APEG websites.

**Legal Considerations**

The following statement applies to the guidelines: ‘Every attempt has been made to locate the most recent evidence. Judgement is necessary when applying evidence in a clinical setting. It is important to note that weak evidence does not necessarily mean that a practice is unadvisable, but may reflect the insufficiency of evidence or the limitations of scientific investigation. The guidelines are intended to act as a guide to practice. The ultimate decision of what to do rests with the practitioner and the consumer and depends on individual circumstances and belief (NHMRC 1999)’.

**Reference List**

1. National Health and Medical Research Council: *How to review the evidence: systematic identification and review of the scientific literature*. AusInfo, 1999
List of Abbreviations

ADA       American Diabetes Association
APEG      Australasian Paediatric Endocrine Group
APS       Autoimmune Polyglandular Syndrome
BMI       Body Mass Index
BP        Blood pressure
CBGM      Continuous Blood Glucose Monitoring
CSII      Continuous Subcutaneous Insulin Infusion
DCCT      Diabetes Control and Complications Trial
DIDMOAD   Diabetes Insipidus Diabetes Mellitus Optic Atrophy Deafness
DKA       Diabetic Ketoacidosis
DPT       Diabetes Prevention Trial
EDIC      Epidemiology of Diabetes Interventions and Complications
EMA       Antiendomysial Antibodies
ENDIT     European Nicotinamide Diabetes Intervention Trial
HDL       High Density Lipoprotein
HLA       Human Leucocyte Antigen
HNF       Hepatic Nuclear Factor
ICA       Islet Cell Antigen
IDDM      Insulin Dependent Diabetes Mellitus
IDF       International Diabetes Federation
IFG       Impaired Fasting Glycaemia
IGT       Impaired Glucose Tolerance
IVGTT     Intravenous Glucose Tolerance Test
JDRF      Juvenile Diabetes Research Foundation
LDL       Low Density Lipoprotein
MODY      Maturity Onset Diabetes in the Young
MRDM      Malnutrition Related Diabetes Mellitus
NATA      National Association of Testing Authorities
NICE      National Institute for Clinical Excellence
NIDDM     Non-insulin Dependent Diabetes Mellitus
OCP       Oral Contraceptive Pill
OGTT      Oral Glucose Tolerance Test
SDS       standard Deviation Score
WHO       World Health Organization

Glossary

Acanthosis nigricans  dark wart-like patches on neck and in skin folds
Genu valgum         knock knee
Genu varum          bow-leg
Hypocapnia          low blood CO₂ level
Hypo(hyper)kalaemia Low(high) blood potassium
Acknowledgements

The Writing Group wishes to acknowledge the outstanding contributions made by Dr Ann Maguire, APEG Fellow, to the development of the guidelines and the referencing and evidence basing the guidelines. The expert secretarial assistance of Ms Jane Haynes is most gratefully acknowledged. The Writing Group also wishes to acknowledge the critical review and advice provided by the ASERNIPS GAR experts (Ms Philippa Middleton and Dr Rebecca Tooher).
Executive Summary of Recommendations and Principles

1. Definition, Epidemiology and Classification

- The diagnosis of diabetes in children and adolescents should be based on the World Health Organization criteria (1999).\(^1\)\(^{(T)}\)
- Worldwide the incidence of type 1 diabetes in childhood varies greatly (0.1 - 37.4 per 100,000), with the Australian incidence being 17.8 and increasing by 3.2% per year since 1990.\(^2\)\(^-\)\(^5\)\(^{(IV)}\)
- Diabetes can be diagnosed if the characteristic symptoms and signs are present and the fasting venous plasma glucose concentration is greater than or equal to 7.0 mmol/L, and/or the random venous plasma glucose concentration taken at least 2 hours after eating is greater than or equal to 11.1 mmol/L.\(^1\)\(^{(T)}\)
- The possibility of type 2 diabetes should be considered in children and adolescents with diabetes who are obese, have a strong family history of type 2 diabetes, come from an ethnic background at high risk for diabetes, produce little or no ketonuria and show evidence of insulin resistance (acanthosis nigricans or polycystic ovary syndrome).\(^1;6\)\(^{(T,C)}\)
- The possibility of other types of diabetes should be considered in children and adolescents with diabetes who have any of the following: an autosomal dominant family history of diabetes, have associated conditions such as deafness, optic atrophy or syndromic features, have marked insulin resistance or require little or no insulin outside the partial remission phase or have been exposed to drugs known to be toxic to beta cells or cause insulin resistance.\(^1;7\)\(^{(T,C)}\)
- An oral glucose tolerance test (OGTT) is rarely indicated in making the diagnosis of type 1 diabetes in childhood and adolescence.\(^1;7\)\(^{(T,C)}\)
- The OGTT may be used in the evaluation of possible glucose intolerance in a child or adolescent suspected of having the metabolic syndrome e.g. an obese adolescent with acanthosis nigricans, a girl with the polycystic ovary syndrome, an obese child with a family history of type 2 diabetes or an obese child from a high risk ethnic background for type 2 diabetes.\(^6\)\(^8\)\(^{(C,T,)}\)
- Targeted screening for type 2 diabetes (fasting plasma glucose or 2 hour post-prandial glucose) is recommended at the point of medical contact if high risk factors are present (obesity, strong family history of type 2 diabetes, high risk ethnic group, acanthosis nigricans, polycystic ovary syndrome) and every 2 years thereafter.\(^8\)\(^9\)\(^{(T,C)}\)

2. Phases of Diabetes

- Health care professionals should be aware that there are no interventions shown to delay or prevent the onset of type 1 diabetes.\(^10\)\(^11\)\(^{(II)}\)
- Neither screening of any population nor intervention in the preclinical phase should occur outside the context of defined clinical studies.\(^12\)\(^{(C)}\)
- Type 1 diabetes is characterised by a preclinical, clinical, partial remission and chronic phase.\(^7\)\(^{(C)}\)
- The clinical presentation of diabetes can vary from non-emergency presentations (e.g. polydipsia, polyuria, weight loss, enuresis) to severe dehydration, shock and diabetic ketoacidosis.\(^1;7\)\(^{(T,C)}\)
- Parents and children with type 1 diabetes should be informed that the partial remission phase of diabetes is transient and does not indicate remission of diabetes.\(^7\)\(^{(C)}\)
3. Medical Management

- Every child and adolescent with type 1 diabetes, including those from rural and remote areas, should have access to optimal medical management.\(^7\)\(^,\)\(^13\)\(^,\)\(^170\) (C)
- Health care professionals who look after children must make advocacy for the child one of their key responsibilities.\(^13\) (C)
- Older children and adolescents who develop diabetes but are not dehydrated or acidotic may be considered for management out of hospital if expert diabetes support teams are available.\(^14\)\(^-\)\(^21\) (I)
- Relative contraindications to ambulatory initiation of insulin therapy include very young age (under 2 years), ketoacidosis, dehydration (moderate or severe), geographic isolation, no telephone at home, language or other communication difficulties, profound grief reaction and significant psychological or psychiatric problems within the family.\(^7\)\(^,\)\(^13\) (C)
- Children and adolescents with type 1 diabetes should have access to care by a multidisciplinary team trained in childhood diabetes.\(^7\)\(^,\)\(^22\)\(^-\)\(^24\) (C)
- The older child and the family should be recognised as being part of the management team. (C)
- Diabetes education should be part of the management of type 1 diabetes in children and adolescents. Educational interventions have beneficial effects on diabetes management outcomes.\(^25\) (I)
- Education should be adapted to each individual’s age, maturity, stage of diabetes, lifestyle and culture.\(^7\) (C)
- After the initial period of diagnosis and education (when frequent contact may be required), the child should be regularly reviewed throughout the year. This should be no less than 3–4 times per year, including one major annual review (paying particular attention to growth, blood pressure, puberty, associated conditions, nutrition and complications) with the multidisciplinary team.\(^7\)\(^,\)\(^23\)\(^,\)\(^24\) (C)
- Children and adolescents with type 1 diabetes should be immunised according to the Australian Standard Immunisation Schedule\(^166\) unless a contra-indication is present. Diabetes is not a contra-indication to immunisation. (C)
- In rural and geographically remote areas within the Australian health care system, children with diabetes may be successfully cared for by a local paediatrician/physician with training and experience in paediatric diabetes, access to resources, support and advice from a tertiary centre diabetes team.\(^26\)\(^,\)\(^27\) (IV)

4. Insulin Preparations and Storage

- Health care professionals, parents and children and adolescents with type 1 diabetes should be informed that insulin is essential for survival. There is no alternative to treatment with insulin.\(^1\) (T)
- Children and adolescents with type 1 diabetes should be treated with human insulin as animal insulin has no advantage over human insulin in terms of metabolic control or hypoglycaemia.\(^28\) (I)
- A wide variety of human, analogue and bovine insulins are available in Australia for use in children and adolescents with type 1 diabetes.\(^13\) (C)
- Rapid-acting insulin should be injected at the time of a meal and short-acting insulin should be injected 15–20 minutes before a meal.\(^29\)\(^,\)\(^30\) (C)
- Rapid-acting insulin can be administered post-prandially in prepubertal children with type 1 diabetes with unpredictable eating habits (eg infants, toddlers and preschool children).\(^29\) (C)
• Insulin glargine is a long-acting basal insulin analogue which has recently been introduced as a treatment option.31(I)
• To avoid confusion and prescribing errors, the use of the terms ‘clear’ to describe rapid-acting or short-acting insulin and ‘cloudy’ to describe intermediate- or long-acting insulin, should be discouraged as the long-acting analogues, glargine and detemir, are clear solutions.(C)
• The action profile of the various insulin preparations is subject to inter- and intra-individual variation. The action profile is also affected by storage conditions and the manufacturer’s storage instruction should be followed.29(C)
• All children should have rapid/short-acting insulin available for sick-day management.7;29(C)
• Families need to ensure that a small supply of spare insulin is always available so that supply is uninterrupted.7(C)
• As there is limited and inconsistent evidence on the use and efficacy of metformin as an adjunct therapy in type 1 diabetes, it should only be considered as an adjunct for difficult to control patients with evidence of insulin resistance. Patients should be warned of and closely monitored for hypoglycaemia during the stabilisation period and the efficacy monitored.32-34(II)

5. Insulin Regimens and Delivery
• There is a variable effect of the number of daily injections on metabolic control.35-37(II,IV)
• Intensive management (including multiple daily injections or pump therapy, education, intensive monitoring and psychosocial support) of type 1 diabetes in adolescents improves metabolic control and reduces the risk of microvascular complications.38,39(II)
• Many insulin regimens are used in the treatment of type 1 diabetes in children and adolescents. Any insulin regimen has to be considered in the wider context of a total diabetes management package, which must include dietary management, exercise and physical activity, blood glucose monitoring, initial and ongoing education, regular medical follow-up and psychological care.7,40(C)
• Insulin doses should be tailored for each patient’s individual circumstances and requirements, taking into account age, weight, stage of puberty, duration of diabetes, food intake and distribution, exercise patterns, daily routines, results of monitoring and intercurrent illness.7,11(C)
• It is recommended that insulin be injected in the abdomen, buttock or non-exercising thighs. The upper arm is generally not recommended because of the thin layer of subcutaneous tissue at this site and the increased risk of intramuscular injection.13,40(C)
• There is a significant risk of accidental intramuscular injections (and hence more rapid absorption) especially in lean individuals. This can be minimised by using a two finger pinch technique, an injection angle of 45 degrees and 8 mm needles.41(II)
• 5 or 6 mm needles may be appropriate in lean children or those using pens.29,40(C)
• Insulin pumps should be considered as a treatment option.42-44(I)
• Insulin pump therapy should be initiated and supervised by a specialised multidisciplinary team trained in pump therapy in children and adolescents with diabetes.42(C)
• Insulin syringes and pen needles need to be disposed of in a safe and hygienic way. Needles should not be recapped to avoid the risk of needle-stick injury. Approved sharps containers should be provided and disposed of according to local authority regulations.40(C)
• Health care professionals should educate and encourage children and their families to acquire skills in insulin adjustment.40(C)

6. Glycaemic Control
• Diabetes Control should be optimised as much as possible as improved glycaemic control reduces the risk of development and progression of microvascular and macrovascular complications in adolescents and adults.38,39,45-48(II)
• Frequent daily blood glucose monitoring as part of a package of care has been shown to be associated with improved glycaemic control.49(T)
• The frequency of blood glucose monitoring should be adapted to the insulin regimen, the age of the child and the stability of the diabetes.29(C)
• The use of memory-glucose meters without daily reviewing of glucose levels is not recommended as patterns of glycaemic changes may not be appreciated by the child or adolescent and the family, and appropriate changes in insulin dosage may not be made.40(C)
• HbA1c is the only measure of glycaemic control that has been shown to be associated with long-term complications of diabetes and best reflects glycaemic levels over the preceding 2-3 months.49(T)
• The American Diabetes Association recommends measuring the HbA1c at least twice per year in patients who are meeting treatment goals, and more frequently (quarterly) in those whose treatment has changed or who are not meeting glycaemic goals.50(C)
• HbA1c results should be available at the time of the clinic visit as this may influence the outcome of the consultation.51(III-1)
• In older children and adolescents the target HbA1c should be <7.5%.7,29(T,C)
• Increased efforts to improve glycaemic control are recommended as fewer than 25% of children and adolescents in NSW had HbA1c levels <7.5%.26,36(IV)
• In younger children, the HbA1c target may be set a little higher because of the dangers of hypoglycaemia to the developing brain.29(IV)
• HbA1c values need to be interpreted in the context of blood glucose readings and clinical parameters (eg a child with a low HbA1c may be experiencing asymptomatic hypoglycaemia).40(C)
• Children whose HbA1c is rising or is persistently elevated should have all aspects of their diabetes management reassessed.29(C)
• Ketones should be tested for when the blood glucose is above 15 mmol/L and the child or adolescent is unwell.7(C)
• Ketones should be tested for in the presence of abdominal pains, rapid breathing, flushed cheeks, high temperature, vomiting, diarrhoea or inappropriate drowsiness even when the blood glucose is <15 mmol/L.40(C)

7. Nutrition
• Nutrition is a fundamental component in the management of type 1 diabetes in childhood and adolescence.52,53(C)
• Nutritional management of children and adolescents with type 1 diabetes should be initiated by an accredited practising dietitian trained in paediatric diabetes.13(C)
• Nutritional reviews should occur 2-4 weeks post-diagnosis and ongoing at least once per year by a paediatric dietitian experienced in diabetes management.13(C)
• Children and adolescents with diabetes should be encouraged to follow the NHMRC Dietary Guidelines for Children and Adolescents in Australia which recommend that:54(C)
  ➔ Carbohydrate should provide 50-55% of total energy intake.
Executive Summary of Recommendations and Principles
Australian Clinical Practice Guidelines: Type 1 Diabetes in Children and Adolescents

- Dietary fat intake should provide between 25 and 40% of total energy intake depending on the child’s age.
- Saturated fat intake should be limited to <10% of total energy intake.
- Dietary protein intake should provide 15-20% of total energy intake.

- Children and adolescents with diabetes should be educated and encouraged to adjust their insulin dose depending upon carbohydrate quantity.55;56(II)
- Day to day consistency in carbohydrate intake is important for those receiving fixed doses of insulin.(C)
- Dietary advice should include information about low glycaemic index food as this can help to improve glycaemic control.57;167-169(I)
- Moderate use of sucrose in the diabetes diet should be allowed as it does not significantly influence glycaemic control in type 1 diabetes.58-62(II)

8. Physical Activity

- Physical activity should be considered part of diabetes management. Children and adolescents with type 1 diabetes should be encouraged to participate in a variety of sport and physical activity and not be limited in their choice of activity.13(C)
- Regular physical activity in children and adolescents with type 1 diabetes should be encouraged as it can improve aerobic capacity and muscle strength; however the reported effect of physical activity on glycaemic control (measured by HbA1c) varies.63-65(II)
- Activities should be approached with caution if they are solo in nature, take place in water or mid-air, or limit the individual’s ability to recognise and self-treat hypoglycaemia and a ‘buddy’ is recommended.13(C)
- Blood glucose levels need to be measured before, during and after physical activity.29(C)
- Physical activity may necessitate extra carbohydrate intake and insulin reduction. Experience and blood glucose monitoring help determine the most appropriate strategies as the requirements vary for each individual.29(C)
- All children and adolescents participating in sport should have access to assistance from a person aware of the management of hypoglycaemia.(C)
- A general recommendation is that 15 gm of easily consumed and quickly absorbed carbohydrate or an extra serving should be taken for every 30 minutes of moderate to intensive sport or physical activity.(C)
- Extra carbohydrate should be consumed if blood glucose level is <7 mmol/L.29;40(C)
- Strenuous physical activity should be avoided if blood glucose levels are >15 mmol/L especially if ketones are present.40(C)

9. Diabetic Ketoacidosis

- The guidelines for the management of diabetic ketoacidosis should take into account the conclusions of a consensus statement resulting from a workshop that took place in the United Kingdom in June 2003 involving the European Society for Paediatric Endocrinology (ESPE), the Lawson Wilkins Pediatric Endocrine Society (LWPES) and other societies including the Australasian Paediatric Endocrine group (APEG).66(C)
- The most common precipitating factors in the development of diabetic ketoacidosis include infection, often as a result of inadequate insulin therapy during intercurrent illness and insulin omission.67-72(IV)
- Diabetic ketoacidosis is the most common cause of death in newly diagnosed type 1 diabetes.68-70;73(IV)
• The greatest risk of mortality from diabetic ketoacidosis is from cerebral oedema.68-70,74,75(IV)
• Although poorly understood, the risk factors for cerebral oedema in diabetic ketoacidosis include presentation with new onset type 1 diabetes,75-77 younger age,76-78 elevated serum urea nitrogen and/or severity of dehydration at presentation, severity of acidosis,74,79 greater hypocapnia at presentation (after adjusting for degree of acidosis), an attenuated rise in serum sodium during treatment for diabetic ketoacidosis,74,80-82 bicarbonate treatment to correct acidosis has also been associated with cerebral oedema.74,83(III,IV)
• Immediate assessment for diabetic ketoacidosis should consist of clinical history, assessment and biochemical confirmation (see algorithm in Chapter 9).7(C)
• 'Low dose' intravenous insulin is recommended for the treatment of moderate to severe diabetic ketoacidosis.66(C)
• A specialist/consultant paediatrician with training and expertise in the management of diabetic ketoacidosis should direct management.66(C)
• The child should be cared for in a unit that has experienced nursing staff trained in monitoring and management of diabetic ketoacidosis, clear written guidelines for managing diabetic ketoacidosis and access to laboratories that can provide frequent and accurate measurement of biochemical variables.66(C)
• Children with ketosis and hyperglycaemia, but who are not vomiting, may be managed at home or in an ambulatory care setting (such as an emergency ward).84,85(IV)
• Children with signs of severe diabetic ketoacidosis or those who may be at increased risk for cerebral oedema should be considered for immediate treatment in an intensive care unit (paediatric if possible) or a children’s ward specialising in diabetes care.(C)
• The management of cerebral oedema in diabetic ketoacidosis is a medical emergency and treatment (fluid restriction, mannitol, neurological assessment) should be initiated in an intensive care facility as soon as the condition is suspected.77,86(IV)

10. Surgery and Fasting
• Surgery on children with diabetes should only be undertaken in hospitals with dedicated paediatric facilities for the care of children with diabetes and expert staff (medical, anaesthetic, surgical and nursing).7,13(C)
• When fasting before an anaesthetic an intravenous glucose infusion should be commenced to prevent hypoglycaemia.7,13(C)
• Children with type 1 diabetes requiring a surgical procedure should receive insulin, even if fasting, to avoid ketoacidosis. There may be increased insulin requirements peri-operatively due to physiological stress and increased counter-regulatory hormones.87(III-3)
• In children and adolescents with type 1 diabetes the optimal method of maintaining metabolic control during major surgery or prolonged post-operative fasting is by an insulin infusion.87(III-3)

11. Sick Day Management
• Families should be informed that intercurrent illnesses can cause high or low blood glucose levels.7,13,40(C)
• All families should receive education about the management of sick days and have a sick day kit at home containing rapid-acting or short-acting insulin, glucose test strips, meters, lancets/pointer pricking devices, urine test strips for glucose and ketone estimation or blood ketone meter and strips, doctor’s/hospital’s phone number, sweet cordial/fruit juice/lemonade or other soft drinks, low joule (diet drinks) or water,
glucagon, diabetes manual or emergency guidelines, sick day foods, thermometer, paracetamol or ibuprofen (sugar-free syrup or tablets).\textsuperscript{7,13,40}(C)

- Insulin should never be omitted even if unable to eat.\textsuperscript{7,13,40}(C)
- Blood glucose and ketones should be monitored frequently.\textsuperscript{7,13,40}(C)
- Any underlying illness should be treated promptly.\textsuperscript{7,13,40}(C)
- Extra oral fluids should be encouraged especially if the blood glucose is high or ketones are present.\textsuperscript{7,13,40}(C)
- Additional boluses of short/rapid-acting insulin equal to 10-20 per cent of the total insulin daily dosage should be given every 2-4 hours if the blood glucose is high and ketones are present.\textsuperscript{7,13,40}(C)
- Patients/carers should seek assistance immediately if, after extra insulin boluses, the blood glucose remains high, ketones persist, or nausea, vomiting or abdominal pain develop.\textsuperscript{7,13,40}(C)
- Severe hypoglycaemia should be treated with intravenous dextrose (in the hospital setting).\textsuperscript{88,89}(II)
- If venous access is difficult or outside the hospital setting, intramuscular glucagon should be used to treat severe hypoglycaemia.\textsuperscript{7,13,40}(C)
- Under the supervision of a doctor or diabetes educator, small doses of subcutaneous glucagon may be used to prevent or treat mild hypoglycaemia in an ambulatory setting.\textsuperscript{90}(IV)

12. Hypoglycaemia

- Hypoglycaemia is the most frequent acute complication of type 1 diabetes.\textsuperscript{26,36,38,45,91}(II)
- Hypoglycaemia is the major factor limiting intensified regimens aiming for near-normoglycaemia.\textsuperscript{26,36,38,45,91}(II)
- Severe hypoglycaemia should be avoided in children, especially in those less than 5 yrs old.\textsuperscript{92-98}(II, III, IV)
- Blood glucose values should be maintained above 4.0 mmol/L in children and adolescents with diabetes.\textsuperscript{7,13,40}(C)
- Children and adolescents with diabetes should wear some form of identification or warning of their diabetes.\textsuperscript{7,13,40}(C)
- All children and adolescents with diabetes should carry glucose tablets or readily absorbed carbohydrate (preferably in waterproof sealed wrap) on their person and have glucagon available at home (and in boarding schools where there is a nurse on staff).\textsuperscript{7,13,40}(C)
- Hypoglycaemia in children is largely preventable; however there is a significant proportion of severe hypoglycaemic episodes in which no obvious cause can be determined.\textsuperscript{13,40}(C)
- School teachers and carers at schools should be informed of the symptoms and appropriate treatment of hypoglycaemia and should have access to advice when necessary.\textsuperscript{7,13,40}(C)
- In the hospital setting severe hypoglycaemia should be treated with intravenous dextrose as this is the most rapid way of treating severe hypoglycaemia.\textsuperscript{88,89}(II)
- The recommended dose of intravenous dextrose is 2-5ml/kg of 10% dextrose. 50% dextrose should not be used because of dangers of tissue necrosis associated with extravasation.\textsuperscript{C}
- Intramuscular or subcutaneous glucagon is an effective way of treating severe hypoglycaemia in a home-care setting or if intravenous dextrose is not possible.\textsuperscript{88,89}(II)
13. Psychosocial Aspects

- Type 1 diabetes in childhood imposes a number of psychological stresses on both the child and the family.\(^7,13,29,40\) (C)
- Non-adherence to the diabetes regimen is common in children and adolescents with type 1 diabetes.\(^72,99-111\) (IV)
- Non-adherence with treatment regimens is common especially during teenage years.\(^72,104-106\) when an underlying psychiatric disorder is present,\(^99,102,109\) when the parents or child have a low level of education,\(^101,111\) when self-care autonomy is promoted or impeded at an inappropriate time,\(^112\) and when there is low level of cohesion within the family.\(^111\) (IV)
- Health care professionals should be aware that adolescents may omit or reduce insulin doses in order to produce glycosuria as a method of weight control.\(^113-115\) (IV)
- Psychological interventions have been shown to improve HbA\(_{1c}\) and psychosocial outcomes.\(^25,116-118\) (I)

14. Diabetes Complications

- Type 1 diabetes confers the risk of long-term diabetes microvascular complications.\(^38,45,48,119\) (II)
- Families with a child or adolescent with diabetes should be made aware of the potential long-term complications of diabetes as part of their diabetes education. Adolescents should be made aware at a rate appropriate to their maturity.\(^7,13\) (C)
- Families with a child or adolescent with diabetes should be made aware that long-term good metabolic control reduces the risk of development and progress of complications.\(^38,45\) (II)
- Families with a child or adolescent with diabetes should be made aware that other modifiable risk factors for diabetic microvascular complications include higher blood pressure, smoking and dyslipidaemia.\(^38,45\) (II)
- Screening for retinopathy should be performed annually in adolescents after 2 years of diabetes and after 5 years of diabetes in those who are prepubertal.\(^7,13\) (C)
- Assessment for retinopathy should be by an observer with special expertise in diabetic eye disease. If stereoscopic fundal photography is used then biennial assessment may be appropriate for those with minimal background retinopathy, diabetes duration of less than 10 years and if the HbA\(_{1c}\) is not significantly elevated. If moderately severe retinopathy is present then more frequent review is necessary.\(^13,120\) (C)
- Clinical examination of the eyes for cataracts should be performed soon after diagnosis, especially if there has been slow or prolonged onset of diabetes.\(^7,13\) (C)
- Screening for microalbuminuria should be performed annually in adolescents after 2 years of diabetes and after 5 years of diabetes in those who are prepubertal. Assessment should be either by timed overnight urine collections or a spot urinary albumin/creatinine ratio. If microalbuminuria is found then screening should be more frequent, and other renal investigations undertaken and specific focus should be placed on blood pressure measurements.\(^7,13\) (C)
- In the presence of poor diabetes control, clinical evaluation of peripheral nerve function should occur annually and should as a minimum include:\(^13\) (C)
  - History (especially of numbness, pain, paraesthesia).
  - Assessment of vibration sensation (by tuning fork or biothesiometer).
  - Assessment of ankle reflexes.
  - Assessment of sensation.
- Type 1 diabetes frequently results in accelerated atherosclerosis. Good glycaemic control can decrease this risk.\(^48,119\) (II)
• Blood pressure measurements should be recorded at diagnosis and, if normal, annually. Hypertension should be considered to be present if repeated blood pressure levels are >95th centile for age, gender and height specific normative data.13(C)
• Screening for lipid disorders should begin within 6-12 months of diagnosis of diabetes, and if normal should be performed every 5 years in prepubertal children and every second year in pubertal children.22;121(C)

15. Other Complications and Associated Conditions
• Monitoring of growth and development and the use of growth charts is a very important part of ongoing care of children and adolescents with type 1 diabetes.7;13(C)
• Screening of thyroid function by Thyroid Stimulating Hormone (TSH) every 2 years is recommended in asymptomatic individuals without a goitre or in the absence of thyroid autoantibodies. More frequent assessment is indicated otherwise.7(C)
• Screening for coeliac disease should be carried out around the time of diagnosis and every 2-3 years thereafter. More frequent assessment is indicated if the clinical situation suggests the possibility of coeliac disease.7;13;29(C)
• Although the benefits of a gluten-free diet have not been proven in those with type 1 diabetes detected to have coeliac disease on routine screening,122;123 these children should be referred to a paediatric gastroenterologist and on confirmation of the diagnosis receive support from a paediatric dietitian with experience in gluten-free diets.13;40(C)

16. Foot Care
• Health care professionals should be aware that the structural and functional abnormalities known to predispose adults with diabetes to plantar ulceration are already present in young people with diabetes.124-126(IV)
• Young people presenting with plantar callus, or detected to have high plantar pressures or limited joint mobility need to be monitored closely for foot complications.13(C)
• Orthosis, cushioning or both in combination may be used to treat high peak plantar pressure.127(IV)

17. Dental Health
• Children and adolescents with type 1 diabetes should be informed that dental decay is increased when glycaemic control is poor.128(IV)
• Health care professionals should be aware that diabetes is a risk factor for periodontal disease especially when metabolic control is poor or when diabetes duration is long.129-132(IV)
• Children and adolescents with type 1 diabetes should be informed that tooth decay and gingivitis can be prevented and/or reversed by brushing and flossing teeth at least twice a day to remove plaque from the surfaces of the teeth and gingivae.13(C)
• The mouth should be examined regularly (twice a year) for the presence of gingivitis or periodontitis.13(C)

18. Adolescent Health Issues
• Health care professionals should be aware that glycaemic control is more difficult in adolescents with type 1 diabetes.38;45(II)
• Adolescents with diabetes have specific health needs relating to physical, emotional, psychological and socio-cultural stages of adolescence.7;133(C)
• The major risks faced by adolescents with diabetes include deterioration of glycaemic control, risk-taking behaviour, hypoglycaemia, recurrent diabetic ketoacidosis and accelerated microvascular complications.  
  
• The transition from a paediatric to an adult service for the adolescent with diabetes is often difficult.

• Ideally the transfer to an adult service should be comprehensive and should involve:
  
  ➤ A preparation phase which is planned well in advance by a special transition service and the adolescent and family.
  
  ➤ A formal transition phase to an adult clinic, with appropriate referral and clear directions for the patient and family (eg in case of emergencies).
  
  ➤ An evaluation phase.

• Adolescents should be taught to do a blood glucose estimation immediately before driving a car and to have rapidly absorbed carbohydrate (eg glucose tablets) readily accessible and to take these at the first indication of hypoglycaemia.

• Smoking should be actively discouraged in diabetes.

• Adolescents with diabetes need to be warned about the dangers of alcohol as part of their diabetes education.

• Issues surrounding sexuality should be approached with confidentiality and empathy.

• Assessment of sexual activity and the need for contraception should be a routine part of adolescent diabetes care.

• Health care professionals should be aware that the incidence of eating disorders is increased in males and females with type 1 diabetes and that adolescent females with type 1 diabetes and anorexia nervosa have a significantly increased mortality rate compared to patients with type 1 diabetes alone.

• Health care professionals should be aware that intentional reduction or omission of insulin to achieve weight loss is common (so-called insulin purging).

• Health care professionals should be aware that increased levels of retinopathy have been found in patients with type 1 diabetes and sub-clinical and clinical eating disorders.

• Treatment of eating disorders should include medical, nutritional and psychological therapy by an experienced multidisciplinary team.

19. School

• Parents/care-givers and teachers should be aware that discrimination or stigmatisation is unacceptable.

• Parents/care-givers and teachers should be aware that diabetes should not be the cause of non-participation in any school activity.

• Parents/care-givers should meet with the relevant school personnel as soon as practicable to discuss the issues involved in the care of their child at school.

• An individual care plan should be developed and reviewed regularly.

• Parents/care-givers and teachers should be aware how to recognise and treat hypoglycaemia.

• An emergency supply of rapidly absorbed carbohydrate should be readily available in the classroom or wherever the school activity is undertaken.

• During or following hypoglycaemia or suspected hypoglycaemia, a child must not be expected to walk to a ‘medical room’ nor left unaccompanied.

• Parents/care-givers and teachers should be aware that cognitive function and mood may be affected for some hours after hypoglycaemia.
• Parents/care-givers and teachers should be aware that decreased cognitive function may occur when hyperglycaemia is present.154(II)
• Parents/care-givers and teachers should be aware that risk factors for cognitive dysfunction include a history of hypoglycaemic seizures,92;96;97 early age of onset and longer duration of diabetes.94;95;96;98;155;156(IV)
• Parents/care-givers, teachers and students should be aware that students with diabetes sitting for the higher examinations may apply for special provisions.13(C)

20. Diabetes Camps for Children and Adolescents
• Diabetes camps should be an integral component of overall care and support for diabetic children and adolescents in Australia.13;40(C)
• Diabetes camps must provide a safe environment for both campers and camp staff.7(C)
• Camps should be organised using an agreed set of standards and protocols. Standards and protocols should specify leader to camper ratios, levels of medical and paramedical support, dietary routines, injection routines, hierarchy and responsibility of camp organisers, leader and camper application processes, emergency and evacuation protocols and indemnity arrangements.157(C)
• A standardised medical information form should be completed for each camper (by his/her family and the managing physician) prior to attending diabetes camp.157(C)

21. Travelling and Holidays
• The detailed management of diabetes during visits to distant locations or foreign countries should be discussed with the diabetes educator or the physician well before the departure date.13;40(C)
• The detailed management of diabetes on long flights crossing many time zones should be discussed with the diabetes educator or the physician well before the departure date.13;40(C)
• The family should be advised to arrange enough insulin, syringes, pen needles, glucometer, blood and urine test strips for the duration of the anticipated stay plus an extra supply.13;40(C)
• The family should be advised to have insulin, glucagon and testing equipment readily available in hand luggage, and to have essential supplies divided between two bags to avoid complete loss in case one bag is lost.13;40(C)
• The child or adolescent with diabetes should be advised to have his/her own food supply and not rely on airline meal times.13;40(C)
• The family should be advised that no major change to the insulin regimen is required for north-south travel.40(C)
• The family should be advised that extra insulin may be required for westward travel as the day will be much longer and extra meals will require extra doses of insulin.158(IV)
• The family should be advised that less insulin may be required during eastward travel as the day is cut short and the time between injections decreases therefore requiring a lower insulin dose.158(IV)
• Switching to a simplified regimen of pre-meal injections of short-acting insulin during long haul flights should be considered as an option.159(IV)

22. Complementary and Alternative Medicine
• Complementary and alternative medicine may include medicinal (herbal remedies, dietary supplements, vitamins and minerals, naturopathic and homeopathic remedies), or non-medicinal remedies (such as chiropractic, osteopathy and naturopathy).160(C)
• Complementary and alternative medicine use is common within the community. 160,161 (IV)

• In order to improve clinical care health care professionals should aim to understand the use of complementary and alternative medicine within the family context. 162,163 (C)

• Families should be advised that no complementary and alternative medicine therapies have been shown to cure diabetes or improve control. 162 (C)

• Ketoacidosis and death have been described when insulin has been omitted as part of an alternative treatment. 164 Parents should be warned that insulin should never be significantly reduced or omitted as part of an alternative treatment. (IV)

• Families should be advised that complementary and alternative medicine therapies have the potential for adverse effects and for interactions with conventional treatments or other complementary and alternative medicine therapies. 162 (C)

• Health care professionals are able to determine the constituents of any complementary or alternative medicine by enquiries to poisons centres and quoting the medicine’s AUST L or AUST R numbers. 165 Drugs without an AUST L or AUST R number should not be considered for use in hospital. 163 (C)

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24. Queensland Health: Best practice guidelines for the management of Type 1 Diabetes in children and Adolescents. 2002


29. National Institute for Clinical Excellence. Type 1 Diabetes (Childhood): Diagnosis and Management of Type 1 Diabetes in Children and Young people. 2004
46. DCCT Research Group: The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. *Diabetes 44:968-983, 1995
55. DAFNE Study Group: Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomised controlled trial. *British Medical Journal* 325:746, 2002


Executive Summary of Recommendations and Principles

Australian Clinical Practice Guidelines: Type 1 Diabetes in Children and Adolescents
Chapter 1: Definition, Epidemiology and Classification

Diabetes mellitus is the most common endocrine disease in childhood and adolescence. This handbook will predominantly deal with the topic of type 1 diabetes, previously known as insulin-dependent diabetes mellitus (IDDM). Fifty percent of individuals with type 1 diabetes are diagnosed before the age of 16 years.

Definition

The World Health Organization (WHO) defines diabetes mellitus as a metabolic disorder of multiple aetiologies characterised by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. Type 1 diabetes is a chronic autoimmune disease in the vast majority and accounts for over 90 percent of childhood and adolescent diabetes in Australia. T-cell mediated destruction of the pancreatic beta cells leads to insulin deficiency. Susceptibility to autoimmune type 1 diabetes is determined by the interaction of multiple genes, with HLA genes having the strongest known association. Progressive beta cell destruction occurs at a variable rate and the disease becomes clinically symptomatic when approximately 90 percent of the pancreatic beta cells are destroyed. Insulin deficiency then manifests itself clinically as blood glucose levels rise to pathological levels. The onset of the disease is predictable, especially in the relatives of affected individuals, using a combination of auto-antibody measurements, intravenous glucose tolerance testing and genetic typing.

The environmental triggers (chemical and/or viral) which start the process of autoimmune destruction of the pancreatic beta cells remain largely unknown. The pathological processes leading to type 1 diabetes are known to start from months to years before clinical symptoms become manifest (see chapter 2).

Non-autoimmune type 1 diabetes has similar clinical features but is characterised by the lack of auto-antibodies against the antigens in the islets of Langerhans (islet cell antibodies-ICA), or beta cell antigens (anti-insulin, anti-GAD65 or anti-IA2 antibodies).

Epidemiology

Epidemiological incidence studies define the ‘onset of type 1 diabetes’ by the date of the first insulin injection because of the variable time between the onset of symptoms and diagnosis.

Figure 1 (data from the IDF Diabetes Atlas) shows annual incidence rates for childhood type 1 diabetes (0-14 years age group) comparing different countries of the world.
Figure 1.1: Annual Incidence Rates for Type 1 Diabetes (0-14 years age group)
Comparing Different Countries in the World

Source: International Diabetes Federation Diabetes Atlas 2003
• Incidence is expressed as the number of new cases per year per 100,000 children under the age of 15 years.
• There are significant variations in the incidence of childhood type 1 diabetes between countries - ranging from 0.1/100,000 in Fiji to 37.4/100,000 in Finland.5,6
• In Europe incidence rates show a close correlation with the frequency of HLA susceptibility genes in the general population.7
• The most recent data on the incidence of childhood diabetes in Australia indicate an incidence of 17.8 per 100,000 from 1990-1996, with an annual increase in incidence of 3.2% per year since 1990.8
• There are two peaks of age of onset, the major peak at 10-12 years and a smaller peak at 5-6 years.9,10
• A well documented rise in the incidence, especially in the group of those under the age of 5 years, has been noted in many countries.11-13
• A seasonal variation in the presentation of new cases is well described, with the peak being in the winter months.14,15,16
• Despite familial aggregation there is no recognisable pattern of inheritance.
  → The risk of diabetes to an identical twin of a patient with type 1 diabetes is about 36 percent,17 compared to a life-time risk of 6 percent for a sibling or offspring (up to 30 years of age) and 0.5 percent for the general population.18
  → Type 1 diabetes is transmitted less frequently to the offspring of diabetic women than to those of diabetic men (1.3% compared with 6.1% of offspring).19

Classification

In 1979, the US National Diabetes Data Group (NDDG), and in 1980, the WHO produced diagnostic criteria and a classification system for diabetes mellitus. This brought order to a chaotic situation in which nomenclature varied and diagnostic criteria showed enormous variations using different oral glucose loads. In 1985 WHO slightly modified their criteria to coincide more closely with the NDDG values.

In 1997, the American Diabetes Association (ADA) published its recommendations on new diagnostic criteria for diabetes. WHO convened a Consultation on the same subject in December 1996 and published these in 1998 (table 1.1). In general, the ADA and WHO groups reached similar conclusions.1,20

The terms Insulin Dependent Diabetes Mellitus (IDDM) and Non Insulin Dependent Diabetes Mellitus (NIDDM) are no longer used as all forms of diabetes may require insulin therapy at some stage.1

The new classification encompasses both clinical stages and aetiological types of diabetes mellitus and other categories of hyperglycaemia.

Clinical Staging of Diabetes

The clinical staging of diabetes, regardless of its aetiology, reflects the new concepts that diabetes progresses through several clinical stages during its natural history:21
• Normoglycaemia.
• Impaired glucose regulation (impaired fasting glycaemia or impaired glucose tolerance).
• Diabetes mellitus.

Moreover, individual subjects may move from stage to stage in either direction. Persons who have, or who are developing, diabetes mellitus can be categorised by the stage according to
clinical characteristics, even in the absence of information concerning the underlying aetiology.

**Aetiologic Classification of Diabetes**

The classification by aetiological type results from improved understanding of the causes of diabetes mellitus.1

Type 1 diabetes encompasses the cases which are primarily due to pancreatic islet beta-cell destruction and are prone to ketoacidosis. Type 1 includes those cases attributable to an autoimmune process, as well as those for which neither an aetiology nor a pathogenesis is known (ie idiopathic). It does not include those forms of beta-cell destruction or failure to which specific causes can be assigned (eg cystic fibrosis, mitochondrial defects, etc.).

Type 2 diabetes includes the common major form of adult diabetes which results from defect(s) in insulin secretion, almost always with a major contribution from insulin resistance. The lean phenotype of type 2 diabetes mellitus in adults found in Japan and the Indian sub-continent may be very distinct from the more characteristic form of type 2 found in white Caucasians which is associated with increased visceral fat. Not enough information is available, however, to characterise such subjects separately.

Malnutrition-related diabetes (MRDM) has been deleted in the new classification.

Impaired Glucose Tolerance is now classified as a clinical stage of impaired glucose regulation, since it can be observed in any hyperglycaemic disorder, and is itself not diabetes.

A clinical stage of Impaired Fasting Glycaemia has been introduced to classify individuals who have fasting glucose values above the normal range, but below the level diagnostic of diabetes.

Gestational Diabetes now encompasses the groups formerly classified as Gestational Impaired Glucose Tolerance (GIGT) and Gestational Diabetes Mellitus (GDM).

**Table 1.1: Aetiological Classification of Disorders of Glycaemia**

<table>
<thead>
<tr>
<th>Type 1</th>
<th>(beta-cell destruction, usually leading to absolute insulin deficiency)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Autoimmune</td>
</tr>
<tr>
<td></td>
<td>• Idiopathic</td>
</tr>
</tbody>
</table>

| Type 2 | (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with or without insulin resistance) |

| Other specific types (see Table 1.2) |

| Gestational diabetes |

1 Australian Clinical Practice Guidelines: Type 1 Diabetes in Children and Adolescents
Table 1.2: Other Specific Types of Diabetes

<table>
<thead>
<tr>
<th>Genetic defects of beta-cell function</th>
</tr>
</thead>
<tbody>
<tr>
<td>• MODY 1-6</td>
</tr>
<tr>
<td>• Mitochondrial DNA mutation</td>
</tr>
<tr>
<td>• Others</td>
</tr>
<tr>
<td>Genetic defects in insulin action</td>
</tr>
<tr>
<td>• Type A insulin resistance</td>
</tr>
<tr>
<td>• Leprechaunism</td>
</tr>
<tr>
<td>• Rabson-Mendenhall syndrome</td>
</tr>
<tr>
<td>• Lipoatrophic diabetes</td>
</tr>
<tr>
<td>• Others</td>
</tr>
<tr>
<td>Diseases of the exocrine pancreas</td>
</tr>
<tr>
<td>• Fibrocalculous pancreatopathy</td>
</tr>
<tr>
<td>• Pancreatitis</td>
</tr>
<tr>
<td>• Trauma / pancreatetomy</td>
</tr>
<tr>
<td>• Agenesis</td>
</tr>
<tr>
<td>• Cystic fibrosis</td>
</tr>
<tr>
<td>• Haemochromatosis/thalassaemia</td>
</tr>
<tr>
<td>• Others</td>
</tr>
<tr>
<td>Endocrinopathies</td>
</tr>
<tr>
<td>• Cushing syndrome</td>
</tr>
<tr>
<td>• Acromegaly</td>
</tr>
<tr>
<td>• Phaeochromocytoma</td>
</tr>
<tr>
<td>• Glucagonoma</td>
</tr>
<tr>
<td>• Hyperthyroidism</td>
</tr>
<tr>
<td>• Somatostatinoma</td>
</tr>
<tr>
<td>• Others</td>
</tr>
<tr>
<td>Drug- or chemical-induced</td>
</tr>
<tr>
<td>• Insulin deficiency (Alloxan, Streptozotocin, Vacor, L-Asparaginase, Tacrolimus, Cyclosporin, Diazoxide, others)</td>
</tr>
<tr>
<td>• Insulin resistance (Glucocorticoids, Growth Hormone, Interferon-alpha, others)</td>
</tr>
<tr>
<td>Infections</td>
</tr>
<tr>
<td>• Congenital rubella</td>
</tr>
<tr>
<td>• Cytomegalovirus</td>
</tr>
<tr>
<td>• Others</td>
</tr>
<tr>
<td>Uncommon forms of immune-mediated diabetes</td>
</tr>
<tr>
<td>• Insulin autoimmune syndrome (antibodies to insulin)</td>
</tr>
<tr>
<td>• Anti-insulin receptor antibodies</td>
</tr>
<tr>
<td>• ‘Stiff Man’ syndrome</td>
</tr>
<tr>
<td>• Polycendocrine autoimmune deficiencies APS I and II</td>
</tr>
<tr>
<td>• Others</td>
</tr>
<tr>
<td>Other genetic syndromes</td>
</tr>
<tr>
<td>• Wolfram, Down, Klinefelter, Turner, Myotonic dystrophy, Friedreich ataxia, Prader Willi, Laurence-Moon-Biedl, Porphyria</td>
</tr>
</tbody>
</table>
Diagnostic Criteria for Diabetes in Childhood and Adolescence

Diagnostic criteria for diabetes are based on:  
- Blood glucose measurements.
  and
- The presence or absence of symptoms.

According to these criteria a diagnosis of diabetes can be made if:
- The characteristic symptoms and signs are present.
  and
- Fasting venous plasma glucose concentration is greater than or equal to 7.0 mmol/L, and/or the random venous plasma glucose concentration taken at least 2 hours after eating is greater than or equal to 11.1 mmol/L.

Diabetes in childhood usually presents with severe symptoms, very high blood glucose levels, marked glycosuria, ketonuria and frequently with ketoacidosis. The diagnosis is usually confirmed quickly by measurement of a marked elevation of the blood glucose level. In this situation treatment is urgent. Waiting another day to confirm the hyperglycaemia is neither necessary nor appropriate for diagnosis in such circumstances. (See chapter 2)

In the absence of symptoms of diabetes both of the aforementioned plasma glucose criteria need to be met and repeated on another day for a diagnosis of diabetes to be made.

In presence of mild symptoms, the diagnosis of diabetes should never be made on the basis of a single abnormal blood glucose value. Diagnosis may require continued observation with a fasting blood glucose measurement, 2 hour post-prandial blood glucose levels and/or an oral glucose tolerance test (OGTT). An OGTT should not be performed if diabetes can be diagnosed using fasting, random or post-prandial criteria as excessive hyperglycaemia can result.

If doubt remains, periodic re-testing should be undertaken until the diagnosis is established.

Table 1.3: WHO Criteria Values for Diagnosis of Diabetes Mellitus and Other Categories of Hyperglycaemia

<table>
<thead>
<tr>
<th></th>
<th>Glucose concentration, mmol/L</th>
<th></th>
<th></th>
<th>Venous plasma*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetes Mellitus:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>≥6.1</td>
<td>≥6.1</td>
<td>≥7.0</td>
<td></td>
</tr>
<tr>
<td>Or 2-h post glucose load</td>
<td>≥10.0</td>
<td>≥11.1</td>
<td>≥11.1</td>
<td></td>
</tr>
<tr>
<td>or both</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Impaired Glucose Tolerance (IGT):</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting (if measured)</td>
<td>&lt;6.1</td>
<td>&lt;6.1</td>
<td>&lt;7.0</td>
<td></td>
</tr>
<tr>
<td>And 2-h post glucose load</td>
<td>≥6.7 and &lt;10.0</td>
<td>≥7.8 and &lt;11.1</td>
<td>≥7.8 and &lt;11.1</td>
<td></td>
</tr>
<tr>
<td><strong>Impaired Fasting Glycaemia (IFG):</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting (if measured)</td>
<td>≥5.6 and &lt;6.1</td>
<td>≥5.6 and &lt;6.1</td>
<td>≥6.1 and &lt;7.0</td>
<td></td>
</tr>
<tr>
<td>And 2-h post glucose load</td>
<td>≤6.7</td>
<td>&lt;7.8</td>
<td>&lt;7.8</td>
<td></td>
</tr>
</tbody>
</table>

* Corresponding values (mmol/L) for capillary plasma are: for Diabetes Mellitus, fasting ≥7.0, 2-h ≥12.2; for Impaired Glucose Tolerance, fasting <7.0 and 2-h ≥8.9 and <12.2; and for Impaired Fasting Glycaemia ≥6.1 and <7.0 and if measured, 2-h <8.9.
Oral Glucose Tolerance Test (OGTT)

An oral glucose tolerance test (OGTT) is rarely indicated in making the diagnosis of type 1 diabetes in childhood and adolescence. If doubt exists, it is easier to monitor the child or adolescent regularly with urine testing for glycosuria and to perform a fasting plasma glucose or post-prandial blood tests to detect hyperglycaemia.\(^1\)

The OGTT is used more frequently in the evaluation of possible glucose intolerance in a child or adolescent suspected of having the metabolic syndrome or type 2 diabetes. Typical clinical scenarios include an obese adolescent with acanthosis nigricans, a girl with the polycystic ovary syndrome, an obese child with a family history of type 2 diabetes or an obese child from a high risk ethnic background for type 2 diabetes.

The dose of glucose used in the OGTT is 1.75 gm/kg of body weight to a maximum of 75 gm.\(^1\) The glucose load or partial hydrolysate of starch of equivalent carbohydrate content is administered in 250-300 ml water over a 5 minute period.

The OGTT should be performed strictly under the following conditions:
- The child or adolescent should not be suffering from any obvious intercurrent illness or be on any medication known to affect blood glucose levels.
- Venous plasma glucose levels are preferred instead of whole blood or capillary glucose levels for which different criteria are used (see table 1.3).
- Glucose estimations should be performed in NATA accredited laboratory using laboratory instrumentation rather than glucose meters for bedside or home use.
- Blood specimens should be collected using sodium oxalate, sodium/potassium EDTA or heparin as anticoagulants and centrifuged immediately or kept on ice if there is delay. This is necessary as the presence of cells reduces the glucose levels by 5 percent per hour at room temperature. Alternatively the specimen can be collected into sodium fluoride or sodium iodoacetate tubes, which inhibit glycolysis and prevent the metabolism of glucose by cells.
- The test should be done in the morning after fasting overnight.
- The diet in the preceding 3 days should be high in carbohydrate.

Interpretation of OGTT

The major change recommended by the WHO and the American Diabetes Association in the revised diagnostic criteria for diabetes mellitus is the lowering of the diagnostic value of the fasting venous plasma glucose concentration to $\geq 7.0\, \text{mmol/L}$, from the former level of $\geq 7.8\, \text{mmol/L}$.\(^1;20\) It is important to note that different criteria apply for capillary whole blood, venous whole blood and venous plasma. For whole blood, the proposed new level is $\geq 6.1\, \text{mmol/L}$, from the former 6.7 mmol/L. It is recommended that venous plasma levels be used for consistency.

Despite the fact that children tend to have lower blood glucose levels than adults, the OGTT criteria used for a diagnosis of diabetes mellitus in children and adolescents are the same as for adults ie
- Elevated fasting venous plasma glucose ($\geq 7.0\, \text{mmol/L}$).
  
  and/or
- Elevated venous plasma glucose at 2 hours ($\geq 11.1\, \text{mmol/L}$).

IFG and IGT both indicate glucose intolerance but are not equivalent in that they measure different parameters. IFG is a measure of disturbed carbohydrate metabolism in the basal
state whilst the IGT is a dynamic measure of carbohydrate intolerance after a standardised glucose load.

Children and adolescents with a fasting venous plasma glucose ≥6.1 mmol/L and <7.0 mmol/L have impaired fasting glycaemia.

Children and adolescents with a fasting venous plasma glucose <7.0 mmol/L AND 2 hour OGTT values between ≥7.8 and <11.1 mmol/L are classified as having impaired glucose tolerance (IGT).

The American Diabetes Association has classified both IFG and IGT as being pre-diabetes as both categories indicate a high risk of progressing to type 2 diabetes over the next 5-10 years. For IGT, the risk for progression to diabetes for adults, remaining IGT or reverting to normal are all approximately 33% over 5-10 years.\(^{22}\)

In borderline diagnostic situations the presence of autoimmune markers such as antibodies against islet cell antigens (ICA), IA-2 and GAD are of assistance in confirming type 1 diabetes. In type 1 diabetes, insulin and C-Peptide levels taken during the OGTT are low for the accompanying blood glucose levels, whereas in type 2 diabetes they are usually elevated.

**Intravenous Glucose Tolerance Test (IVGTT)**

The IVGTT is a research tool. Interpretation of the test can be difficult.

The main use of IVGTT is to measure the early insulin response following an intravenous glucose load.

In type 1 diabetes intervention studies, the IVGTT responses help to determine insulin reserve in pre-diabetic individuals with elevated islet antibodies and other autoimmune markers.

In studies of the metabolic syndrome (including IFG and IGT), the IVGTT is used to obtain measures of insulin sensitivity, glucose disposal and beta cell function (minimal model).\(^{23}\)

**Metabolic Syndrome**

Although there is no international consensus on the definition of the Metabolic Syndrome, the WHO has suggested the following working definition for adults. The Metabolic Syndrome consists of glucose intolerance (impaired glucose tolerance or diabetes mellitus) and/or insulin resistance with two or more of the following:\(^ {1}\)

- Raised arterial blood pressure ≥140/90 mmHg.
- Raised plasma triglycerides and/or low HDL cholesterol.
- Central obesity (males: waist to hip ratio >0.90; females: waist to hip ratio >0.85) and/or BMI >30 kg/m\(^2\).
- Microalbuminuria (urinary albumin excretion rate ≥20 µg/min or albumin:creatinine ratio ≥30 mg/g or >2.5 mg/mmol.

Other components not necessary for the recognition of the condition include hyperuricaemia and coagulation disorders.

Persons with hypertension, central obesity, and dyslipidaemia, with or without hyperglycaemia, are at high risk of macrovascular disease. Management should include controlling blood glucose, and reducing the other cardiovascular risk factors (dyslipidaemia, hypertension, smoking, obesity and hypercoagulability).
Type 2 Diabetes

Type 2 diabetes is rapidly increasing in children and adolescents, accounting for approximately 5 percent of diabetes in this age group in Australia. The aetiology is unknown. There may be predominantly insulin resistance with relative insulin deficiency or a predominantly secretory defect (non-autoimmune mediated) with or without insulin resistance.

The possibility of type 2 diabetes should be considered in children and adolescents who:
- Are obese.
- Have a strong family history of type 2 diabetes.
- Come from an ethnic background at high risk for diabetes.
- Produce little or no ketonuria.
- Show evidence of insulin resistance (acanthosis nigricans or polycystic ovary syndrome).

The rising incidence of type 2 diabetes is associated with the epidemic of obesity. Aborigines and Torres Strait Islanders are at high risk. Lifestyle factors such as little exercise and overeating leading to obesity have profound effects. Whilst many indigenous ethnic groups are liable to type 2 diabetes (eg Pima Indians in Arizona, Cree-Ojibee Indians in Canada, Pacific islanders, Australian Aborigines, Torres Strait islanders), the increased risk is now being seen in many populations (eg Indians and Indian communities originating from the Indian subcontinent, Chinese, Africans, Afro-Americans, Arabs and Hispanic-American). A positive family history for type 2 diabetes is present in over 80%. Identical twins have a concordance rate for type 2 diabetes approaching 100 percent.

Type 2 diabetes is often asymptomatic but may present with ketosis and even mild to moderate ketoacidosis. It may be the underlying cause of hyperglycaemia associated with infections and severe illness in some patients (see Stress Hyperglycaemia).

Treatment is difficult because of the chronicity and the need to incorporate lifestyle changes. The long term microvascular complications of diabetes occur as frequently, as quickly, and as severely as in type 1 diabetes. Because type 2 diabetes may have a prolonged asymptomatic phase screening for complications should start at diagnosis or soon after. The risks for macrovascular complications are also increased and reflect the underlying Metabolic Syndrome in type 2 diabetes.

The principles of treatment for type 2 diabetes are:
- Weight reduction if the patient is obese.
- Exercise and a healthy lifestyle.
- Carbohydrate- and fat-controlled diet.
- Metformin.
- Occasionally insulin replacement.
- Occasionally sulphonylurea or other oral hypoglycaemics.
- Occasionally insulin sensitisers (eg thiazolidinediones).
- Occasionally combination therapy of above medications.
- Control of associated macrovascular risk factors (hypertension, dyslipidemia, avoiding smoking).
Screening for Type 2 Diabetes

Population screening for type 2 diabetes in children and adolescents cannot be justified in Australia because of the low prevalence (in Japan, however, annual school glycosuria screening programmes are in place). Targeted screening (fasting plasma glucose or 2 hour post-prandial glucose) is recommended at the point of medical contact if high risk factors are present (obesity, strong family history of type 2 diabetes, high risk ethnic group, acanthosis nigricans, polycystic ovary syndrome). The Consensus Panel of the American Diabetes Association recommends that testing of high risk subjects should be done every 2 years starting at age 10 years or at onset of puberty, whichever is earlier.

The World Health Organization states that opportunistic screening, as described above, may be justified provided the individual being tested is appropriately informed and counselled, and the health care system has the capacity to manage positive cases.

Other Types of Diabetes

The possibility of other types of diabetes should be considered in children and adolescents who:

- Have an autosomal dominant family history of diabetes.
- Have associated conditions such as deafness, optic atrophy or syndromic features.
- Have marked insulin resistance or require little or no insulin outside the partial remission phase.
- Have been exposed to drugs known to be toxic to beta cells or cause insulin resistance.

Maturity Onset Diabetes of the Young (MODY)

Maturity onset diabetes of the young (MODY) is a disorder with the following characteristics:

- Onset before 25 years of age.
- Nonketotic diabetes mellitus.
- Autosomal dominant inheritance.
- Primary defect in the function of the pancreatic beta cells.

MODY is genetically heterogeneous and includes at least 6 forms, all dominantly inherited. There is great variation in the degree of hyperglycaemia, need for insulin and risk for future complications. Apart from MODY 2, all other forms of MODY are due to transcription factor gene mutations. It is likely that other genetic causes for the MODY phenotype will be defined in the future. Gene diagnosis is now possible but expensive to obtain.

- MODY 1 - mutations of Hepatic Nuclear Factor-4α (HNF-4α) gene on chromosome 20.
- MODY 2 - mutations of the glucokinase gene (GCK) on the short arm of chromosome 7. Glucokinase is a beta cell enzyme which appears to function as the glucose sensor of the beta cell. Patients with MODY 2 tend to present late, have mild hyperglycaemia, a low risk for diabetes complications and may not require treatment (unless they are homozygous for the condition).
- MODY 3 - mutations of HNF-1α gene on chromosome 12. These patients have a severe defect in insulin secretion and major hyperglycaemia.
• MODY 4 - mutations of IPF-1 (Insulin Promoter Factor-1) gene on chromosome 7. Homozygous patients have pancreatic aplasia.33;34
• MODY 5 - mutations of HNF-1β gene on chromosome 17.33;34
• MODY 6 - mutations of Neurogenic Differentiation Factor-1 (beta 2- NeuroD1) gene.33;34
• MODY X - others.33;34

Adults with MODY are liable to the same microvascular and macrovascular complications of diabetes as patients with type 2 diabetes. Complications are rare in MODY 2.33;34

The principles of treatment in MODY are the same as for type 2 diabetes:
• Weight reduction if the patient is obese.
• Exercise and a healthy lifestyle.
• Carbohydrate- and fat-controlled diet.
• Sulphonylurea drugs or metformin (MODY 3 may be very sensitive to small doses of sulphonylureas.34
• Insulin replacement.

DIDMOAD Syndrome (Wolfram Syndrome)

DIDMOAD syndrome (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, Deafness) is a rare autosomal recessive condition associated with non-autoimmune degeneration of the pancreatic beta cells.35 The Wolfram gene (WSF-1) has been cloned and is on chromosome 4. Diabetes is usually the first manifestation and all cases reported also have optic atrophy. Other manifestations are more variable and include:
• Diabetes mellitus (median age 8.2 years).
• Optic atrophy (median age 13.1 years).
• Diabetes insipidus (median age 14.1 years).
• Sensorineural deafness (median age 15.0 years).
• Neurological degeneration (with CNS atrophy on MRI).
• Psychiatric disturbances.
• Death (median age 28 years).

Mitochondrial Diabetes

Maternal transmission of mutated mitochondrial DNA (mtDNA) can result in maternally inherited diabetes. Although several mutations have been implicated, the strongest evidence relates to a point substitution at nucleotide position 3243 (A to G) in the mitochondrial tRNA (leu(UUR)) gene. Mitochondrial diabetes is commonly associated with sensorineural deafness and often presents with progressive non-autoimmune beta-cell failure.36

Neonatal Diabetes

Insulin-requiring hyperglycaemia in the first month of life is known as neonatal onset diabetes mellitus. This rare condition (1/400,000 births) may be associated with intrauterine growth retardation.37 Approximately half of the cases are temporary and have been associated with paternal isodisomy of chromosome 6.38;39 The permanent cases are associated with pancreatic aplasia, mutations of Insulin Promoter Factor-1 (chromosome 7), complete glucokinase deficiency (chromosome 7)40 and mutations of the FOXP3 gene (T cell regulatory gene) as part of the IPEX syndrome.41
Cystic Fibrosis and Diabetes

Diabetes in Cystic Fibrosis is primarily due to insulin deficiency. However, insulin resistance secondary to infections and medications (bronchodilators and glucocorticoids) may contribute significantly during acute illness. Diabetes tends to occur late in the disease, typically in adolescence and early adulthood. Concurrent cirrhosis, if present, may contribute to insulin resistance. The onset of diabetes is a poor prognostic sign. Poorly controlled diabetes will interfere with immune responses to infection and promote catabolism.

Screening recommendations vary from testing a random blood glucose level annually in all children with cystic fibrosis ≥14 years old, to performing an oral glucose tolerance test annually in all those >10 years old. Insulin therapy initially may only be needed during respiratory infections due to acute on chronic infective episodes, but eventually ongoing therapy is frequently necessary. Initially insulin doses are small (supplemental rather than total insulin replacement). In some patients, early insulin therapy prior to symptoms of hyperglycaemia may provide metabolic effects beneficial to growth, weight and pulmonary function.

Drug Induced Diabetes

The most frequent scenarios for drug induced diabetes occur in neurosurgery, chemotherapy for malignancies and immunosuppression post transplant.

In neurosurgery, large doses of dexamethasone are frequently used to prevent cerebral oedema (eg dexamethasone 24 mg per day). The additional stress of the surgery may add to the drug-induced insulin resistance, and cause a relative insulin deficiency, sufficient to cause a transient form of diabetes. This will be exacerbated if large volumes of intravenous dextrose are given for diabetes insipidus. An intravenous insulin infusion is the optimal way to control the hyperglycaemia which is usually transient.

In oncology, protocols which employ L-asparaginase, high dose glucocorticoids, cyclosporin or tacrolimus (FK506) may be associated with diabetes. L-asparaginase usually causes a reversible form of diabetes. Tacrolimus and cyclosporin may cause a permanent form of diabetes possibly due to islet cell destruction. Often the diabetes is cyclic and associated with the chemotherapy cycles, especially if associated with large doses of glucocorticoids.

In transplantation medicine, secondary diabetes most frequently occurs with the use of high dose steroids and tacrolimus.

Stress Hyperglycaemia

Stress hyperglycaemia is hyperglycaemia detected in the presence of fever, infection, surgery, respiratory distress, head trauma, or other stress. It is usually transitory and should not be regarded as diagnostic of diabetes.

One large study describes the occurrence of stress hyperglycaemia in up to 5% of children presenting to an emergency department with acute illness or injury, and identifies traumatic injuries, febrile seizures and elevated body temperature (>39 degrees) as the most commonly associated features. Of 41 children with stress hyperglycaemia, none had developed diabetes after a mean follow-up period of 3.5 years. In other smaller studies, the reported incidence of progressing to overt diabetes varied from 0% to 33%. Children who develop hyperglycaemia without a serious illness are more likely to develop diabetes than those who have hyperglycaemia in response to a serious illness.
Follow-up of patients with a history of stress hyperglycaemia varies from centre to centre. Autoantibody screening for antipancreatic antibodies is a practical and useful method of follow-up. Islet cell antibodies and insulin autoantibodies have a high positive predictive value for type 1 diabetes in children with stress hyperglycaemia.\(^{53}\)

**The Evidence**

The evidence on the prevalence/incidence of type 1 diabetes in children in Australia and worldwide is shown in Evidence table 1.1.

- Worldwide the incidence of type 1 diabetes in children under the age of 15 ranges from 0.1 - 37.4 per 100,000.\(^{5,6}\)(IV)
- The most recent data on the incidence of childhood type 1 diabetes in Australia (New South Wales) indicates an incidence of 17.8 per 100,000 from 1990-1996, with an annual increase in incidence of 3.2% per year since 1990.\(^{8,16}\)(IV)

Additional Technical Reports and Consensus Statements used to formulate the recommendations and principles of clinical practice are listed in Evidence table 1.2.

**Recommendations and Principles**

- The diagnosis of diabetes in children and adolescents should be based on the World Health Organization criteria (1999).\(^{1}\)(T)
- Worldwide the incidence of type 1 diabetes in childhood varies greatly (0.1 - 37.4 per 100,000), with the Australian incidence being 17.8 and increasing by 3.2% per year since 1990.\(^{5,6,8,16}\)(IV)
- Diabetes can be diagnosed if the characteristic symptoms and signs are present and fasting venous plasma glucose concentration is greater than or equal to 7.0 mmol/L, and/or the random venous plasma glucose concentration taken at least 2 hours after eating is greater than or equal to 11.1 mmol/L.\(^{1}\)(T)
- The possibility of type 2 diabetes should be considered in children and adolescents who are obese, have a strong family history of type 2 diabetes, come from an ethnic background at high risk for diabetes, produce little or no ketonuria and show evidence of insulin resistance (acanthosis nigricans or polycystic ovary syndrome).\(^{1,28}\)(T,C)
- The possibility of other types of diabetes should be considered in children and adolescents who have any of the following: an autosomal dominant family history of diabetes, have associated conditions such as deafness, optic atrophy or syndromic features, have marked insulin resistance or require little or no insulin outside the partial remission phase or have been exposed to drugs known to be toxic to beta cells or cause insulin resistance.\(^{1,57}\)(T,C)
- An oral glucose tolerance test (OGTT) is rarely indicated in making the diagnosis of type 1 diabetes in childhood and adolescence.\(^{1,57}\)(T,C)
- The OGTT may be used in the evaluation of possible glucose intolerance in a child or adolescent suspected of having the metabolic syndrome eg an obese adolescent with acanthosis nigricans, a girl with the polycystic ovary syndrome, an obese child with a family history of type 2 diabetes or an obese child from a high risk ethnic background for type 2 diabetes.\(^{28,35}\)(T,C)
- Targeted screening for type 2 diabetes (fasting plasma glucose or 2 hour post-prandial glucose) is recommended at the point of medical contact if high risk factors are present (obesity, strong family history of type 2 diabetes, high risk ethnic group, acanthosis nigricans, polycystic ovary syndrome) and every 2 years thereafter.\(^{31,32}\)(T,C)
Reference List


Chapter 2: Phases of Diabetes

Type 1 diabetes is characterised by:
- Preclinical diabetes.
- Presentation of diabetes.
- Partial remission or honeymoon phase.
- Chronic phase of lifelong dependency on administered insulin.

Preclinical Diabetes

Preclinical diabetes refers to the months or years preceding the clinical presentation of type 1 diabetes when islet antibodies can be detected as markers of beta cell autoimmunity. In addition to these immunological markers, the risk of type 1 diabetes can further be determined by genetic markers. The parameters currently helping to define the preclinical phase include:
- Islet cell autoantibodies.
- Glutamic acid decarboxylase autoantibodies (65K GAD isoform).
- IA2 (also known as ICA 512 or tyrosine phosphatase) autoantibodies.
- Insulin autoantibodies.
- HLA typing.

Risks of progression to diabetes

Genetic markers conferring increased or decreased risk include:
- a) HLA DR3 - DQA1*0501 - DQB1* 0201 (susceptible genotype).
- b) HLA DR4 - DQA1*0301 - DQB1* 0302 (susceptible genotype).
- c) HLA DR2 - DQA1*0102 - DQB1* 0602 (protective genotype).

Islet autoimmunity can be transient and one raised islet antibody alone has little prognostic value.1-3 If an individual is under 45 years and does not have HLA DR2 - DQA1*0102 - DQB1* 0602 then:
- Impaired first phase insulin release on intravenous glucose tolerance testing confers a 60% risk over the next 5 years.4
- Two or more islet antibodies raised without impaired first phase insulin release confer a 25-50% risk over the next 5 years.5,6

Neither screening of any population nor intervention in the preclinical phase should occur outside the context of defined clinical studies.7 Individuals who screen positive for genetic or immunological markers of type 1 diabetes should have access to appropriate counselling and to centres participating in intervention and other defined studies. Intervention studies should be registered as part of an international network of investigation and information about ongoing studies should be readily available.7

To date, all clinical trials attempting to prevent or delay the onset of type 1 diabetes in those at high risk have been unsuccessful. The most important of these intervention studies are:
- European Nicotinamide Diabetes Intervention Trial (ENDIT), a multinational randomised placebo-controlled, double blinded intervention study, in which nicotinamide did not delay or prevent the onset of type 1 diabetes in high-risk first-degree relatives.8
- Diabetes Prevention Trial (DPT), in which low dose subcutaneous insulin therapy did not delay or prevent the onset of clinical diabetes in first-degree relatives.4
The one proven environmental trigger of type 1 diabetes is congenital rubella.\textsuperscript{9,10} Other potential environmental triggers are enteroviral infections (particularly coxsackie) and ECHO viruses, casein, cow’s milk protein and gluten. Low levels of intercurrent infection and improved hygiene may be associated with increased risk. International trials following children at increased genetic risk from birth are investigating potential trigger and protective factors.\textsuperscript{11,12}

**Presentation of Type 1 Diabetes**

Prospective follow-up of high-risk subjects shows that diagnosis of type 1 diabetes can be made in asymptomatic individuals in the majority of cases.\textsuperscript{4} In the Diabetes Prevention Trial (DPT), when high-risk individuals were followed up, 73% of participants who were diagnosed with diabetes were asymptomatic.\textsuperscript{4}

A child presenting with a classical history of increasing polyuria, polydipsia and weight loss over 2-6 weeks does not usually pose a diagnostic difficulty. Failure to consider the possibility of diabetes or atypical presentations may result in late diagnosis.

Some children may have a rapid onset of symptoms and present within a few days in diabetic ketoacidosis, but others may have a slow onset of symptoms over several months.

Urinary ‘dipstick’ testing for glycosuria and ketonuria provides a simple and sensitive tool for excluding diabetes with less typical presentation. A blood glucose measurement (plasma glucose $>$11.1 mmol/L) would confirm the diagnosis. The blood glucose measurement should be a laboratory estimation rather than a bedside reading.

**Non-emergency presentations**

Non-emergency presentations of diabetes include:

- Recent onset of enuresis in a previously toilet-trained child, which may be misdiagnosed as a urinary tract infection or the result of excessive fluid ingestion.
- Vaginal candidiasis, especially in prepubertal girls.
- Vomiting, which may be misdiagnosed as gastroenteritis.
- Chronic weight loss or failure to gain weight in a growing child.
- Irritability and decreasing school performance.
- Recurrent skin infections.

**Emergency presentations**

The usual emergency presentation of diabetic ketoacidosis in a child or adolescent includes the following clinical features:

- Severe dehydration.
- Shock (rapid pulse rate, poor peripheral circulation, mottling and peripheral cyanosis).
- Hypotension (a late sign and rare in children with diabetic ketoacidosis).
- Frequent vomiting.
- Continuing polyuria despite the presence of dehydration.
- Weight loss due to fluid loss and loss of muscle and fat.
- Flushed cheeks due to the ketoacidosis.
- Acetone detected on the breath.
- Hyperventilation of diabetic ketoacidosis (Kussmaul respiration) is characterised by a high respiratory rate and large tidal volume of each breath, which gives it a sighing quality.
- Disordered sensorium (disoriented, semicomatose or rarely comatose).
Diagnostic difficulties leading to late diagnosis
The following situations may result in a late diagnosis of diabetic ketoacidosis:

- The very young child may present in severe ketoacidosis because of a more rapid onset of severe insulin deficiency and because the diagnosis was not considered early.
- The hyperventilation of ketoacidosis may be misdiagnosed as pneumonia or asthma (cough and breathlessness distinguish these conditions from diabetic ketoacidosis).
- The abdominal pain associated with ketoacidosis may simulate an acute abdomen and lead to referral to a surgeon.
- The polyuria and enuresis may be misdiagnosed as a urinary tract infection.
- The polydipsia may be thought to be psychogenic.
- The vomiting may be misdiagnosed as due to gastroenteritis or sepsis.

Untreated, diabetic ketoacidosis is fatal. Therapy is urgent and referral to specialised services is essential.

Differentiating between type 1 and type 2 diabetes at diagnosis
Features suggesting the diagnosis of type 2 diabetes rather than type 1 diabetes at diagnosis are:

- Obesity.
- Strong family history of type 2 diabetes.
- Acanthosis nigricans.
- High risk racial or ethnic group.
- Undetectable islet antibodies.
- Normal to high C-Peptide levels.

Partial Remission or Honeymoon Phase
In approximately 80 percent of children and adolescents, insulin requirements decrease transiently following initiation of treatment.

Most studies define a partial remission phase as that when the patient requires less than 0.5 units of insulin per kg of body weight per day and has a HbA1c <7%.

The partial remission phase commences within days or weeks of the start of insulin therapy and may last for weeks to months. During this phase blood glucose levels are frequently stable within the normal range, despite fluctuations in diet and exercise. It is important for the families to be advised of the transient nature of the partial remission phase so as to avoid the false hope that the diabetes is spontaneously remitting.

Intensive therapy (continuous subcutaneous insulin infusion) has not been shown to prolong the partial remission phase.

In a few children and adolescents, requirements for insulin may decrease to the point of being able to withdraw insulin therapy temporarily and still maintain normoglycaemia. As low dose subcutaneous insulin therapy does not prolong residual beta cell function in the preclinical phase, it is unlikely to do so in the remission phase. Therefore, continuing insulin seems unlikely to prolong endogenous insulin production, or provide any other advantage other than maintaining established diabetes routines for the child.

Ketoacidosis at presentation and young age reduce the likelihood of a remission phase.

Chronic Phase of Lifelong Dependence on Insulin
The progression from the partial remission phase into the chronic phase of lifelong dependence on insulin is usually gradual but can be accelerated by an intercurrent illness.
Exogenous insulin replacement remains the only form of replacement therapy for children and adolescents with type 1 diabetes. As mentioned in the previous section whilst intensive therapy for type 1 diabetes has not been shown to prolong the partial remission phase there is evidence it helps sustain some endogenous insulin secretion (measured by C-Peptide level), which, in turn, is associated with better metabolic control. Intervention trials from diagnosis are in progress as part of an international network of intervention trials to preserve beta cell function either in the pre-clinical phase or from diagnosis.

Transplantation

Islet transplantation has become more successful since the introduction of less beta cell toxic immunosuppressive agents and refined techniques to harvest adequate numbers of viable beta cells. The numbers of subjects who remain insulin independent falls with follow-up and several donor pancreases are required for adequate beta cell numbers in the transplant. The induction of immunologic tolerance without the need for chronic immunosuppressive therapy is a major goal and the potential use of haematopoietic stem cell therapy for induction of tolerance and islet cell neogenesis in vitro are rapidly expanding research directions.

Pancreas transplantation provides high rates of graft survival at 1 year but there are significant surgical risks and the requirement for long term immunosuppression precludes its use in children and adolescents.

The Evidence

The evidence on intervention trials to delay or prevent the onset of type 1 diabetes is listed in Evidence Table 2.1.

- European Nicotinamide Diabetes Intervention Trial (ENDIT), a multinational quasi-randomised placebo-controlled, double blinded intervention study, demonstrated that nicotinamide did not delay or prevent the onset of type 1 diabetes in high-risk first-degree relatives. (III-1)
- The National Institute of Health Diabetes Prevention Trial (DPT) demonstrated in a randomised controlled trial that low dose subcutaneous insulin therapy did not delay or prevent the onset of clinical diabetes in high-risk first-degree relatives. (II)

Additional Technical Reports and Consensus Statements used to formulate the recommendations and principles of clinical practice are listed in Evidence table 2.2.

Recommendations and Principles

- Health care professionals should be aware that there are no interventions shown to delay or prevent the onset of type 1 diabetes. (II)
- Neither screening of any population nor intervention in the preclinical phase should occur outside the context of defined clinical studies. (C)
- Type 1 diabetes is characterised by a preclinical, clinical, partial remission and chronic phase. (C)
- Clinical presentation of diabetes can vary from non-emergency presentations (eg polydipsia, polyuria, weight loss, enuresis) to severe dehydration, shock and diabetic ketoacidosis. (C,T)
- Parents and children with type 1 diabetes should be informed that the partial remission phase of diabetes is transient and does not indicate remission of diabetes. (C)

II = NHMRC Level II: Evidence from at least one properly-designed RCT
IV = Evidence obtained from case series
T = WHO technical reports produced by expert panels
C = Consensus statements endorsed by professional organisations
Reference List

12. TRIGR study group. Trial to reduce IDDM in the Genetically at risk (TRIGR) 2003. http://www.trigr.org/ Ref Type: Electronic Citation
Chapter 3: Medical Management

Every child and adolescent with type 1 diabetes, including those from rural and remote areas, deserves to have access to optimal medical management. A child cannot fight for these rights. Health care professionals looking after children must make advocacy for the child one of their key responsibilities.

Suboptimal medical management leads to poor diabetes control which may impair growth, delay puberty and lead to irreversible long-term diabetic microvascular and macrovascular complications. Quality of life and life expectancy may be significantly reduced under these circumstances.

Poor metabolic control, younger age of onset and lower socioeconomic group are predictors of re-hospitalisation rates which may indicate poor adjustment to diabetes. These outcomes occur for a variety of reasons but many are potentially preventable.

Aims of Diabetes Management

The aims of diabetes management are to have:

- Optimal psychosocial adjustment.
- Optimal metabolic (glycaemic) control.
- Normal growth and development.
- An individualised plan of diabetes care incorporating the particular needs of the child or adolescent and the family.

Hospital versus Ambulatory Stabilisation

At diagnosis the decision should be made between hospital admission or ambulatory initiation of treatment.

A systematic review and other studies have concluded that in appropriately chosen patients there are no disadvantages of ambulatory management compared to inpatient management of children and adolescents with newly diagnosed type 1 diabetes. Older children and adolescents who develop diabetes but are not dehydrated or acidic may be successfully managed out of hospital if expert diabetes support teams are available.

The importance of expert care at diagnosis cannot be over-emphasised. In a questionnaire survey parents reported that care provided by paediatricians without a special interest in diabetes is more likely to result in a longer hospital admission, whilst parental satisfaction with the outpatient care and school liaison is lower than in those cared for by paediatricians with a special interest in diabetes.

Relative contra-indications to ambulatory initiation of insulin therapy include:

- Very young age (under 2 years).
- Ketoacidosis
- Dehydration (moderate or severe).
- Profound grief reaction in family.
- Geographic isolation.
- No telephone in the home.
- Language or other communication difficulties.
- Significant psychological or psychiatric problems within the family.

Children, if hospitalised, should be admitted to paediatric hospital wards. Following the treatment of acidosis or dehydration it is often possible to continue management on an
ambulatory basis. Children should not be admitted to adult wards. Adolescents, if requiring hospitalisation, should preferably be accommodated in adolescent wards. The parents should always be allowed open and free access to their child at all times.

The Australian Diabetes Educators Association have published minimum national standards for the ambulatory initiation of insulin. These standards are not specific to paediatric care, however, they describe process standards required in Australia to initiate insulin effectively and safely.

Children and adolescents should have access to care by a multidisciplinary team trained in childhood and adolescent diabetes. It should be recognised that the members of the management team include the patient with diabetes and his/her family. The members of the team are therefore:

- The patient and his/her family.
- Paediatric endocrinologist or physician trained in the care of children and adolescents with diabetes.
- Diabetes educator.
- Dietitian.
- Psychologist/social worker.

Care provided by a specialised diabetes multidisciplinary team has been shown to result in:

- Fewer days in hospital.
- Higher level of diabetes self care practices.
- Decreased re-admission rates.
- Lower HbA1c.
- Delayed development of complications.

After the initial period of diagnosis and education (when frequent contact may be required), the child should be regularly reviewed throughout the year. This should be no less than 3–4 times per year, including one major annual review (paying particular attention to review of regular growth data, blood pressure, puberty, associated conditions, nutrition and complications) with the multidisciplinary team. More frequent reviews by expert teams may result in improved control.

Foundations of Diabetes Management

The foundations of successful diabetes management include:

- Diabetes education.
- Insulin replacement.
- Blood glucose monitoring.
- Nutritional plan.
- Psychological adjustment and wellbeing of the whole family.

In addition, exercise should be encouraged because of its beneficial effects on glycaemic control and wellbeing.

Diabetes Education

Ideally diabetes and nutritional education should be provided by Credentialled Diabetes Educators and dietitians who have undertaken specialised training in paediatric diabetes
education and nutrition. If specialised diabetes and nutritional education is not available, options include transfer to a centre with the necessary expertise or shared care with such a centre able to provide outreach support.

Educational interventions have beneficial effects on diabetes management outcomes. Education is a continuous process and should be provided to the child or adolescent and their family at diagnosis and repeated as required at follow up. Diabetes education is more than a transfer of knowledge and should aim to result in the appropriate behaviour changes needed for achieving and maintaining diabetes control.

Education should also be appropriate to the age and developmental level of the child or adolescent.

Initial diabetes education is usually with the educator and the child and parent, but continuing education can be provided in group settings. The relative merits of individual versus group education have not been studied. Diabetes education can either be provided in a hospital setting or on an ambulatory basis if there are no contra-indications to day care. Diabetes education should also be made available to other care-providers such as grandparents, teachers and staff in childcare centres.

Education should be adapted to each individual’s age, maturity, stage of diabetes, lifestyle and culture. The following topics should be covered:

- The cause of diabetes.
- Insulin storage.
- Insulin injection techniques.
- Blood glucose measurement.
- Insulin adjustment.
- Exercise.
- Psychological and family adjustment.
- Hypoglycaemia, prevention and its management.
- Diabetes management during illness.
- Travel.
- Diabetes and exercise.
- Dietetic principles.
- Contraception.
- Alcohol and Drugs.
- Diabetes complications. When age appropriate
- Driving.
- Smoking.

**Insulin Replacement Therapy**

The terms ‘conventional’ and ‘intensive’ insulin replacement regimens are becoming historical terms and are losing their meaning as the emphasis has shifted from simply equating intensified management with the number of injections given. The aim is to achieve the best possible control of glycaemia in all children and adolescents with diabetes. See Chapter 5 for details of various insulin regimens.

**Immunisation**

It is recommended that children and adolescents with type 1 diabetes should be immunised according to the Australian Standard Immunisation Schedule unless a contra-indication is present. Diabetes is not a contra-indication to immunisation.
In addition to the routine immunisations, the use of the Influenza and Pneumococcal vaccines is being evaluated in people with diabetes.30,31

**Outreach Services**

In rural and geographically remote areas with low population density and very small numbers of children with diabetes, it may not be possible to provide a local multidisciplinary team. In these situations, care may be successfully provided by a local paediatrician/physician with access to resources, support and advice from a tertiary centre diabetes team.32,33

In an audit of almost 1200 children with type 1 diabetes living in New South Wales and the Australian Capital Territory, there was no significant difference in glycaemic control between those from urban and those from rural areas. HbA1c and the incidence of severe hypoglycaemia were used as measures of glycaemic control. This audit confirmed homogeneity of metabolic control regardless of location or system of care in NSW/ACT.32

Support to isolated patients may be in the form of outreach clinics or telemedicine consultations including access to telephone support 24 hours a day and regular telephone contact.32,34-36

Where local resources are lacking, the annual review should be performed by a tertiary centre diabetes team.

**Transition to Adult Services**

The importance of an effective transition process for adolescents cannot be overemphasised (see Chapter 18).

**Cost Issues**

The cost of hospitalisation for children and adolescents with type 1 diabetes in New South Wales was estimated to be approximately $1.5 million per year in 1990.37 The management of type 1 diabetes in children and adolescents with type 1 diabetes results is significant health care costs at diagnosis and for subsequent readmissions to hospital.37 Since this analysis was done ambulatory care at diagnosis has become more common, however no Australian study has reassessed the cost implications of the changing pattern of care.

Two relevant studies were located addressing the cost of ambulatory care versus hospital care at diagnosis. One RCT found that although ambulatory care increased hospital costs mainly by increasing nursing consultation costs and the requirement for telephone support, this increase was offset by significant cost savings for parents.38,39 Overall there was no significant cost difference between the two modes of care. This study was in the Canadian health care system and may not be directly applicable to the Australian setting. A second study (also in Canada) retrospectively compared the costs of hospital care versus ambulatory care and found that hospital costs were much higher for hospital care, however nurse education, parental and societal costs were not accounted for.11

**The Evidence**

The evidence for the benefits of ambulatory care versus hospital inpatient care of patients with newly diagnosed type 1 diabetes is listed in **Evidence Table 3.1**.

- A Cochrane systematic review and other studies have concluded that in appropriately chosen patients there are no disadvantages of ambulatory management compared to
inpatient management of children and adolescents with newly diagnosed type 1 diabetes.\textsuperscript{5-12} (I)

The evidence comparing metabolic control in urban and rural children and adolescents with type 1 diabetes is listed in Evidence Table 3.2.

- In a population based audit of children with type 1 diabetes living in New South Wales and the Australian Capital Territory, there was no significant difference in glycaemic control between those from urban and those from rural areas. This audit confirmed homogeneity of metabolic control regardless of location or system of care in NSW/ACT.\textsuperscript{32} Similar results were obtained in an audit of Victorian urban and rural diabetic youths.\textsuperscript{33} (IV)

The evidence on the effect of educational interventions on glycaemic control and psychosocial outcome is listed in Evidence table 3.3.

- A Health Technology Assessment has concluded that educational interventions have beneficial effects on diabetes management outcomes.\textsuperscript{28} (I)

Additional Technical Reports and Consensus Statements used to formulate the recommendations and principles of clinical practice are listed in Evidence table 3.4.

**Recommendations and Principles**

- Every child and adolescent with type 1 diabetes, including those from rural and remote areas, should have access to optimal medical management.\textsuperscript{1,5,14} (C)
- Health care professionals who look after children should make advocacy for the child one of their key responsibilities.\textsuperscript{14} (C)
- Older children and adolescents who develop diabetes but are not dehydrated or acidic may be considered for management out of hospital if expert diabetes support teams are available.\textsuperscript{5-12} (I)
- Relative contraindications to ambulatory initiation of insulin therapy include very young age (under 2 years), ketoacidosis, dehydration (moderate or severe), geographic isolation, no telephone at home, language or other communication difficulties, profound grief reaction and significant psychological or psychiatric problems within the family.\textsuperscript{2,14} (C)
- Children and adolescents with type 1 diabetes should have access to care by a multidisciplinary team trained in childhood diabetes.\textsuperscript{2,17,18,19} (C)
- The older child and the family should be recognised as being part of the management team. (C)
- Diabetes education should be part of the management of type 1 diabetes in children and adolescents. Educational interventions have beneficial effects on diabetes management outcomes.\textsuperscript{28} (I)
- Education should be adapted to each individual’s age, maturity, stage of diabetes, lifestyle and culture.\textsuperscript{2} (C)
- After the initial period of diagnosis and education (when frequent contact may be required), the child should be regularly reviewed throughout the year. This should be no less than 3-4 times per year), including one major annual review (paying particular attention to growth, blood pressure, puberty, associated conditions, nutrition and complications) with the multidisciplinary team.\textsuperscript{2,18,19} (C)
- Children and adolescents with type 1 diabetes should be immunised according to the Australian Standard Immunisation Schedule\textsuperscript{29} unless a contra-indication is present. Diabetes is not a contra-indication to immunisation. (C)
- In rural and geographically remote areas within the Australian health care system, children with diabetes may be successfully cared for by a local paediatrician/physician with
training and experience in paediatric diabetes access to resources, support and advice from a tertiary centre diabetes team.\textsuperscript{32,33}\textsuperscript{(IV)}

<table>
<thead>
<tr>
<th>T</th>
<th>Technical Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>Evidence obtained from case series, either post-test or pre-test and post-test</td>
</tr>
<tr>
<td>III-3</td>
<td>Evidence from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group</td>
</tr>
<tr>
<td>I</td>
<td>Evidence obtained from a systematic review of all relevant randomized controlled trials</td>
</tr>
</tbody>
</table>

**Reference List**

2. International Society for Pediatric and Adolescent Diabetes: ISPAD Consensus Guidelines for the Management of Type 1 Diabetes Mellitus in Children and Adolescents. Zeist, Netherlands, Medforum, 2000
19. Queensland Health: Best practice guidelines for the management of Type 1 Diabetes in children and adolescents. 2002
Chapter 4: Insulin Preparations and Storage

Children and adolescents with type 1 diabetes are dependent on insulin for survival. There is no alternative to treatment with insulin. Insulin is not normally used in combination with any other hypoglycaemic agents.

Insulin Action

Despite the published data on the duration of action of the various insulin preparations there is much inter- and intra-individual variation (see Table 4.1 and Figure 4.1). The onset, peak effect and duration of insulin action may vary both between individuals and for the same individual depending on a number of factors including:

- Age.
- Fat mass.
- Pubertal stage.
- The dose of insulin used.
- The site of the injection.
- Exercise.
- Insulin concentration, type and formulation.
- Ambient and body temperature.

Types of Insulin

Until the development of recombinant DNA technology in the 1980s, insulin was purified from porcine or beef pancreatic tissue. Human recombinant insulins are now the most widely used forms and are the recommended first line preparations in the paediatric age group. Human recombinant insulins are preferred because of their availability through modern manufacturing techniques using recombinant DNA technology and because of their low immunogenicity.

A Cochrane Collaboration systematic review of 45 RCT’s (including 4 paediatric studies) found no significant differences in metabolic control or hypoglycaemic episodes between animal or human insulins.

Porcine insulins are now only available in Australia under the ‘Special Access Scheme’ (SAS) provisions. Requests for porcine insulin need to be forwarded to the Therapeutic Goods Administration (TGA) before requesting the stock from the company. These insulins are occasionally useful in children with allergic reactions attributable to human recombinant insulin preparations.

Beef insulin is still available in Australia (isophane and short-acting). It is occasionally tried in children with type 1 diabetes not able to be satisfactorily stabilised on human insulin.

The types of insulin currently available are outlined in the table below:
Table 4.1: Insulins Currently in Use in Australia

<table>
<thead>
<tr>
<th>Insulin Preparation</th>
<th>Onset of Action (h)</th>
<th>Peak of Action (h)</th>
<th>Duration of Action (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-acting (neutral)</td>
<td>0.5-1</td>
<td>2-4</td>
<td>5-8</td>
</tr>
<tr>
<td>Intermediate-acting (isophane)</td>
<td>1-2</td>
<td>4-12</td>
<td>16-24</td>
</tr>
<tr>
<td>Intermediate-acting (lente)</td>
<td>1-2.5</td>
<td>6-15</td>
<td>≤24</td>
</tr>
<tr>
<td>Long-acting (ultralente)</td>
<td>4-8</td>
<td>12-24</td>
<td>20-30</td>
</tr>
<tr>
<td>Bovine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-acting (neutral)</td>
<td>0.5-1</td>
<td>3-6</td>
<td>6-8</td>
</tr>
<tr>
<td>Intermediate-acting (isophane)</td>
<td>2</td>
<td>6-12</td>
<td>18</td>
</tr>
<tr>
<td>Analogue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapid-acting</td>
<td>0.25-0.5</td>
<td>1-3</td>
<td>3-5</td>
</tr>
<tr>
<td>Basal (glargine)</td>
<td>2-4</td>
<td>None</td>
<td>24</td>
</tr>
<tr>
<td>Basal (detemir)*</td>
<td>1-2</td>
<td>6-12</td>
<td>20-24</td>
</tr>
<tr>
<td>Biphasic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-acting/intermediate</td>
<td>0.5</td>
<td>1-12</td>
<td>16-24</td>
</tr>
<tr>
<td>Ratio 20/80</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ratio 30/70</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ratio 50/50</td>
<td>0.5</td>
<td>1-12</td>
<td>16-24</td>
</tr>
<tr>
<td>Rapid-acting analogue/intermediate</td>
<td>0.5</td>
<td>1-12</td>
<td>16-24</td>
</tr>
<tr>
<td>Ratio 25/75</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ratio 30/70</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Anticipated availability in 2004/2005

**Rapid-acting insulin**

Insulin has a tendency to aggregate into dimers and hexamers which retard the absorption and biological availability. Insulin lispro and insulin aspart are now widely used rapid-acting insulin analogues which prevent the insulin molecule from forming dimers or hexamers. These monomeric insulins are clear solutions that have a very rapid onset of action, peak within 1 hour and have duration of action of up to 5 hours.

In accordance with the manufacturers’ recommendations rapid-acting insulin should be injected at the time of a meal.

Rapid-acting insulins are used in:
- Twice daily insulin regimens.
- Basal-bolus insulin regimens.

These analogues are effective in other specific situations such as:
- Rapid-acting insulin given at afternoon tea reduces high blood glucose levels commonly seen before the evening meal in children and adolescents on twice daily injections of rapid-acting or regular insulin in combination with an isophane insulin.8
- Rapid-acting insulin has been shown to be effective when given post-prandially in prepubertal children with type 1 diabetes with unpredictable eating habits (eg infants, toddlers and preschool children).9 However, its effect on post-prandial blood glucose levels has been variable.10 The NICE Guidelines on Diagnosis and Management of Type 1 Diabetes in Children and Young People have indicated that post-prandial rapid–acting insulin is an option in the management of these patient groups.30
- Rapid-acting insulin analogues are used in continuous subcutaneous insulin infusion (CSII) therapy.11;12
- Rapid-acting insulin analogues may also be used for the management of hyperglycaemia and ketosis during sick days.
Short-acting insulin
Short-acting insulin is also known as ‘soluble’ or ‘regular’ insulin and is a clear solution. It is used in the management of diabetic ketoacidosis and as a component of daily replacement therapy. It can be used by itself as a pre-meal bolus injection in a basal-bolus regimen or in combination with intermediate-acting insulin in a twice-daily injection regimen.

Data are inconsistent on the optimal timing of short-acting insulin in relation to meals. However, in accordance with the manufacturers’ recommendations, short-acting insulin should be injected 15-20 minutes before a meal. The American Diabetes Association discourages eating within a few minutes after (or before) injecting short-acting insulin as the likelihood of a rapid rise of blood glucose is increased and it may increase the risk of delayed hypoglycaemia.13

Intermediate-acting insulin
These insulins are present in the form of a suspension and are therefore referred to as ‘cloudy’ insulins. Their time-course of action makes them suitable for twice-daily insulin regimens and for pre-bed dosage in basal-bolus regimens. The vials need to be gently but properly mixed prior to each use to ensure a uniform concentration. Pens containing isophane need to be tipped at least 20 times for adequate mixing, however, vigorous mixing may cause protein degradation.

The two principal preparations currently used are:
- Isophane or NPH (Neutral Protamine Hagedorn) insulins.
- Crystalline zinc-acetate insulins (lente insulins).

To avoid confusion and prescribing errors, the use of the terms ‘clear’ to describe rapid-acting or short-acting insulin and ‘cloudy’ to describe intermediate- or long-acting insulin, should be discouraged as the long-acting insulin analogues, glargine and detemir, are clear solutions.

Long-acting insulins
These preparations may be used to meet basal insulin requirements, especially in basal bolus injection regimens.

Basal insulin analogues
Insulin glargine is a new long-acting basal insulin analogue (see Table 4.1 and Figure 4.1). It is a soluble insulin which precipitates in situ after injection. It is important to note that insulin glargine cannot be mixed with any other insulin. This modified insulin molecule has a stable and smooth 24-hour profile.14 In a multicentre randomised study, insulin glargine was compared with NPH insulin in children aged 5 to 16 on a basal-bolus regimen.15 The glargine treated group had a greater reduction in fasting blood glucose levels, although overall HbA1c improvement was similar in both groups. Glargine may decrease the risk of severe nocturnal hypoglycaemia in children and adolescents.15-17 A recent Technology Appraisal Guidance from the UK National Institute of Clinical Excellence concluded that insulin glargine should be considered as a treatment option for people with type 1 diabetes.16

Insulin detemir is another basal insulin (see Table 4.1 and Figure 4.1). It is an acylated insulin which binds to albumin. Preliminary studies in adults suggest that it has advantages over isophane insulins when used in a basal/bolus regimen, with a significant reduction in hypoglycaemia despite comparable HbA1c levels.18 A recent study of the pharmacokinetics of insulin detemir showed no difference in serum concentration of insulin with time when
comparing children aged 6 to 12 years with adolescents aged 13-17 years and adults aged over 18 years. There was less variability in response to insulin detemir compared with NPH.19

**Premixed insulin preparations**

Several premixed combinations of rapid-acting, short-acting and isophane insulins are available in Australia with variable ratios available as detailed in Table 4.1.

In Australia, premixed insulin preparations are not generally recommended for first line use in childhood and adolescent diabetes because of changing needs in the ratios of the two insulins. Their use generally indicates a compromise; however the premixed combinations may be helpful in some situations:

- When there are difficulties in accurately drawing up and mixing insulins.
- When ratios remain stable.
- When there are severe individual or family psychosocial problems disturbing diabetes management.
- When adolescents are experiencing difficulty in complying with insulin regimens.

Typical action profiles of the various insulin preparations are illustrated in figure 4.1, although there is much inter- and intra-individual variation.

**Local Reactions to Insulin**

Local reactions to insulin injections are uncommon, but when they do occur they are more likely to be due to sensitivity to the added preservatives (metacresol, phenol or methylhydroxybenzoate) than to the insulin itself.20,21 Two types of reaction have been reported, a localised wheal and flare with itching due to histamine reactions, and generalised anaphylaxis, which is extremely rare. A trial of insulin with a different preservative may solve this problem. Formal identification of the preservative is possible using preservative-only preparations available from the manufacturers. Antihistamine creams can also assist with localised reactions. Cold-sensitivity urticaria should also be considered if the patient develops a local reaction on using a vial directly from the refrigerator. Latex sensitivity (due to transfer of latex particles from the septum of the insulin bottle) should also be considered.22

**Mixing Insulins**

In order to maintain uniformity, short/rapid-acting insulin should be drawn up into the syringe before the intermediate- or long-acting insulin. This strategy prevents contamination of the short/rapid-acting insulin by the longer-acting insulin and eliminates the possibility of converting the short/rapid-acting insulin into a longer-acting form.

Isophane insulin can be premixed with rapid-acting or short-acting insulin in the same syringe or vial without altering the absorption profile of the rapid-acting or short-acting insulin.23,24

Lente insulin can be safely given together with rapid-acting or short-acting insulin in the same syringe providing the injection is administered immediately after mixing.25 Lente insulin should never be premixed with rapid-acting or short-acting insulin and stored in the same syringe or in a vial because of conversion of the short-acting insulin into a longer-acting form.25

Isophane and lente insulins should never be mixed in the one syringe or vial.

Insulin glargine cannot be mixed with any other insulin.
Insulin Concentrations

One unit of insulin corresponds to approximately 36 micrograms or 6 nanomoles of insulin. Australia and New Zealand have a single insulin concentration of 100 U/ml (U 100).

Insulins must be administered by insulin syringes calibrated to the concentration of the insulin.

The availability of insulins of other concentrations (eg U 40) still exists in some countries overseas. This is important information for Australian patients travelling internationally.

In very young children with very low insulin requirements, the insulin preparations may need to be diluted in order to deliver doses accurate to 0.1 unit safely. The diluents are obtained from the insulin manufacturers (the physician needs to obtain approval from the Department of Health under the Special Access Scheme). The diluted preparations can be stored for 3 months under refrigeration although the vial that is in use must be discarded after 1 month whether stored under refrigeration or at room temperature. When using diluted insulins, special care must be taken to ensure that the correct dose is administered when using standard insulin syringes. 25-unit syringes are extremely useful when small doses need to be given.

Storage Conditions

The following storage conditions should be recognised:

- Insulin is stable at room temperature for several weeks providing there are no extremes of temperature.
- Unused vials should be refrigerated (stored at 4 to 8°C) but never frozen.
- Insulin may lose its potency after opening the vial or when exposed to high temperatures (eg in the tropics or if left in the car).
- Insulin vials should be discarded after 3 months of opening if kept refrigerated and after 1 month if kept at room temperature.
- Penfill cartridges and disposable insulin pens should be discarded after 21-28 days at room temperature as per the manufacturer’s instructions for storage.
- The manufacturer’s expiry date should be adhered to.

Adjunct Therapy with Oral Antidiabetic Drugs

There is only limited experience of using metformin as an adjunct therapy to insulin in children and adolescents with type 1 diabetes exhibiting insulin resistance. One randomised controlled trial involving 27 adolescents with type 1 diabetes resulted in a decrease in HbA1c of 0.6%, a slight decrease in insulin requirements, but also a slight increase in mild hypoglycaemia. Another randomised controlled trial reported a decrease in HbA1c of 0.9% over 3 months of metformin treatment however this change was not significant when the changes in the pre- and post-test differences in HbA1c were re-calculated between the trial arms. A non-randomised, uncontrolled study involving 10 adolescents and young adults showed a decrease in HbA1c (for 7 of the 10 patients) after 6 months of metformin treatment. This decrease did not reach statistical significance. After stopping metformin, those who did respond to metformin showed a return of HbA1c to pre-treatment levels.
Figure 4.1: Schematic Action Profiles of Insulin Preparations (profiles will vary with dosage, injection site, depth of injection and other factors-see text)

<table>
<thead>
<tr>
<th>Insulin Preparation</th>
<th>Time-action Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-acting human insulin (neutral)</td>
<td></td>
</tr>
<tr>
<td>Intermediate-acting human insulin (isophane)</td>
<td></td>
</tr>
<tr>
<td>Intermediate-acting human insulin (lente)</td>
<td></td>
</tr>
<tr>
<td>Long-acting human insulin (ultralente)</td>
<td></td>
</tr>
<tr>
<td>Bovine short-acting</td>
<td></td>
</tr>
<tr>
<td>Bovine intermediate-acting isophane</td>
<td></td>
</tr>
<tr>
<td>Rapid-acting (analogue)</td>
<td></td>
</tr>
<tr>
<td>Basal analogue (glargine)</td>
<td></td>
</tr>
<tr>
<td>Basal analogue (detemir)</td>
<td></td>
</tr>
<tr>
<td>20% short &amp; 80% intermediate human insulin</td>
<td></td>
</tr>
<tr>
<td>30% short &amp; 70% intermediate-acting human insulin</td>
<td></td>
</tr>
<tr>
<td>60% short &amp; 50% intermediate-acting human insulin</td>
<td></td>
</tr>
<tr>
<td>30% rapid-acting analogue &amp; 70% intermediate-acting insulin</td>
<td></td>
</tr>
</tbody>
</table>
Cost Issues

A recent Health Technology Appraisal assessed the clinical and cost-effectiveness of the long-acting insulin analogue glargine in the management of diabetes. They found no relevant economic evaluations in the medical literature. The manufacturer’s submission included only 2 economic models relevant to type 1 diabetes, which the reviewers felt were significant underestimates of the incremental cost effectiveness ratio (that is, insulin glargine may be significantly less cost effective than is suggested by the manufacturer’s analysis). However, on the balance of effectiveness and cost effectiveness evidence, the reviewers concluded that insulin glargine could be considered as a treatment option in people with type 1 diabetes. This appraisal was conducted with the UK health system in mind and was not specific to paediatrics, and, therefore, may not be generalisable to Australia.

The Evidence

The evidence comparing animal insulin with human insulin use in children and adolescents with type 1 diabetes is listed in Evidence Table 4.1.

- A Cochrane Collaboration systematic review of 45 RCT’s (including 4 paediatric studies) found no significant differences in metabolic control or hypoglycaemic episodes between animal or human insulins.7(I)

The evidence on insulin glargine use in children and adolescents with type 1 diabetes is listed in Evidence Table 4.2.

- A recent Technology Appraisal Guidance from the UK National Institute of Clinical Excellence concluded that insulin glargine should be considered as a treatment option for people with type 1 diabetes.16(I)

The evidence on metformin as an adjunct therapy to insulin in children and adolescents with type 1 diabetes is listed in Evidence Table 4.3.

- There is only limited experience of metformin as an adjunct therapy to insulin in children and adolescents with type 1 diabetes exhibiting insulin resistance. One randomised controlled trial involving 27 adolescents with type 1 diabetes resulted in a decrease in HbA1c of 0.6% compared with placebo, a slight decrease in insulin requirements, but also a slight increase in mild hypoglycaemia. Another randomised controlled trial showed a non-significant decrease in HbA1c of 0.9% over 3 months of metformin treatment.27(II)

- A non-randomised, uncontrolled study involving 10 adolescents and young adults showed a non statistically significant decrease in HbA1c (for 7 of the 10 patients) after 6 months of metformin treatment.28(IV)

Additional Technical Reports and Consensus Statements used to formulate the recommendations and principles of clinical practice are listed in Evidence Table 4.4.

Recommendations and Principles

- Health care professionals, parents and children and adolescents with type 1 diabetes should be informed that insulin is essential for survival. There is no alternative to treatment with insulin.1(T)

- Children and adolescents with type 1 diabetes should be treated with human insulin as animal insulin has no advantage over human insulin in terms of metabolic control or hypoglycaemia.7(I)

- A wide variety of human, analogue and bovine insulins are available in Australia for use in children and adolescents with type 1 diabetes.29(C)
• Rapid-acting insulin should be injected at the time of a meal and short-acting insulin should be injected 15-20 minutes before a meal.\textsuperscript{13,30}(C)
• Rapid-acting insulin can be administered post-prandially in prepubertal children with type 1 diabetes with unpredictable eating habits (eg infants, toddlers and preschool children).\textsuperscript{30}(C)
• Insulin glargine is a long-acting basal insulin analogue which has recently been introduced as a treatment option.\textsuperscript{16}(I)
• To avoid confusion and prescribing errors, the use of the terms ‘clear’ to describe rapid-acting or short-acting insulin and ‘cloudy’ to describe intermediate- or long-acting insulin, should be discouraged as the long-acting analogues, glargine and detemir, are clear solutions.
• The action profile of the various insulin preparations is subject to inter- and intra-individual variation. The action profile is also affected by storage conditions and the manufacturer’s storage instruction should be followed.\textsuperscript{30}(C)
• All children should have rapid/short-acting insulin available for sick-day management.\textsuperscript{30,31}(C)
• Families need to ensure that a small supply of spare insulin is always available so that supply is uninterrupted.\textsuperscript{31}(C)
• As there is limited and inconsistent evidence on the use and efficacy of metformin as an adjunct therapy in type 1 diabetes, it should only be considered as an adjunct for difficult to control patients with evidence of insulin resistance. Patients should be warned of and closely monitored for hypoglycaemia during the stabilisation period and the efficacy monitored.\textsuperscript{26,27,28}(II)

\textsuperscript{I} = Evidence from a systematic review of all relevant controlled trials
\textsuperscript{II} = Evidence from at least one properly-designed RCT
\textsuperscript{C} = Consensus statement endorsed by professional organisations
\textsuperscript{T} = WHO technical reports produced by expert panels

Reference List


Chapter 5: Insulin Regimens and Delivery

The ultimate aim of insulin therapy is to provide physiological insulin replacement. However, commonly used insulins and delivery methods have approximated this very poorly. The availability of new (and future) insulin analogues and alternate delivery methods (e.g., insulin pumps) offers the potential more closely to approximate normal physiology in suitable subjects.

The choice of insulin types and regimen has to be guided by a variety of factors, including:
- Age of the patient.
- Lifestyle factors.
- Patient and family preferences and management skills.
- Metabolic targets.
- Duration of diabetes.
- Experience of the health care team.
- Affordability and sustainability.
- Associated complications, including hypoglycaemia.

Any insulin regimen has to be considered in the wider context of a total diabetes management package, which must include dietary management, exercise, blood glucose monitoring, initial and ongoing education, regular medical follow-up and psychological care. The use of terms such as conventional insulin therapy and intensive insulin therapy is becoming blurred and less useful as management options increase.

Insulin Regimens

The insulin regimen needs to aim to:
- Provide appropriate basal insulin requirements to cover the needs across 24 hours.
- Provide sufficient insulin levels when needed to cover food intake.
- Have adequate provision for adjustment and correction when needed.
- Minimise blood glucose fluctuation and risk of hypoglycaemia and hyperglycaemia.
- Achieve short-term and long-term metabolic targets.

Many regimens are in common use and there are many more that have had limited trials or are in occasional use. The most commonly used regimens are listed and discussed below. Children and adolescents will often evolve from one regimen to another in order to meet the goals of therapy.

- **One injection daily:**
  Either intermediate-acting insulin or short/rapid-acting plus intermediate-acting insulin. Such a regimen is rarely appropriate for children and adolescents with type 1 diabetes, although it is occasionally seen for short periods in those experiencing a profound remission phase.

- **Two injections daily:**
  A mixture of short/rapid-acting and intermediate-acting insulin given before breakfast and before the main-evening meal. This can be custom mixed or supplied in a variety of pre-mixed insulins. This regimen is commonly used in younger children.
• **Three injections per day:**
  A mixture of short/rapid-acting and intermediate-acting insulin given before breakfast, short/rapid-acting insulin before the afternoon snack or main evening meal and intermediate-acting insulin in the evening.

  This regimen is commonly used in older children and teenagers when a 2 injection per day regimen is inadequate.

• **Four injections per day (basal-bolus regimen):**
  Short/rapid-acting insulin given before main meals, with intermediate-acting insulin given in the evening or in the morning and evening, or with glargine given once daily (morning or evening).

  This regimen is used extensively in adolescents and adults with type 1 diabetes. There are many variations of multiple injection regimens that are being tried.

• **Insulin pump therapy (continuous subcutaneous insulin infusion – CSII)**
  The pump contains a rapid-acting insulin analogue only and is programmed to deliver basal rates to match the individual’s needs. To cover meals and correct hyperglycaemia bolus doses are activated by the patient. It should be noted that short-acting insulins are not suitable for use in this regimen.

• **Other less common regimens**
  Other insulin regimens may be suitable for some patients based on their individual circumstances (eg 5 injections per day). Some of these are reported in the literature, but will not be further discussed here.

In a recent audit in NSW of type 1 diabetes in the 0-15 years age group, 61.3% were treated with 2 injections per day, 23.1% with three injections per day, 12.1% with four or more injections daily, 3.2% with one injection and 0.2% with insulin pumps2 (it should be noted that insulin pump programs have increased since this time). In an international multi-centre audit, number of injections per day increased with age and duration of diabetes as expected.3

**Use of Short-Acting Insulin**

In the above regimens, short-acting or rapid-acting insulins may be used. This is selected according to the individual’s needs, especially considering food intake and energy expenditure. The administration of rapid-acting analogues immediately before meals has been considered to be preferable to patients and families and data suggest reductions in post-prandial glucose rise.4,5 Insulin regimens using rapid-acting insulin analogues have been shown to be associated with improved metabolic control compared to those using regular insulin, however limited data in children has not confirmed this advantage.6 Patients using rapid-acting analogues in physiological regimens overall have fewer hypoglycaemic episodes than those using traditional insulins,7 however a review of studies in children including physiological and non-physiological regimens did not show an overall difference between rapid-acting analogues and short-acting insulin.62

In considering the timing of insulin injections, data are inconsistent on the optimal timing of short-acting insulin in relation to meals, however pharmacokinetic data suggest that short-acting insulin should be given before meals and preferably up to 30 minutes prior.8,63 It is recommended that rapid-acting insulins be given immediately prior to meals (within 15 minutes) to avoid hypoglycaemia.7 Giving rapid-acting insulin after meals has been shown to be a useful option, particularly in infants and young children with unpredictable eating patterns, allowing the dose to be judged after the amount of food ingested has been observed.5
Use of Intermediate and Long-Acting Insulins

Intermediate-acting insulin is generally isophane insulin, however intermediate-acting lente insulins are preferred by some, and some of the above regimens are also used with long-acting insulins. It is likely that new long-acting insulin analogues will find a major role in insulin regimens. One of the major limitations of regimens using conventional intermediate-acting or long-acting insulins is the known intra-individual variation in absorption, which is up to 45% in healthy subjects. These insulins are also problematical in that their peak of action may not suit the individual and they have dose dependent pharmacokinetics - ie peak effect and duration of effect vary with dose.

Insulin glargine is characterised by reproducibly flat basal profiles without significant dose effects on pharmacokinetics and is the first long-acting analogue available in Australia. Adult studies indicate similar HbA\textsubscript{1c} levels with insulin glargine but reduction in hypoglycaemia. There are insufficient data to draw conclusions on the efficacy of insulin glargine in children and adolescents, although data to date suggests similar efficacy but less hypoglycaemia.

Glargine seems most suited to use in basal-bolus regimens. However, trials are under way to investigate its use as the evening long-acting insulin in twice daily regimens in children.

Detemir insulin is another basal analogue under clinical trial. It is reported to have a more reproducible profile of action compared to isophane insulins and preliminary studies suggest reduction in hypoglycaemia with comparable HbA\textsubscript{1c} levels.

Regimens using Pre-mixed Insulins

Studies have not demonstrated any difference in glycaemic control between pre-mixed or custom-mixed insulin doses. Pre-mixed insulins are used in some centres for children on twice-daily injections and also to have a simplified regimen when adherence difficulties are present. They are usually used in pen devices. The potential disadvantage is that independent adjustment of the component insulins is not possible, thereby reducing adjustment flexibility.

Number of Injections per Day

In adults with type 1 diabetes, it is clearly established that multiple injection regimens (basal-bolus regimens) are superior to simpler injection regimens, preferably using rapid-acting analogues as the bolus insulin. In adolescents in the DCCT, the intensively treated group also had improved metabolic control and complication reduction, although this was part of a broader intensive management package. Weight gain and hypoglycaemia rates were increased in the intensively treated group. Most adolescents with type 1 diabetes should receive intensive therapy aimed at achieving glycaemic control as close to normal as possible to reduce the risk of microvascular complications.

In the pre-adolescent age group, the superiority of multiple injection regimens has not been clearly established and there continues to be wide differences in practice. It has been common in children to use the simplest insulin regimen that achieves the goals of therapy and thus many children are treated with 2 injections per day regimens. An additional rationale for this approach is that most children enter a partial remission phase making achievement of satisfactory glycaemia relatively easy during this time. However there are some paediatric centres that advocate multiple injection regimens for all children and adolescents from the start of therapy. A cross-sectional, multi-centre study of 2873 children and adolescents (age range 1–18 years) from 18 countries demonstrated no effect of the number of insulin injections per day on metabolic control. One large RCT (n=186, age 10-18 yrs) reported improved metabolic control with a 3 injections per day regimen compared to 2 injections per day.
In a recent NSW audit including 1190 subjects, number of injections was not a predictor of HbA1c, however multiple injections (more than 3 injections per day) was a predictor of hypoglycaemia.

**Total Daily Insulin Dosage and Distribution**

Insulin doses are tailored for each patient’s individual circumstances and requirements and change often in children and adolescents. Factors affecting insulin doses are age, weight, stage of puberty, duration of diabetes, food intake and distribution, exercise patterns, daily routines, results of monitoring and intercurrent illness. As a general guide, total daily insulin doses are as follows:

- Partial remission phase (any age): <0.5 unit/kg/day.
- Pre-adolescent children (beyond remission phase): 0.7 to 1 unit/kg/day.
- During puberty (beyond remission phase): 1.2-1.5 units/kg/day or higher.

The distribution of the total daily insulin dose varies greatly between individuals and requires individual titration. Typical distributions are discussed.

Twice daily insulin injection regimens: typically approximately 60-75% of the total daily insulin dose is given in the morning and 25-40% at night with approximately 30% of each dose being short-acting insulin.

Basal-bolus regimens: typically 40-60% of the total daily insulin dose is given as intermediate acting or long-acting insulin before bed, with the remainder divided up into pre-meal boluses.

Insulin pump therapy: typically 45-60% (lower end of this range in young children and higher end of this range often in adolescents) of the total daily insulin is given as basal insulin and the remainder is provided by pre-meal boluses.

Basal insulin requirements are usually considerably reduced (about 20%) when using physiological regimens involving glargine or insulin pumps.

**Insulin Administration**

**Insulin absorption**

The rate of absorption of insulin is affected by many factors as follows:

- **Insulin type**
- **Injection site**

Soluble insulin is absorbed more slowly and consistently from the subcutaneous site compared to intramuscular injections. There is less difference with rapid-acting analogues. Thus subcutaneous injections are preferred. Insulin is also absorbed at different rates from different anatomical locations. Absorption is quickest from the abdomen, followed by the buttock and slowest from the thigh (non-exercising). However, these differences are less pronounced with both rapid-acting and long-acting analogues. Thus it is recommended that short/rapid-acting insulin or mixed doses of insulin be injected in the abdomen. It is recommended that evening doses of intermediate-acting insulin be given in the (non-exercising) thigh to optimise the overnight profile of action. The upper arm is used by some for injections, however this is not generally recommended in younger children because of the thin layer of subcutaneous tissue at this site and the increased risk of intramuscular injection.

Rotation between different anatomical sites from day to day is not recommended since this has been shown to be associated with higher and more variable blood glucose levels.
Injection depth

Table 5.1: Mean Cutis/Subcutis Thickness

<table>
<thead>
<tr>
<th>Site</th>
<th>Male Child</th>
<th>Female Child</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdomen</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>- thigh anterolateral</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>- thigh anterior</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Buttock</td>
<td>19</td>
<td>26</td>
</tr>
</tbody>
</table>

Adapted from Birkebaek NH, Johansen A, Solvig J. Diabetic Medicine 1998; 15(11):965-971.27

In assessing the suitability of different injection sites, studies have examined subcutaneous tissue thickness and site of deposition of injections.27-29 There is a significant risk of intramuscular injections (and hence more rapid absorption) which is increased in lean individuals, especially boys. This can be minimised by using a two finger pinch technique and an injection angle of 45 degrees. Shorter needles reduce the risk of intramuscular injections.30 In general most children and adolescents should use 8 mm needles with a pinch-technique and 45 degree angle, and if lean and using pens, 5 or 6 mm needles may be appropriate.

Intramuscular injection of insulin can increase absorption from the thigh by up to 50%, but it has been reported that there is no difference between subcutaneous and intramuscular absorption from the abdomen.31

- Insulin dose
  Insulin has dose-dependent absorption kinetics. Small doses are absorbed more quickly than large doses.32

- Temperature
Insulin absorption is increased with increased ambient and body temperature, related to increased subcutaneous blood flow. Therefore care should be taken in hot weather and warm baths/saunas after insulin injections.

- **Exercise**
  Exercise increases insulin absorption, again predominantly related to increased subcutaneous blood flow. For this reason the thigh is not recommended prior to exercise.

- **Age of child and fat mass**
  Large fat mass is associated with increased subcutaneous tissue thickness and therefore slower absorption. Since younger children are often leaner, insulin absorption is often faster.

- **Presence of lipohypertrophy or lipoatrophy**
  Adverse changes at the injection site can considerably affect absorption. Lipohypertrophy is a common problem in diabetes management and absorption of insulin from these sites is delayed and erratic. This can be avoided by moving the injection site from day to day within the same anatomical area of the body, or periodically moving to another anatomical site. Prevalence of lipohypertrophy has been estimated at 20-30% in patients with type 1 diabetes. Other factors associated with risk of lipohypertrophy are presence of insulin antibodies.

  Lipoatrophy is now much less common with modern pure insulins. However, it still occurs in a small number of subjects and also leads to erratic insulin absorption. An immunological basis has been suggested, including sensitivity to components of the insulin preparation or latex.

**Insulin Delivery Devices**

**Insulin syringes and pens**
Insulin syringes are disposable plastic syringes, designed for single use only and are available in a range of sizes (25, 50 and 100 units) and needles lengths (8 mm, 12 mm and 12.7 mm). The lowest volume syringe that will hold the required dose should be used to increase accuracy of dose. It is common for children receiving mixed injections of insulin to have these drawn up into the same syringe to reduce the number of injections. Not all insulin types are compatible for mixing - (see chapter 4). U100 insulin is exclusively used in Australia, although occasionally dilution is performed for babies or infants requiring very small doses.

Insulin pens are also available which contain pre-filled cartridges of insulin. Cartridges are available for the rapid-acting analogues, short-acting and isophane insulins but not for lente and ultralente insulins which are not stable in pen systems. Needle lengths available are 5, 6, 8, 12 and 12.7 mm. Families should know how to use an insulin syringe even if the delivery device is primarily a pen in case of unexpected failure of the pen. Disposable pens are also available for some insulin types which gives added convenience of being able to have pens stored in various locations. Increased satisfaction with pens has been shown in some studies. Side-effects are not different between syringe or pen delivery.

The accuracy of pen versus syringe delivery has been studied. In one study, attempting a dose of 1 unit of insulin was found on average to deliver a mean of 0.89 units with a pen and 1.23 units with an insulin syringe (small but significant differences). Another study found pens more accurate than syringes for doses less than 5 units, but no differences for larger doses. Available pens generally are adjustable in 1 unit increments, although one pen is available that can be adjusted in 0.5 unit dose increments.
**Automatic injection devices**

Devices that automatically insert the needle into the skin are available for attachment to some pens or for syringes. These may be preferred by some patients who find it difficult to insert the needle through the skin and also because the needle is hidden until the device is activated. Reduced pain perception has been reported with the use of an automatic injection device.\(^{68}\)

**Jet injection devices**

A jet injector uses high pressure to form a thin stream of insulin that penetrates the skin. Metabolic control has been reported to be similar in the short-term but patient acceptance is less than for needle injections\(^ {39}\) and higher adverse event rates are reported.\(^ {40}\) Jet injectors may have an occasional role for extreme needle phobia.

**Indwelling cannulas**

Indwelling subcutaneous cannulas are in use in some centres as an alternative to repeated needle injections to reduce injection pain, especially at the onset of diabetes.\(^ {69}\) Cannulas are usually replaced very 4 to 5 days. Insulin absorption and metabolic control has been reported to be unchanged,\(^ {41,42}\) making this a possible option if preferred by the patient.

**Insulin pumps (CSII)**

Insulin pumps have been proposed as offering more physiological insulin delivery and therefore advantages in metabolic control, reduction in hypoglycaemia and improvement in lifestyle flexibility and patient acceptability (see also insulin pump adjustments).

A meta-analysis of 12 RCT’s, mainly in adults but with some adolescents, reported that pump patients had lower mean BG level by 1.0mmol/L, lower HbA1c by 0.51% and lower insulin requirements by 14% compared to patients on optimised insulin injections.\(^ {43}\) In another meta-analysis including 52 studies with 1547 adult, adolescent and paediatric subjects, improvement in glycaemic control was also reported.\(^ {44}\) Overall, hypoglycaemia is markedly less frequent with pumps than in intensive injection regimens.\(^ {45}\) It has been suggested that pump therapy increases the risk of diabetic ketoacidosis, but this may only be with pumps used prior to 1993.

There are limited RCT’s in adolescents and none exist for children. Observational studies have reported significant improvements in HbA1c, reduction in hypoglycaemia and higher satisfaction,\(^ {46-48}\) but not in all studies. A NICE technical appraisal recommended that insulin pump therapy should be available as an option for people with type 1 diabetes who have failed multiple-dose insulin therapy (HbA1c >7.5% or >6.5% in the presence of complications, or disabling hypoglycaemia).\(^ {49}\) Full economic analysis that takes into account possible long-term reduction in morbidity and mortality has not been possible. However, insulin pump therapy costs more than injection therapy in the short-term.

Management with insulin pump therapy is increasing in Australia, however not all patients are suitable and individual units should have suitability assessment criteria. Accessibility to this therapy is also currently significantly limited by financial costs. Additional training and expertise for health care professionals is required for units initiating and maintaining insulin pump therapy.

**Practical Aspects of Insulin Administration**

Disinfection of the skin is not necessary prior to insulin injections. However, injections should be given through clean, healthy skin.\(^ {7}\) Some patients inject through clothing at times for reasons of convenience and no significant problems have been reported with this practice.\(^ {50}\)
The age at which children can reliably draw up and administer an insulin injection or use an insulin pen varies markedly between children. Many children assist in the insulin injection routine from 9-10 years of age and many can easily use an insulin pen from that age. Drawing up of two different insulin types into a syringe requires more concentration and dexterity and is often not appropriately mastered until sometime after 10 years of age. Appropriate supervision by carers is recommended to avoid insulin dose errors or omissions which have not been quantified, but practical experience suggests that these are common.

While insulin syringes and needles are recommended for single use only, surveys indicate that some patients re-use syringes and needles and that this is not associated with increased infections or other adverse events.

Insulin syringes and pen needles need to be disposed of in a safe and hygienic way. Needles should not be recapped to avoid the risk of needle-stick injury. Approved sharps containers should be provided and disposed of according to local authority regulations. Unfortunately there are not yet uniform or appropriate arrangements for sharps disposal in all areas of Australia.

Thorough re-suspension of intermediate-acting and long acting insulins that are in suspension (all currently available types, except glargine) is critical to avoid dosage error and variation and many patients re-suspend inadequately. Pens containing isophane need to be tipped at least 20 times for adequate mixing.

**Insulin Adjustment**

Appropriate adjustment of insulin doses is critical if goals of diabetes therapy are to be achieved. This is particularly important in children and adolescents in whom insulin requirements can change rapidly with growth and puberty and changes are also needed to cope with variations in activity and food intake and intercurrent illness. However insulin adjustment is a skill that is often not well mastered by patients and families with diabetes. Insulin adjustment by a diabetes nurse educator has been shown to improve glucose control and strategies employing electronic transmission of glucose monitoring to a diabetes centre for advice have been reported to be successful.

Children and their families need to acquire skills in the following areas of insulin adjustment:

- **Adjusting usual doses of insulin based on blood glucose patterns over several days or longer**

  Patients on insulin injection therapy are advised to make adjustments to the appropriate dose in approximately 10% increments and observe the effects of this over several days before making further changes. Half unit increments can be made in patients on small doses (<5 units). Patients on insulin pump therapy need to evaluate whether changes need to be made in basal or bolus doses from their monitoring and basal rate tests; incremental changes of 5-10% are also appropriate. More rapid changes may be appropriate in some circumstances eg severe hypoglycaemia.

  The routine use of sliding scales for daily insulin adjustment has not been systematically studied. However, it is generally not recommended as a primary tool for insulin adjustment because of its retrospective nature. Used in in-patients, sliding scales have been shown to be inferior to alternative management strategies.
**Pro-active day to day adjustments to insulin based on activity and food intake**
These adjustments should be pro-active and, as far as possible, take into account activity levels and meals during the period of action of the dose. Larger short-term adjustments can sometimes be needed eg up to 50% reductions for vigorous or prolonged exercise.

**Adjustments to correct the current BG level when it is outside the desired range**
Patients and families should have skills to correct high BG levels when these are not transient. Recommendations are usually to give an additional short/rapid-acting insulin dose of between 5% and 10% of the total daily insulin dose to correct high BG levels without significant ketones. However, higher doses may be required for ketosis and sick days (see chapter 11). Formulas are also available to guide correction doses and these are often used by patients on insulin pumps. Patients who give additional corrective doses when needed between usual doses have been shown to have improved metabolic control.

**Insulin pump adjustments**
Insulin pump therapy should be initiated and supervised by a specialised multi-disciplinary team trained in pump therapy in children and adolescents with diabetes.

Rapid-acting insulin analogues are recommended for pump use. As a guide, patients starting on insulin pump therapy have the previous total daily dose on injections reduced by approximately 25%. The pump is initially programmed to deliver 45-60% of the new total daily dose as the basal insulin. Often, a single hourly basal rate is used over the 24 hours and this is subsequently modified on the basis of blood glucose monitoring. Adjustments to hourly rates are usually no more than 10% at a time. Most pump users have 2-5 different basal rates for different periods of the day. For example, it is common for people to need a little less basal insulin in the late evening (between 8pm and 2 am) and during the day when more active (between 10 am and 4 pm). Slightly higher basal rates are often needed in the early evening (from 4 pm to 8 pm) and morning hours (from 2 am to 10 am) because of the tendency of the blood glucose to rise toward morning (the dawn phenomenon). Many prepubertal children need a higher basal rate late in the evening (9 pm to 12 midnight).

Bolus doses are needed for meals and for correction of hyperglycaemia. A useful guide to estimate bolus doses for meals is to employ the ‘500’ rule (the total daily dose is divided into 500 to estimate the number of gm of carbohydrate that 1 unit of insulin will cover). This is then used to derive a more practical figure of how many units of insulin are needed to cover each 15 gm exchange of carbohydrate in each meal or snack (for a patient on 50 units of insulin per day, a 1.5 unit bolus would be needed for each 15 gm exchange of carbohydrate).

It is recommended that calculations be made at least to the half exchange, and some advocate calculations to the gram if practical.

Correction boluses to correct hyperglycaemia can be given at any time or added to meal boluses. A useful guide to estimate correction doses is to employ the ‘100’ rule (the total daily dose is divided into 100 to estimate the number of mmol/L that the blood glucose will fall by giving 1 unit of insulin). For example, for a patient on 50 units of insulin per day, the blood glucose should fall by approximately 2 mmol/L for each additional 1 unit of insulin. This calculation can also be used to estimate a negative correction to correct for hypoglycaemia (in a patient on 50 units of insulin a day, giving 1 unit less at meal times should allow the blood glucose to rise by 2 mmol/L).

Correction doses given for hyperglycaemia should take into consideration the residual effect of any previous meal or correction bolus dose. A useful guide is to use the ‘unused bolus rule’ (approximately 30% of a rapid-acting insulin bolus is absorbed each hour). The correction dose should be reduced accordingly. For example, if 5 units had been given as a meal bolus 2 hours previously, 60% would have been absorbed and the remaining 40% or 2
units would still be exerting an effect. This should be subtracted from any correction dose. The pump should not be used to correct hyperglycaemia when ketones are present - control should be regained with an insulin injection via pen or syringe (see chapter 11).

Basal rates, meal bolus doses and correction bolus doses calculated by the above methods are a starting point. Fine-tuning adjustments are then made on the basis of blood glucose response and patterns. Adjustment of basal rates is assisted by doing basal rate tests, which involve testing different periods of the day by omitting or having a carbohydrate-free main meal and snack and monitoring blood glucose frequently during that period - if the basal rate is appropriate, the blood glucose should remain steady or rise or fall only minimally during that time.

Pumps are becoming available that assist the user in making many of the adjustment calculations.

Cost Issues

A recent Health Technology Assessment attempted to establish the cost effectiveness of Continuous Subcutaneous Insulin Infusion versus Multiple Daily Injections. The results were inconclusive due to the paucity of reliable information about cost effectiveness derived from the formal clinical evidence. Another cost effectiveness analysis using a Markov model concluded that Continuous Subcutaneous Insulin Infusion was most cost effective in patients who required more frequent admission to hospital and had more frequent severe hypoglycaemic events. Both studies were based on the UK health system and may not be generalisable to the Australian health care system.

The Evidence

The evidence relating to the number of daily injections to diabetes control is listed in Evidence Table 5.1.

- In adolescents in the DCCT, the intensively treated group had improved metabolic control and complication reduction, although this was part of a broader intensive management package.17,18 (II)
- A cross-sectional, multi-centre study of 2873 children and adolescents (age range 1-18 years) from 18 countries demonstrated no effect of the number of insulin injections per day on metabolic control.3 (IV)
- One large RCT (n=186, age 10-18 yrs) reported improved metabolic control with a 3 injections per day regimen compared to 2 injections per day.20 (II)
- A NSW audit including 1190 subjects, number of injections was not a predictor of HbA1c, however multiple injections (more than 3 injections per day) was a predictor of hypoglycaemia. (IV)

The evidence on the length of needle for the injection for insulin therapy in the treatment of children with type 1 diabetes is contained in Evidence Table 5.2.

- A randomised controlled trial in 50 children with type 1 diabetes demonstrated that using shorter needles (8 mm compared to 12.7 mm) resulted in significantly fewer accidental intramuscular injections of insulin.30 (II)

The evidence on whether children and adolescents with type 1 diabetes should be treated with insulin pump therapy is contained in Evidence Table 5.3.

- A meta-analysis of 12 RCT’s mainly in adults but with some adolescents reported that pump patients had lower mean BG level by 1.0 mmol/L, lower HbA1c by 0.51% and lower insulin requirements by 14% compared to patients on optimised insulin injection.43 (I)
• In another meta-analysis including 52 studies with 1547 adult, adolescent and paediatric subjects on insulin pumps, improvement in glycaemic control was also reported.\textsuperscript{44(I)}
• This meta-analysis found that hypoglycaemic episodes are less frequent with pumps than in intensive injection regimens.\textsuperscript{44(I)}
• A National Institute of Clinical Excellence (NICE) Technology Appraisal Report from the UK referred to in Evidence Table 5.3 recommended that insulin pump therapy should be available as an option for people with type 1 diabetes who have failed multiple-dose insulin therapy (HbA\textsubscript{1c} >7.5\% or >6.5\% in the presence of complications, or disabling hypoglycaemia).\textsuperscript{49(T)}

Additional Technical Reports and Consensus Statements used to formulate the recommendations and principles of clinical practice are listed in Evidence table 5.4.

Recommendations and Principles
• There is a variable effect of the number of daily injections on metabolic control.\textsuperscript{2,3,20(II, IV)}
• Intensive management (including multiple daily injections or pump therapy, education, intensive monitoring and psychosocial support) of type 1 diabetes in adolescents improves metabolic control and reduces the risk of microvascular complications.\textsuperscript{17,18(II)}
• Many insulin regimens are used in the treatment of type 1 diabetes in children and adolescents. Any insulin regimen has to be considered in the wider context of a total diabetes management package, which must include dietary management, exercise and physical activity, blood glucose monitoring, initial and ongoing education, regular medical follow-up and psychological care.\textsuperscript{1,61(C)}
• Insulin doses should be tailored for each patient’s individual circumstances and requirements, taking into account age, weight, stage of puberty, duration of diabetes, food intake and distribution, exercise patterns, daily routines, results of monitoring and intercurrent illness.\textsuperscript{1,61(C)}
• It is recommended that insulin be injected in the abdomen, buttock or non-exercising thighs. The upper arm is generally not recommended because of the thin layer of subcutaneous tissue at this site and the increased risk of intramuscular injection.\textsuperscript{1,61(C)}
• There is a significant risk of accidental intramuscular injections (and hence more rapid absorption) especially in lean individuals. This can be minimised by using a two finger pinch technique, an injection angle of 45 degrees and 8 mm needles.\textsuperscript{30(II)}
• 5 or 6 mm needles may be appropriate in lean children or those using pens.\textsuperscript{55,62(C)}
• Insulin pumps should be considered as a treatment option.\textsuperscript{43,44,49(I)}
• Insulin pump therapy should be initiated and supervised by a specialised multi-disciplinary team trained in pump therapy in children and adolescents with diabetes.\textsuperscript{49(C)}
• Insulin syringes and pen needles need to be disposed of in a safe and hygienic way. Needles should not be recapped to avoid the risk of needle-stick injury. Approved sharps containers should be provided and disposed of according to local authority regulations.\textsuperscript{55(C)}
• Health care professionals should educate and encourage children and their families to acquire skills in insulin adjustment.\textsuperscript{55(C)}

I = Evidence from a systematic review of all relevant controlled trials
II = Evidence from at least one properly-designed RCT
C = Consensus statement endorsed by professional organisations

Reference List


42. Hanas SR, Ludvigsson J. Metabolic control is not altered when using indwelling catheters for insulin injections. Diabetes Care 17(7):716-718, 1994


68. Owens DR, Coates PA, Luzio SD, Tinbergen JP, Kurzhals R: Pharmacokinetics of 125I-labeled insulin glargine (HOE 901) in humans. Diabetes Care. 22(1):177-184, 1999


70. Owens DR, Coates PA, Luzio SD, Tinbergen JP, Kurzhals R: Pharmacokinetics of 125I-labeled insulin glargine (HOE 901) in humans. Diabetes Care. 22(1):177-184, 1999


Chapter 6: Glycaemic Control

Intensive Diabetes Management

The Diabetes Control and Complications Trial (DCCT) confirmed the benefit of maintaining near normoglycaemia in reducing the development and progression of diabetic microvascular complications in adolescents and adults.\(^1,2\) Even in patients with the same HbA\(\text{1c}\) intensive therapy was superior to conventional.\(^3\) In the DCCT there was no lower threshold of HbA\(\text{1c}\) below which the risk of complications was eliminated, and any improvement in HbA\(\text{1c}\) conferred a reduction in risk.\(^3,4\) Longer follow-up of patients after the completion of the DCCT, in the EDIC (Epidemiology of Diabetes Interventions and Complications) study showed increasing reduction of microvascular and macrovascular complications with optimal early metabolic control.\(^5,6\)

Achieving excellent glycaemic control is more difficult in children and adolescents than in many adults because of the following factors:

- Insulin deficiency is often more complete.
- Variable food intake.
- Recurrent infections during childhood.
- Variable exercise patterns.
- Varying rates of growth and development.
- Hormonal changes, including insulin resistance during puberty, necessitating high and changing insulin requirements.
- Behavioural problems associated with psychosocial difficulties.
- Conflict between being dependent upon parental involvement and wish for increased independence during adolescence.
- Difficulty with adherence to diabetes regimens, particularly during adolescence when insulin omission and infrequent blood glucose monitoring is common (thereby preventing the benefits of more intensive insulin regimens).

Risks and Side Effects of Intensive Diabetes Management

Long-term benefits of intensifying management need to be weighed against the risks of:

- Increased frequency and severity of hypoglycaemia.\(^2\)
  - In a longitudinal Australian study, severe hypoglycaemia was associated with lower verbal and full-scale intelligence quotient scores. Attention, processing speed, and executive skills were particularly affected in children with younger onset of diabetes.\(^7\)
- Weight gain.\(^2\)
- Increased risk of precipitating rebellion and rejection of diabetes routines altogether.

Indicators of Poor Glycaemic Control

The indicators of poor glycaemic control may include the following clinical and biochemical features:

- Polyuria and polydipsia.
- Enuresis and nocturia.
- Blurred vision.
- Weight loss or failure to gain weight with growth.
- Poor growth.
• Pubertal delay.
• Skin infections (staphylococcal and candidal).
• Deteriorating school performance and absenteeism.
• Signs of diabetes complications.
• Elevated HbA\textsubscript{1c} and fructosamine.
• Elevated blood lipids.

**Glycaemic Goals**

The National Institute of Clinical Excellence Guideline ‘Type 1 Diabetes (Childhood): Diagnosis and Management of Type 1 Diabetes in Primary and Secondary Care’ makes the following recommendation: Children with type 1 diabetes and their parents should be informed that the optimal target for long-term glycaemic control is an HbA\textsubscript{1c} level of less than 7.5% without an increase in hypoglycaemia.

In England an audit of children (0-16years) with type 1 diabetes found that in all age groups fewer than 20% of children managed to achieve a HbA\textsubscript{1c} level of 7.5% or below.\textsuperscript{8}

In 1999 in NSW, fewer than 25% of children and adolescents had a HbA\textsubscript{1c} levels <7.5%, with the median HbA\textsubscript{1c} being 8.2% [interquartile range 7.6-9.1%].\textsuperscript{9,10}

In order to achieve an HbA\textsubscript{1c} <7.5%, everyday blood glucose targets (ie. glycaemic goals) need to be defined and while they still need to be individualised reasonable values to aim for are:

- A pre-prandial blood glucose level of 4-8 mmol/L.\textsuperscript{11}
- A post-prandial blood glucose level of less than 10 mmol/L.\textsuperscript{11}

In very young children, in whom there is the greatest concern about the effects of hypoglycaemia on the developing brain, glycaemic targets need to be at the upper part of these ranges or a little higher.

Glycaemic targets need to take into account such additional factors as:

- Hypoglycaemia unawareness.
- Unpredictability of hypoglycaemia in some children.
- Past history of recurrent severe hypoglycaemia.
- Ability to comply with blood glucose monitoring.
- Presence of psychological or psychiatric disturbances.
- Presence of any coexisting disease which may affect the diabetes (eg infections).
- Presence of any coexisting disease (eg epilepsy).

Realistic goals for individual patients have to be reassessed at each visit. Appropriate therapeutic strategies to reach the goals have to be clearly formulated, taking into consideration the psychosocial and developmental aspects of the child and family.

Patients during the pubertal phase may have particular difficulties in maintaining good control due to physiological and psychological changes, and therefore frequently require special counselling services and support.

While blood glucose testing provides much data on glycaemic control, it also has placed a very great burden on the child, adolescent and family in the quest for achieving optimal blood glucose levels. Health care professionals must avoid using judgemental terms such as good or bad control and aim to achieve good communication, understanding and cooperation.
Parameters of Glycaemic Control

Prior to 1978 urine testing was the only means of monitoring glycaemic control. Unfortunately urine tests do not reliably reflect blood glucose values.\textsuperscript{11-14}

Several different parameters are used to measure glycaemic control. These include:

- Blood glucose levels.
- Glycated haemoglobin (eg HbA\textsubscript{1c}).
- Glycated serum protein (eg fructosamine).

Blood Glucose Monitoring

Blood glucose measurement is essential in the management of children and adolescents with diabetes for the following reasons:

- To monitor daily control.
- To detect hypoglycaemic and hyperglycaemic episodes.
- To make possible the safe management of acute illnesses at home.

The frequency of blood glucose monitoring should be adapted to the insulin regimen, the age of the child and the stability of the diabetes. Frequent daily blood glucose monitoring as part of a package of care is associated with improved glycaemic control.\textsuperscript{11,15}

Older children and adolescents will be able to measure their own blood glucose levels while the younger child will be dependent on his/her parent or care giver for glucose monitoring.

Information obtained from blood glucose monitoring should be used in association with HbA\textsubscript{1c} and clinical parameters to evaluate and modify management to improve glycaemic control.

Timing of blood glucose testing

The blood glucose levels should be measured:

- At different times of the day pre- and post-prandially in order to obtain a profile over the 24 hours.
- Before, during and after sport.
- During intercurrent illnesses.
- If hypoglycaemia is suspected.
- Following treatment for hypoglycaemia.

Most children on two injections a day do 3-4 tests a day; pre-breakfast, pre-dinner and the third test at varying times to obtain pre-lunch, bedtime and night-time data.

More tests may be needed in multiple dose insulin regimens\textsuperscript{11} or for insulin pump use.

If the diabetes is very stable, then the frequency of testing may be reduced (eg to obtain a profile over the day several times a week).\textsuperscript{11} Similarly if there is resistance to regular blood glucose testing then a compromise situation of reduced testing should be negotiated with the older child or adolescent.

Options for reduced testing include a:

- Full profile over the day several times a week with no intervening tests.
- Composite profile obtained by a single blood test each day taken at different time points.
Techniques for blood glucose testing

Test strips and meters are sufficiently accurate and precise when used properly according to the manufacturer’s instructions. Correct technique includes:

- Following manufacturer’s instructions.
- Washing and drying of hands (to reduce infection risk and to wash glucose off fingers).
- Calibrating the meter for the lot number of the reagent strips.
- Using control solutions periodically with known glucose concentrations to assess meter accuracy.
- Performing the test within defined temperature and humidity limits.
- Use of sufficient blood for the strip.
- Proper storage of blood glucose reagent strips and use before expiry date.

Devices for blood glucose testing

Meters and Reagent Strips

Meters are available for bedside or self-monitoring of blood glucose levels. They are used in conjunction with blood glucose reagent strips which can be divided into those which result in:

- Change of colour.
- Change in electrical current (bioelectric).

Those that depend on a change of colour can be read either visually against calibrated colour blocks or with a reflectance blood glucose meter. Reflectance meters have largely been superseded.

Most modern meters employ bioelectric strips that can only be read in the meter and cannot be read visually. Bioelectric strips usually require less than 5 microlitres blood (a large drop of blood measures 50 microlitres). Many meters are able to store results of previous readings, including date and time of the reading. Some meters are able to download the data to a computer and appropriate software programmes are able to transform the data into a variety of display formats.

All children and adolescents should have an appropriate meter. Rebates for meters are available to those in most health insurance plans. Families suffering financial hardship are able to obtain these devices through various government safety-net schemes (details available through diabetes centres and Diabetes Australia).

Finger-prickers and other prickers

Special spring-loaded finger-pricking devices are available in order to reduce pain. Some devices are able to vary the depth of penetration by the lancet or utilise lancets with finer gauges. These are highly recommended for use in children and adolescents. Other devices are available which allow blood to be sampled from other parts of the body (e.g., forearm). There is a strong correlation between forearm blood glucose monitoring and finger blood glucose monitoring.16-20

Continuous glucose monitoring systems (CBGM)

Intermittent capillary blood glucose monitoring gives a limited glimpse of blood glucose levels. CBGM may be a useful tool in giving detailed information on blood glucose trends during stabilisation of diabetes or during initiation and monitoring of insulin pump therapy.21 Invasive and non-invasive types of CBGM exist. Both types of CBGM need to be calibrated against capillary samples.
Invasive CBGM
Invasive CBGM monitoring systems available in Australia measure interstitial blood glucose via an indwelling sensor in the subcutaneous tissue of the abdomen or buttocks. The glucose levels measured by this technique correlate well with those obtained by conventional blood glucose monitoring.\(^{22-25}\) These monitors give useful insight into the individual blood glucose profile and are especially useful in detecting asymptomatic hypoglycaemia\(^{26,27}\) and may assist in stabilisation and motivation of patients.\(^{28}\) At present they are only available for short-term use in individual patients attending large paediatric centres.

Non-invasive CBGM
These devices have not been released in Australia.

- **Electrochemical enzyme sensor**
  This device is worn like a wristwatch and provides frequent glucose readings. Glucose is extracted non-invasively via reverse iontophoresis for collection in a gel disc biosensor.\(^{29}\) The blood glucose readings correspond well with conventional finger prick blood glucose monitoring (\(r = 0.85\) in the clinic setting and \(0.90\) in the home settings).\(^{30}\) Mild skin reactions can occur at the site of the adhesive pad.\(^{31}\)

- **Infrared spectroscopy**
  Infrared spectroscopy technology is also being developed to measure blood glucose non-invasively.\(^{32-34}\)

**Record keeping and review of records**
A daily record of all testing performed should be kept in a logbook and this should be reviewed frequently to ensure optimal adjustments in management are made.

The use of memory-glucose meters without daily reviewing of glucose levels is not recommended as patterns of glycaemic changes may not be appreciated by the child or adolescent and the family, and appropriate changes in insulin dosage may not be made.

The record should be available at the time of consultation and should contain:

- Blood glucose levels.
- Time and date of test.
- Insulin dosage.
- Events which could influence metabolic control, such as birthday parties, illness, exercise, menses, etc.
- Hypoglycaemic episodes.

A variety of logbooks are provided by different companies. It is necessary to choose the most suitable for the child’s care. Depending on the child’s age, it is helpful to encourage his/her involvement in documenting blood glucose levels and activities. There are logbooks for young children that include stickers or diaries for teenagers which include a section for recording blood glucose levels, insulin doses and activities.

The family should understand that the record book is not a ‘report card’ on which their efforts will be judged, but rather a diary of blood glucose levels, insulin dosages and special comments.

The causes of a discrepancy between the logbook and other indices of glycaemic control (clinical, HbA1c) include:

- Poor technique of blood glucose measurements.
- Falsification of results.
• Failure to test at different times in order to detect episodes of unsuspected hyperglycaemia (eg testing pre-prandially only).
• Malfunction of the meter.

**HbA1c**

The most appropriate measure of long-term glycaemic control is the use of HbA1c, a subfraction of glycated haemoglobin. It is the only measure of glycaemic control that has been shown to be associated with long-term complications of diabetes and best reflects glycaemic levels over the preceding 2-3 months.15,35

Glycated haemoglobin (HbA1) occurs in several variants and can be measured using several different methods. Haemoglobin A1 contributes <10% of the total haemoglobin. Use of cation-exchange chromatography has shown that haemoglobin A1 can be separated into at least three components HbA1a, HbA1b and HbA1c. These components have been found to be elevated in diabetic patients. Studies have found a strong relationship between HbA1c and fasting blood glucose levels over the preceding weeks in both adults and children with diabetes, and in non-diabetic subjects.36,37 HbA1c is the most frequently used measure of glycated haemoglobin in clinical practice.

HbA1c is detected by high-pressure cation-exchange chromatography, electrophoresis or immunoturbidimetric methods.15

The non-diabetic reference range for HbA1c should be established by each laboratory but is approximately 4-6%.

The International Federation of Clinical Chemistry and Laboratory Medicine has recommended the adoption of new reference ranges for HbA1c based on more accurate mass spectroscopy methods. These would reduce the non-diabetic reference range for HbA1c by 1.5-2.0%. Currently the IFCC recommendations are being considered and if adopted, extensive education would need to be provided to both patients and health care professionals.38

The American Diabetes Association recommends measuring the HbA1c at least twice per year in patients who are meeting treatment goals, and more frequently (quarterly) in those whose treatment has changed or who are not meeting glycaemic goals.12 Other professional bodies suggest similar monitoring.11,39 In Australia Medicare reimburses the cost of four HbA1c measurements in any 12 month period. However in children under the age of 6 years with unstable diabetes, Medicare reimburses six HbA1c measurements annually.

HbA1c results should be available at the time of the clinic visit, as this influences the outcome of the consultation in a substantial proportion of cases.39,40 Although a HbA1c <7.5% should be aimed for, the target that is achieved for an individual will depend on the interaction of the many factors. In children under the age of 6 years, the HbA1c target may be set a little higher because of the dangers of hypoglycaemia to the developing brain.

HbA1c values need to be interpreted in the context of blood glucose readings and clinical parameters (eg a child with a low HbA1c may be experiencing asymptomatic hypoglycaemia).

Whilst treatment aims to achieve near normoglycaemia, it must be noted that even in the DCCT, the mean HbA1c of the intensively treated adult group was still elevated at 7.2% (non-diabetic range <6.05%) and was 8.1% in the adolescent cohort of the study. It is relevant that adolescents in the DCCT had significantly higher HbA1c levels than adults in both intensively treated and conventionally treated groups. Despite these higher HbA1c levels they experienced more severe and moderate hypoglycaemic episodes underlining the difficulties in achieving ideal metabolic control in this age group.1,2

Children whose HbA1c is rising or persistently elevated should have all aspects of their diabetes management reassessed.
Fructosamine

Fructosamine measures the glycation of serum proteins. The term ‘fructosamine’ refers to the nature of the chemical bond between glucose and the amino acid on the protein and has nothing to do with fructose. Because the turnover of albumin is more rapid than that of haemoglobin, HbA1c and fructosamine measurements reflect different periods of blood glucose control (3 months versus 3 weeks).12

Urine Testing for Glucose

Urinary glucose measurements are not recommended for monitoring glycaemic control because of poor correlations between glucose levels in the blood and urine.11-14 Urinary glucose levels will not provide any information about hypoglycaemia (the renal threshold for glycosuria is usually approximately 10 mmol/L).12 If blood glucose monitoring is not possible because of psychological reasons, then urine tests using glucose-specific strips will at least provide some information.

The testing of urine for glucose reflects glycaemia a few hours preceding the test. The accuracy of the test in evaluating glucose control may be increased if a urine test is performed on a second specimen of urine obtained 30 minutes after initially emptying the bladder.

Urine testing for glucose is relatively inexpensive and is performed using glucose-specific dipsticks for glucose alone, or combined with ketonuria testing or as part of a multiple urine-testing strip.

The manufacturer’s instructions suggest that a urinary glucose reading of:

- 5.5 mmol/L corresponds to a trace of glycosuria.
- 14 mmol/L corresponds to + of glycosuria.
- 28 mmol/L corresponds to ++ of glycosuria.
- 55 mmol/L corresponds to +++ of glycosuria.
- ≥111 mmol/L corresponds to ++++ of glycosuria.

Testing for Ketones

Ketone acids include acetoacetic acid and beta-hydroxybutyric acid. Acetoacetic acid spontaneously degrades to form a molecule of acetone and carbon dioxide. The blood levels of beta-hydroxybutyric acid are usually four times that of acetoacetic acid.41 During hypoxia, severe shock or when there is lactic acidosis, this ratio may be greatly increased and a measure of the acetoacetic acid level may greatly underestimate the actual total level of ketone acids.

The recently released meter and strips for bedside or home blood ketone testing measures beta-hydroxybutyrate levels whereas urine ketone strips only measure acetoacetic acid.

Blood ketones

A meter that reliably measures blood ketone (beta-hydroxybutyrate) levels is available for home or bedside use. Specific strips for this purpose need to be used. The manufacturer’s instructions need to be followed carefully. The same meter, using different strips, can also be used to measure blood glucose.

In a study of children measuring β-hydroxybutyrate 8 times per day for 2 weeks, only 6.0% of the β-hydroxybutyrate measurements were ≥0.2 mmol/L.42
As a general guide to aid interpretation of blood ketone readings the manufacturer’s recommendations indicate:

- The normal range is <0.6 mmol/L.
- 0.6 - 1.5 mmol/L indicates developing ketosis.
- ≥1.5 mmol/L is significantly elevated and at risk of developing diabetic ketoacidosis.

**Urine ketones**

The testing of urine for the presence of ketonuria is an essential part of diabetes monitoring. Urine test strips need to be stored in an airtight container and used within their expiry date as per the manufacturer’s instructions.

The manufacturer’s instructions suggest that a urinary ketone reading of:

- 0.5 mmol/L corresponds to a trace of ketones.
- 1.5 mmol/L corresponds to small ketones.
- 4 mmol/L corresponds to moderate ketones.
- ≥8 mmol/L corresponds to large ketones.

Urine should be tested for ketones in the following circumstances:

- If vomiting occurs.
- Any time the blood glucose is above 15 mmol/L, especially if the child or adolescent is unwell and especially if the blood glucose has been high for more than 24 hours.
- If inappropriate drowsiness is present.
- In the presence of high temperature, vomiting or diarrhoea, even when the blood glucose is <15 mmol/L.
- If abdominal pains occur.
- If breathing is rapid and suggestive of ketoacidosis.
- If the child or adolescent has flushed cheeks.

Ketonuria in the presence of hyperglycaemia is indicative of severe insulin deficiency and calls for urgent therapy to prevent progression into ketoacidosis (see Chapter 9 and Chapter 11).

Ketonuria in the presence of low blood glucose levels is indicative of a starvation state or is the result of a counter-regulatory response to hypoglycaemia. Persistent ketonuria in the presence of hypoglycaemia may be seen in prolonged nausea and vomiting states. It is best managed by an infusion of 5-10% dextrose in N/2 Saline at maintenance rates (plus correction of dehydration if indicated) together with insulin to maintain the blood glucose at 5-10 mmol/L.

**The Evidence**

The evidence for the benefits of near patient testing of HbA1c at outpatient visits is listed in Evidence Table 6.1.

- A quasi-randomised trial found that having the HbA1c result available at the time of the clinic visit, influences the outcome of the consultation in a substantial proportion of cases.40(III-1)

The evidence for the benefits of improved glycaemic control on development of microvascular and macrovascular complications is listed in Evidence Table 6.2.

- The Diabetes Control and Complications Trial (DCCT) confirmed the benefit of maintaining near normoglycaemia in reducing the development and progression of diabetic microvascular complications in adolescents and adults.1,2(II)
• In the DCCT there was no lower threshold of HbA1c below which the risk of complications was eliminated, and any improvement in HbA1c conferred a reduction in risk.3;4 (II)
• Longer follow up of patients after the completion of the DCCT, in the EDIC (Epidemiology of Diabetes Interventions and Complications) study showed increasing reduction of microvascular and macrovascular complications with optimal early metabolic control.5;6 (II)
• In 1999 in NSW, fewer than 25% of children and adolescents had HbA1c levels <7.5%, with the median HbA1c being 8.2% [interquartile range 7.6-9.1%].9;10 (IV)

Additional Technical Reports and Consensus Statements used to formulate the recommendations and principles of clinical practice are listed in Evidence table 6.3.

**Recommendations and Principles**

• Diabetes control should be optimised as much as possible as improved glycaemic control reduces the risk of development and progression of microvascular and macrovascular complications in adolescents and adults.1;2;3;4;5;6 (II)
• Frequent daily blood glucose monitoring as part of a package of care has been shown to be associated with improved glycaemic control.15 (T)
• The frequency of blood glucose monitoring should be adapted to the insulin regimen, the age of the child and the stability of the diabetes.11 (C)
• The use of memory-glucose meters without daily reviewing of glucose levels is not recommended as patterns of glycaemic changes may not be appreciated by the child or adolescent and the family, and appropriate changes in insulin dosage may not be made.43 (C)
• HbA1c is the only measure of glycaemic control that has been shown to be associated with long-term complications of diabetes and best reflects glycaemic levels over the preceding 2-3 months.15 (T)
• The American Diabetes Association recommends measuring the HbA1c at least twice per year in patients who are meeting treatment goals, and more frequently (quarterly) in those whose treatment has changed or who are not meeting glycaemic goals.12 (C)
• HbA1c results should be available at the time of the clinic visit as this may influence the outcome of the consultation.40 (III-1)
• In older children and adolescents the target HbA1c should be <7.5%.11;39 (T,C)
• Increased efforts to improve glycaemic control are recommended as fewer than 25% of children and adolescents in NSW had HbA1c levels <7.5%.9;10 (IV)
• In younger children, the HbA1c target may be set a little higher because of the dangers of hypoglycaemia to the developing brain.11 (C)
• HbA1c values need to be interpreted in the context of blood glucose readings and clinical parameters (eg a child with a low HbA1c may be experiencing asymptomatic hypoglycaemia).39 (C)
• Children whose HbA1c is rising or persistently elevated should have all aspects of their diabetes management reassessed.11 (C)
• Ketones should be tested for when the blood glucose is above 15 mmol/L and the child or adolescent is unwell.39 (C)
• Ketones should be tested for in the presence of abdominal pains, rapid breathing, flushed cheeks, high temperature, vomiting, diarrhoea or inappropriate drowsiness even when the blood glucose is <15 mmol/L.43 (C)

I = Evidence from a systemic review of all relevant RCT’s  
II = Evidence from at least one properly designed RCT
Reference List


3. DCCT Research Group: The relationship of glycaemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. Diabetes 44:968-983, 1995


20. Peled N, Wong D, Gwalani SL: Comparison of glucose levels in capillary blood samples obtained from a variety of body sites. Diabetes Technology and Therapeutics 4:35-44, 2002


41. Laffel L: Ketone bodies: a review of physiology, pathophysiology and application of monitoring to diabetes. *Diabetes Metabolism Research and Reviews* 15:412-426, 2000


Chapter 7: Nutrition

Nutrition is a fundamental component in the management of diabetes.\(^1\)

There are few long-term studies to support current dietary recommendations, particularly for children. Nutritional management of children and adolescents with type 1 diabetes should be by an accredited practising dietitian trained in paediatric diabetes.

Nutrition Therapy

The aims of nutrition therapy in type 1 diabetes are to ensure:

- Adequate energy and nutritional intake for normal growth and development.
- Optimal glycaemic control without severe hypoglycaemic and/or prolonged hyperglycaemic episodes.
- Optimal blood lipid control.
- Meeting the psychosocial needs of the individual by incorporating food and insulin regimens into usual eating habits, appetite, usual routines and exercise patterns.

Nutritional Assessment

Nutritional assessment on initial diagnosis should include:

- Family history of diabetes, including:
  - Parental beliefs about diabetes.
  - Individual beliefs about diabetes.
- Medical history- including conditions that may impact on dietary intake.
- Social situation- family structure, cultural background and influences.
- Growth (height and weight, including growth history, BMI) and development.
- Diet history to establish usual dietary intake including energy intake, total and saturated fat, carbohydrate intake and distribution, variations in appetite and usual food preferences.
- Usual routines and activities, including organised sport, school/pre-school timetables, after-school activities and any variations including weekend variations.
- Parent/child’s learning ability and motivation to ensure appropriate nutrition intervention.

Nutrition Review

Ongoing nutritional monitoring of the individual with diabetes by a dietitian experienced with paediatric diabetes management is essential.

The initial review should occur 2-4 weeks post-diagnosis. Ongoing reviews should occur every 12 months or more often depending on the age of the child or the needs of the child/family.

Ongoing review should include:

- Usual nutritional intake including appetite satisfaction.
- Growth including height, weight and BMI centiles (Figures 7.1 and 7.2).
- Insulin regimen including any regular insulin adjustments.
- HbA\(_{1c}\) and day to day blood glucose monitoring including patterns of hypo- or hyperglycaemia.
- Method of treatment of hypoglycaemia.
- Exercise regimen and carbohydrate intake pre-exercise.
• Individual or parental concerns about dietary management.
• Assessment of changes in lifestyle impacting on dietary intake and quality of life (e.g., body image perception, alcohol, cigarettes and/or drugs depending on the age of the child).
• Re-education where required, including education of the individual with diabetes as he/she becomes older and increasingly more responsible for self-care.
• Consideration of new medical conditions that may impact on management (e.g., hypercholesterolemia, coeliac disease, bulimia, family history of newly diagnosed cardiovascular disease).

Dietary Recommendations

There is no research on the nutrient requirements for children and adolescents with diabetes; therefore nutrient recommendations are based on requirements for all healthy children and adolescents. These recommendations are summarised by the ‘The Dietary Guidelines for Children and Adolescents in Australia’ (Table 7.1).^2^

The recommended meal plan should consider the child’s usual appetite and food intake pattern. Some modification to usual intake may be necessary to reduce saturated fat intake and sugars intake and to distribute carbohydrate evenly over regular meals and snacks.

Table 7.1: The Dietary Guidelines for Children and Adolescents in Australia

| Encourage and support breastfeeding |
| Children and adolescents need sufficient nutritious foods to grow and develop normally |
| - Growth should be checked regularly |
| - Physical activity is important for all children and adolescents |

| Enjoy a wide variety of nutritious foods |
| Children and adolescents should be encouraged to: |
| - Eat plenty of vegetables, legumes and fruits |
| - Eat plenty of cereals (including breads, rice, pasta and noodles), preferably wholegrain |
| - Include lean meat, fish, poultry and/or alternatives |
| - Include milks, yoghurts, cheese and/or alternatives |
| - Reduced-fat milks are not suitable for young children under 2 years, because of their high energy needs, but reduced fat varieties should be encouraged for older children and adolescents |
| - Choose water as a drink |

| And care should be taken to: |
| - Limit saturated fat and moderate total fat intake (NB low fat diets are not suitable for infants) |
| - Choose foods low in salt |
| - Consume only moderate amounts of sugars and foods containing added sugars |

| Care for your child’s food: prepare and store it safely |

Source: Dietary Guidelines for Children and Adolescents (National Health and Medical Research Council 2003)

Energy Intake

Many children have increased energy requirements initially to allow for regain of lost weight. Children and adolescents with established and stable diabetes have the same basic energy requirements as their peers. The estimates of energy requirements are made from an
individual’s food nutrition history of a typical daily intake obtained from 24 hr recall or a 3-
day food record.
Consideration needs to be given to changing appetite and activity levels. Individual
adjustment is required with regular monitoring of growth using standard height and weight
charts ideally at 3-6 month intervals.3

Dietary Carbohydrate

A diet providing 50-55% total energy as carbohydrate is recommended for children and
adolescents with diabetes.2
Carbohydrates directly affect the blood glucose level and the amount, timing and type of
carbohydrate need to be considered in relation to the insulin regimen.1,4
Practical quantification of carbohydrate intake is necessary as part of management.5
Methods of carbohydrate quantification include use of 15 gm carbohydrate exchanges or
the use of the individual’s usual serving size as the basis for the meal plan.6
In practice, carbohydrate amounts are suggested for each meal and snack for those on
fixed insulin doses that are based on the individual’s previous dietary intake, activity, appetite
and insulin regimen.
Day to day consistency in carbohydrate intake is important for those receiving fixed doses
of insulin.1
Prescriptive meal plans are not recommended. Compliance is poor with rigid prescriptive
meal plans and quality of life is decreased.6 The DCCT and the Dose Adjustment for
Normalised Eating (DAFNE) Study which included adolescents on intensive insulin therapy
demonstrated better metabolic outcomes are achieved if insulin is adjusted for carbohydrate
quantity.4,7
For those on multiple daily injections or pump therapy a 1% decrease in HbA1c can be
achieved by adjusting meal time insulin doses based on carbohydrate quantities.4

Glycaemic Index (GI)

The GI is a ranking of foods based on their acute glycaemic impact compared to the reference
standard glucose.8 The GI is one of several tools used to assist with glycaemic control.
Carbohydrates with a low GI result in a slower and more gradual rise in blood glucose
levels and reduce the postprandial glycaemic response compared to carbohydrates with a
higher GI.
Low GI food sources include wholegrain breads, legumes, pasta, temperate fruits, dairy
foods. Not all low GI foods are good everyday choices (eg chocolate, fructose) (see table
7.2).
Many factors may influence a food’s glycaemic response. However, the ranking of foods
on the basis of their GI value is generally consistent.9 The GI is also reproducible and
predictable within the context of mixed meals10;11;12 and has also been shown to have a
clinically important ‘carry-over’ effect on the subsequent meal.13
It has been suggested that low-GI diets are difficult to understand, may limit food choice
and variety and deteriorate overall dietary quality.14,15 However, studies have shown that low
GI diets are easy to understand, and have no detrimental effect on food variety or nutritional
quality.6,16
A recent meta-analysis comparing low GI diets with conventional or high GI diets, using
glycaemic control (HbA1c or fructosamine) as the outcome measure concluded that low GI
diets have a small but clinically useful effect on medium term glycaemic control.17 This
meta-analysis analysed both adult and paediatric studies together.15 There were only two
paediatric studies which have investigated low GI diets in children and adolescents with type 1 diabetes.\textsuperscript{6,16,18} The larger study, a randomised controlled trial, showed that a flexible low-GI diet resulted in a significantly better HbA\textsubscript{1c} outcome after 12 months (8.05 ±0.95 vs. 8.61 ±1.37\%, \(p = 0.05\)) and a better reported quality of life, with no decrease in number of food choices or macronutrient composition compared to a measured 15g carbohydrate exchange diabetic diet.\textsuperscript{6,16} The other study was of short duration (6 weeks) with only 7 patients enrolled, and although the glycated serum albumin was lower in the patients who received a low GI diet, these patients also had a higher daily fibre intake.\textsuperscript{18}

<table>
<thead>
<tr>
<th>Low GI Foods (&lt;55)</th>
<th>Moderate GI Foods (55-69)</th>
<th>High GI Foods (≥70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fructose 20</td>
<td>Lactose 57</td>
<td>White bread 70</td>
</tr>
<tr>
<td>Whole milk 27</td>
<td>Honey 58</td>
<td>Watermelon 72</td>
</tr>
<tr>
<td>Apple 36</td>
<td>Sucrose 59</td>
<td>Waffles 76</td>
</tr>
<tr>
<td>Apple juice 41</td>
<td>Basmati rice 59</td>
<td>Wholemeal bread 77</td>
</tr>
<tr>
<td>Apple muffin 44</td>
<td>Banana 60</td>
<td>Puffed Wheat 80</td>
</tr>
<tr>
<td>Fruit loaf 47</td>
<td>Regular ice-cream 61</td>
<td>Jelly beans 80</td>
</tr>
<tr>
<td>Sweet potato 48</td>
<td>Shortbread 64</td>
<td>Baked potato 85</td>
</tr>
<tr>
<td>Chocolate 49</td>
<td>Crumpet 69</td>
<td>Honey-glucose enriched 87</td>
</tr>
<tr>
<td>Rolled oats 50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pasta 50</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Foster-Powell, Holt et al., 2002

Sugar

The term sugars is conventionally used to describe monosaccharides (e.g., glucose, fructose) and disaccharides such as sucrose and lactose. These can be found naturally in foods or can be added in processing. Sugar, by contrast, is used to describe purified sucrose, as are the terms refined sugar and added sugar. The term no added sugar means no sugars have been added during the manufacturing process; it does not mean that no sugar or other sugars are present, since most foods contain sugars in some form.

Australian school children consume about 50\% of their daily energy intake as carbohydrates, with total sugars contributing 25\% of energy intake (15\% as added sugars and 10\% as natural sugars).\textsuperscript{19} A recent WHO/FAO report on population nutrition strategies to reduce obesity, cardiovascular disease and diabetes recommends that added sugars be reduced to <10\% of daily energy intake.\textsuperscript{20}

Dietary guidelines for children and adolescents recommend the consumption of moderate amounts of sugars and foods containing added sugars.\textsuperscript{2}

When sucrose is the main ingredient, such as in soft drinks and cordials, choosing the sugar-free alternative is desirable.

Overall, the evidence supports moderate use of sugars (including sucrose) in the diabetes diet.\textsuperscript{21-25}

Artificially sweetened products

There are two main types of artificial sweeteners:

- Nutritive.
- Non-nutritive.

Nutritive sweeteners include fructose and polyols (sugar alcohols such as sorbitol, mannitol and xylitol). Foods containing these sweeteners are often labelled as ‘carbohydrate modified’.
They are only partially absorbed from the small intestine and excessive use will cause diarrhoea in children.26  
Non-nutritive sweeteners include aspartame, saccharin, sucralose and acesulfame K. All have been extensively studied for safety and their use in food products in Australia is governed by the Food Standards Code for Australia and New Zealand.

Fibre

The Australian Dietary Guidelines aim to ensure adequate dietary fibre intake (soluble and insoluble). High fibre diets help to prevent constipation and optimise bowel health. An adequate fibre intake is calculated using the age of the child (years) plus 5 gm.27

Controversy remains whether high fibre diets have direct effects on glycaemic control.28-30

Dietary Fat Intake

The major types of dietary fats are:
- Saturated (animal fats including dairy, meat and butter).
- Monounsaturated (olive and canola oils).
- Polyunsaturated fats (vegetable fats including margarine and vegetable oils).

The Australian Dietary Guidelines for Children and Adolescents recommend limiting saturated fat intake and moderate total fat intake.2 The recommended targets for fat intakes do not differ for children with diabetes (Table 7.3).

Table 7.3: Summary of the Australian Dietary Guidelines for Dietary Fat Intake during Childhood

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Recommendations</th>
</tr>
</thead>
</table>
| Birth to two years of age  | • during the first 6 months fat should compromise 50% total energy intake by breast milk or formula.  
|                            | • from 6-12 months the target is 40% total energy.  
|                            | • skim milk and reduced fat milk should not be used in children under the age of two years. |
| Two to five years          | • target is 30% total energy from fat.  
|                            | • no more than 10% energy from saturated fat.  
|                            | • reduced fat milks are suitable but not skim milk. |
| Five to fourteen years     | • target is 30% total energy from fat.  
|                            | • no more than 10% total energy from saturated fat. |
| Adolescence                | • target is 25% total energy from fat.  
|                            | • no more than 10% total energy from saturated fat. |

Source: (National Health and Medical Research Council 2003).

The National Nutrition Survey (1995) reported that children and adolescents in the general population (2-18 years) had an average intake of 33% total energy from fat.31 Children with diabetes have similar high fat intakes ranging between 33%-36% total energy.16,32

International recommendations for nutrition in the population have recommended the diet contain 30% of energy from fat, with saturated fats contributing less than 10% of total energy, while polyunsaturated and monounsaturated fats each contribute more than 10% to the daily energy content.20
Protein

Protein should provide approximately 15-20% of total energy intake for children and adolescents.

Lean sources of protein are recommended which include lean cuts of meat and fat-reduced dairy products as appropriate.

High protein, low carbohydrate diets are not generally recommended for children and adolescents with diabetes. There are no studies that investigate the long-term effects of such diets on the growth and development in children. Restricting carbohydrate intake may impact on the nutritional adequacy of the diet and may cause hypoglycaemia. High protein diets result in ketosis, which may result in dehydration, loss of appetite, irritability, lethargy, loss of lean body mass and other abnormalities.  

Variations in Advised Meal Patterns and Insulin Regimens

There are numerous variations in insulin regimens that are used to manage type 1 diabetes in children and adolescents. Expert nutritional guidance is an essential component of the overall management.

Twice daily injection regimen
This usually involves a combination of short/rapid-acting and intermediate-acting insulin injected twice daily, usually before breakfast and the evening meal. The meal plan should consist of three meals and three snacks a day based on carbohydrate-containing foods. Meals and snacks should not be missed or delayed (toddlers, however, tend to graze over the day).

Three injections per day
A mixture of short/rapid-acting and intermediate-acting insulin given before breakfast, short/rapid-acting insulin before the afternoon snack or main evening meal and intermediate-acting insulin in the evening is commonly used in older children and teenagers when a 2 injection per day regimen is inadequate.

Multiple daily injection regimens
This usually involves a total of four injections per day with short/rapid-acting insulin given three times daily before breakfast, lunch and dinner and either intermediate- or long-acting insulin given at supper. The suggested meal plan is three main meals and an evening snack based on carbohydrate foods. Morning tea and afternoon tea snacks are not necessary but may still be eaten if desired (this may influence choice of rapid-acting versus short-acting insulin). This regimen allows some increased flexibility in meal timing and in the carbohydrate quantity for meals, and is usually better suited to the lifestyle of the older child or adolescent. For those requiring a large afternoon tea the pre dinner short/rapid-acting insulin may be given before afternoon tea.

Insulin pump therapy
Insulin pump therapy provides basal insulin with additional insulin bolus doses for each carbohydrate-containing meal/snack consumed (see insulin pump adjustment). It provides a greater degree of flexibility, especially in relation to the diet. Meal and snack times can be delayed or omitted and/or the carbohydrate content can be varied with the insulin bolus adjusted accordingly.
Intensified glycaemic control coupled with greater food flexibility (quality and quantity) can lead to undesirable weight gain. It is prudent to monitor closely for undesirable weight gain and to encourage healthy eating habits including 3 main meals per day.

Age-group Specific Advice

Approaches to the management of diabetes vary greatly at different ages and stages of development.

Infants

Exclusive breastfeeding for the first 6 months is recommended for all infants. If the mother chooses not to breastfeed, an appropriate infant formula should be used. Regular breast or bottle feeds (approx 3 hourly) will help to maintain blood glucose levels. Introduction of solids is recommended at around 6 months similar to other infants.

Toddlers

Tantrums, food fads and food refusal are common toddler behaviours. Such behaviours in a toddler with diabetes increase parental anxiety and accentuate problem meal behaviours. Toddlers eat erratically and have unpredictable activity levels. Rigid meal plans of three meals and three snacks per day are impractical and not recommended. It is normal for toddlers to ‘graze’ throughout the day. Appetite will fluctuate and toddlers generally regulate their own intakes.

Practical advice includes substituting carbohydrate foods for those refused without offering excessive choices, maximising carbohydrate finger foods and monitoring blood glucose levels regularly if parents feel that there has been insufficient intake of carbohydrate foods. Toddlers are encouraged to eat the family’s usual meals. Parents should not offer too many choices, substitute carbohydrate foods with ‘junk foods’, or force feed their child as this may encourage negative food related behaviours.

Primary school-aged children

Children’s energy needs constantly increase as they grow and increase their activity. Weight gain is about 2.5 to 3 kg/year in boys and girls from 6 to 12 years of age, with energy intakes nearly doubling in this time. Frequent review of meal plans is essential.

School-age children are encouraged to carry ‘hypo food’ and be aware of the need for extra carbohydrate for exercise.

School introduces increasing peer influence and more independence, with less direct parental supervision. Issues such as lunch swapping, forgetting to eat meals, throwing away food and purchasing foods independently from school canteens need to be addressed.

Adolescents

In adolescence, growth patterns and nutrient requirements change rapidly.

Eating habits may include large afternoon tea, skipped meals, increased snacking, more meals away from home, increased intake of high fat convenience foods and frequent consumption of sweets and soft drinks.

There is also increased influence of peer pressure about issues such as sexuality, body weight and dieting, experimentation with alcohol, cigarettes and drugs and challenging boundaries, including those related to diabetes self-management (see Chapter 18) for discussion on insulin purging, insulin omission and eating disorders in adolescence.

Many adolescents manage their diabetes on a basal-bolus insulin regimen which provides greater flexibility. However, special attention should be given to adolescents on multiple
injections because of the two-fold increased risk of obesity and increased incidence of severe hypoglycaemia.36

The Evidence
The evidence for the benefits of low glycaemic index diets in the management of type 1 diabetes in children and adolescents is listed in Evidence Table 7.1.

- A recent meta-analysis17 (including mostly adult but some paediatric studies6;16;18) comparing low GI diets with conventional or high GI diets, using glycaemic control (HbA1c or fructosamine) as the outcome measure concluded that low GI diets have a small but clinically useful effect on medium term glycaemic control.17(I)

The evidence for the benefits of adjusting insulin dose for carbohydrate quantity in the management of type 1 diabetes in children and adolescents is listed in Evidence Table 7.2.

- The DCCT and the Dose Adjustment for Normalised Eating (DAFNE) Study which included adolescents on intensive insulin therapy demonstrated better metabolic outcomes are achieved if insulin is adjusted for carbohydrate quantity.4;7(II)

The evidence for the effect on glycaemic control of the moderate use of sugars in children and adolescents with type 1 diabetes is listed in Evidence Table 7.3.

- Five small RCTs show that moderate use of sugars (including sucrose) in the diabetes diet does not adversely affect glycaemic control.21-25(II)

Additional Technical Reports and Consensus Statements used to formulate the recommendations and principles of clinical practice are listed in Evidence table 7.4.

Recommendations and Principles

- Nutrition is a fundamental component in the management of type 1 diabetes in childhood and adolescence.15(C)

- Nutritional management of children and adolescents with type 1 diabetes should be initiated by an accredited practising dietitian trained in paediatric diabetes.37(C)

- Nutritional reviews should occur 2-4 weeks post-diagnosis and ongoing at least once per year by a paediatric dietitian experienced in diabetes management.37(C)

- Children and adolescents with diabetes should be encouraged to follow the NHMRC Dietary Guidelines for Children and Adolescents in Australia which recommend that:2
  - Carbohydrate should provide 50-55% of total energy intake.
  - Dietary fat intake should provide between 25 and 40% of total energy intake depending on the child’s age.
  - Saturated fat intake should be limited to <10% of total energy intake.
  - Dietary protein intake should provide 15-20% of total energy intake.(C)

- Children and adolescents with diabetes should be educated and encouraged to adjust their insulin dose depending upon carbohydrate quantity.4;7(II)

- Day to day consistency in carbohydrate intake is important for those receiving fixed doses of insulin.(C)

- Dietary advice should include information about low glycaemic index food as this can help to improve glycaemic control.6;16;17;18(I)

- Moderate use of sucrose in the diabetes diet should be allowed as it does not significantly influence glycaemic control in type 1 diabetes.21-25(II)
Figure 7.1: Body Mass Index-for-age Percentiles: Girls, 2-20 Years
Figure 7.2: Body Mass Index-for-age Percentiles: Boys, 2-20 Years

SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
Reference List


Chapter 7: Nutrition
Australian Clinical Practice Guidelines: Type 1 Diabetes in Children and Adolescents

Chapter 8: Physical Activity

Need for Physical Activity and General Recommendations

The benefits of regular physical activity for people of all ages are well known and accepted. Physical activity is more than organised sport and includes playing at school, running, walking, dancing and other activities of daily living. The benefits of physical activity include improved insulin sensitivity, weight management, musculo-skeletal benefits, functional movement development, psychological wellbeing, social interaction and cardiovascular fitness. There is no evidence to say that these benefits are not the same for people with diabetes.

As diabetes is associated with an increased risk of macrovascular disease, the benefit of physical activity in improving known risk factors for atherosclerosis (eg overweight/obesity, hypertension, hypercholesterolaemia) should be remembered.

Education of the child with type 1 diabetes and their carer should include insulin administration, blood glucose control, carbohydrate intake and management of hypoglycaemia prior to undertaking any physical activity.

Children and adolescents with type 1 diabetes should be encouraged to participate in sport and not be limited in their choice of activity. However, certain sports require special consideration and others are contraindicated in people with insulin treated diabetes.

Activities should be approached with caution if they are solo in nature, take place in water or mid-air, or limit the individual’s ability to recognise and self-treat hypoglycaemia. Those involved in strenuous or water sports should have a ‘buddy’ able to offer assistance. These activities include:

- Rock climbing.
- Flying.
- Abseiling.
- Car/motorbike racing.
- Cross country skiing.
- Swimming in open water or snorkelling.

People with insulin-treated diabetes are generally advised to avoid the following activities unless special precautions to avoid hypoglycaemia are taken and a full understanding of the possible dangers are appreciated:

- Hang-gliding (except in tandem).
- Scuba diving (The Australian Diabetes Society in 1994 produced a position paper stating that type 1 diabetes is an ‘absolute contra-indication’ to Entry Level SCUBA diving).

Short-Term Effects

The normal physiological response to physical activity is to decrease plasma insulin levels and increase plasma glucagon in order to increase hepatic glucose production and prevent hypoglycaemia. These normal hormonal adaptations to exercise are essentially lost in children and adolescents with type 1 diabetes. Hypoglycaemia during physical activity rarely occurs in nondiabetic individuals. High insulin levels due to exogenous insulin administration, can prevent the mobilisation of hepatic glucose, making hypoglycaemia more likely in a patient with type 1 diabetes. Hypoglycaemia may occur during, immediately after or many hours after physical activity. Therefore, it is recommended that:

- Blood glucose levels need to be measured before, during and after physical activity.
• Physical activity may necessitate extra carbohydrate intake and insulin reduction. A general recommendation is that 15 gm of easily absorbable carbohydrate or an extra serving should be taken for every 30 minutes of moderate to intensive sport or physical activity. Experience and blood glucose monitoring help determine the most appropriate strategies as the requirements vary for each individual.

• All children and adolescents participating in sport should have access to assistance from a person aware of the management of hypoglycaemia during physical activity.

• Extra carbohydrate should be consumed if blood glucose level is <7 mmol/L. Exercise should be delayed if blood glucose is <3.5 mmol/L.

• Special attention should be given to children and adolescents performing intensive sports, especially those involving endurance training, due to the association with delayed hypoglycaemic reactions which may occur in the middle of the night or before breakfast the next day.

• Advice should be sought from a dietitian for carbohydrate foods suitable for those undertaking endurance sports.

• Intensive physical activity needs to have appropriate reductions made in dosages of the insulin acting during and for the following 12-24 hours after the physical activity. In some cases decreasing insulin before physical activity reduces the need for extra food.

Those who are underinsulinised may experience an excessive release of counter-regulatory hormones during physical activity. This may increase already high levels of glucose and ketones and can even precipitate ketoacidosis. Therefore, it is recommended that children with type 1 diabetes should avoid physical activity if blood glucose levels are >15 mmol/L especially if ketosis is present.

**Long-term Effects**

Regular physical activity in children and adolescents with type 1 diabetes can improve aerobic capacity and muscle strength; however the reported effect of physical activity on glycaemic control (measured by HbA1c) varies.

One small RCT (n=9) showed an improvement in HbA1c with regular sustained physical activity compared with 30 minutes vigorous physical activity three times per week (HbA1c 11.3% versus 13.3%); however this group of patients was in very poor metabolic control. Another small study (n=12) found that the HbA1c in both ‘poorly’ (HbA1c >9%) and ‘well’ controlled (HbA1c <9%) diabetic patients was not affected by 12 weeks of supervised training. During the ensuing 12 week period of unsupervised training, any improvement in aerobic capacity decreased to pre-training levels suggesting that compliance with unsupervised training was poor. In a third study of a 12 week physical activity program, the HbA1c of subjects with type 1 diabetes was reduced (only in those with poor glycaemic control) by 1% (p <.05).

**The Evidence**

The evidence for the long term effects of physical activity in children and adolescents with type 1 diabetes is listed in Evidence Table 8.1.

- Regular physical activity in children and adolescents with type 1 diabetes can improve aerobic capacity and muscle strength; however the reported effect of physical activity on glycaemic control (measured by HbA1c) varies. (II, IV)

Additional Technical Reports and Consensus Statements used to formulate the recommendations and principles of clinical practice are listed in Evidence Table 8.2.
The role of physical activity in health promotion and disease prevention has been emphasised by the World Health Organization.\(^1\)\(^{(T)}\) There are no published studies which indicate that these benefits are changed by having type 1 diabetes.\(^2\)\(^{(T)}\)

**Recommendations and Principles**

- Physical activity should be considered part of diabetes management. Children and adolescents with type 1 diabetes should be encouraged to participate in a variety of sport and physical activity and not be limited in their choice of activity.\(^4\)\(^{(C)}\)
- Regular physical activity in children and adolescents with type 1 diabetes should be encouraged as it can improve aerobic capacity\(^6\)-\(^8\) and muscle strength;\(^7\) however the reported effect of physical activity on glycaemic control (measured by HbA\(_{1c}\)) varies.\(^{II,IV}\)
- Activities should be approached with caution if they are solo in nature, take place in water or mid-air, or limit the individual’s ability to recognise and self-treat hypoglycaemia and a ‘buddy’ is recommended.\(^4\)\(^{(C)}\)
- Blood glucose levels need to be measured before, during and after physical activity.\(^2\)\(^{(C)}\)
- Physical activity may necessitate extra carbohydrate intake and insulin reduction. Experience and blood glucose monitoring help determine the most appropriate strategies as the requirements vary for each individual.\(^2\)\(^{(C)}\)
- All children and adolescents participating in sport should have access to assistance from a person aware of the management of hypoglycaemia.\(^{(C)}\)
- A general recommendation is that 15 gm of easily consumed and quickly absorbed carbohydrate or an extra serving should be taken for every 30 minutes of moderate to intensive sport or physical activity.\(^{(C)}\)
- Extra carbohydrate should be consumed if blood glucose level is <7 mmol/L.\(^{2,9}\)\(^{(C)}\)
- Strenuous physical activity should be avoided if blood glucose levels are >15 mmol/L especially if ketones are present.\(^9\)\(^{(C)}\)

C = Consensus statement endorsed by professional organisations

T = Technical Report

**Reference List**

Chapter 9: Diabetic Ketoacidosis

The following guidelines for the management of diabetic ketoacidosis take into account the conclusions of a consensus statement resulting from a workshop that took place in the United Kingdom involving the European Society for Paediatric Endocrinology (ESPE) and the Lawson Wilkins Pediatric Endocrine Society (LWPES). The Consensus statement was developed with close partnership between the ESPE and LWPES and the International Society for Pediatric and Adolescent Diabetes (ISPAD), all three organisations being represented by members who participated in the writing process. The statement was also endorsed by and contributed to by related organisations; the Juvenile Diabetes Research Foundation International (JDRFI), the World Federation of Pediatric Intensive and Critical Care Societies, the European Society for Pediatric Critical Care, the European Society of Paediatric and Neonatal Intensive Care (ESPNIC) and the Australian Pediatric Endocrine Group (APEG) were represented by invited participants.1

Definition and Aetiology

Diabetic ketoacidosis is a life-threatening disorder that is due to decreased effective circulating insulin concentration,2 in association with insulin resistance3,4 and increased production of counter-regulatory hormones such as glucagon, catecholamines, cortisol and growth hormone.5-8

The hormonal changes cause:

- Increased hepatic and renal glucose production and impaired peripheral glucose utilisation, leading to hyperglycaemia and hyperosmolality.
- Increased lipolysis and unrestrained production of ketoacids (beta-hydroxybutyrate and acetoacetate),9 resulting in ketonaemia and eventual metabolic acidosis.

Hyperglycaemia leads to osmotic diuresis, loss of electrolytes and dehydration, which can exacerbate the metabolic acidosis.10

The biochemical criteria for the diagnosis of diabetic ketoacidosis include:

- Hyperglycaemia, defined by a blood glucose (BG) level >11 mmol/L.
- Venous pH <7.3
- Bicarbonate <15 mmol/L.

Rarely, young or partially treated children and pregnant adolescents may present in diabetic ketoacidosis with near-normal glucose values (‘euglycaemic ketoacidosis’).10

Diabetic ketoacidosis may be classified by the severity of the acidosis:

- Mild (venous pH 7.25 to 7.30, bicarbonate concentration 10-15 mmol/L).
- Moderate (pH 7.1 to 7.24, bicarbonate 5-10 mmol/L).
- Severe (pH <7.1, bicarbonate <5 mmol/L).10

Diabetic ketoacidosis is usually associated with at least 5% dehydration, vomiting and/or drowsiness.

Factors associated with diabetic ketoacidosis in children with newly diagnosed type 1 diabetes include younger age (those aged less than five years are at greatest risk),11 children without a first degree relative with type 1 diabetes,12 and those from families of lower socioeconomic status.2,11,13 High dose glucocorticoids,14 antipsychotics,16 diazoxide and
immunosuppressive drugs have been reported to precipitate diabetic ketoacidosis in individuals not previously diagnosed with type 1 diabetes. Diabetic ketoacidosis has been reported in at least 25% of children with newly diagnosed type 2 diabetes.\textsuperscript{17;18}

The risk of diabetic ketoacidosis in established type 1 diabetes is increased in children and young people with poor metabolic control or previous episodes of diabetic ketoacidosis.\textsuperscript{11;15} The most common precipitating factors in the development of diabetic ketoacidosis include infection,\textsuperscript{10;19} often as a result of inadequate insulin therapy during intercurrent illness and insulin omission.\textsuperscript{11;20-22} Adolescent girls,\textsuperscript{23-25} children with psychiatric disorders,\textsuperscript{25,26} such as eating disorders, and those from families of lower socio-economic status are also at increased risk.\textsuperscript{22,27} Diabetic ketoacidosis is rare in children whose insulin is administered by a responsible adult.\textsuperscript{21} Furthermore, after medical and educational interventions, metabolic control improved and diabetic ketoacidosis decreased.\textsuperscript{21}

Diabetic ketoacidosis has been reported in association with continuous subcutaneous insulin infusion (CSII), as inappropriate interruption of insulin pump therapy can precipitate diabetic ketoacidosis.\textsuperscript{11;28,29} Recent studies, however, have failed to find an increased risk of diabetic ketoacidosis in patients treated with CSII.\textsuperscript{30,31} Children and adolescents are advised to have needles and syringes in reserve in case of insulin pump malfunction.

**Epidemiology**

The frequency of diabetic ketoacidosis ranges from 16%-80% of children newly diagnosed with diabetes, depending on geographic location.\textsuperscript{13,32,33} Diabetic ketoacidosis is the leading cause of morbidity and is the most common cause of diabetes-related deaths in children and adolescents with type 1 diabetes.\textsuperscript{34} Mortality is predominantly due to cerebral oedema which occurs in 0.3% to 1% of all episodes of diabetic ketoacidosis.\textsuperscript{35,36}

The aetiology and pathophysiology of cerebral oedema are poorly understood. Factors associated with cerebral oedema include:

- Newly diagnosed type 1 diabetes.\textsuperscript{35,37,39}
- Younger age.\textsuperscript{37,38,39}
- Longer duration of symptoms.\textsuperscript{39}
- Indices of greater severity of diabetic ketoacidosis, such as dehydration and acidosis.\textsuperscript{36}
- During treatment of diabetic ketoacidosis, a smaller rise in measured serum sodium concentration.\textsuperscript{36,40-42}

Specifically, elevated blood urea at presentation of diabetic ketoacidosis has been associated with increased risk of cerebral oedema,\textsuperscript{36} which probably reflects greater dehydration. The severity of acidosis correlates with risk of cerebral oedema\textsuperscript{43} and bicarbonate treatment for correction of acidosis has also been associated with an increased risk of cerebral oedema.\textsuperscript{36,44} Furthermore, after adjusting for the degree of acidosis, more severe hypocapnia at presentation of diabetic ketoacidosis has been associated with cerebral oedema in two studies.\textsuperscript{36,45}

In contrast, an association between volume or sodium content of intravenous fluids, and risk of cerebral oedema has not been found.\textsuperscript{36,39,42,45,46} Therefore, the association between sodium change and cerebral oedema may be a consequence of cerebral salt wasting rather than excessive fluid administration. Neither degree of hyperglycaemia at presentation nor rate of change in serum glucose during treatment of diabetic ketoacidosis have been associated with an increased risk of cerebral oedema.\textsuperscript{36,45}
Management

Whenever possible a specialist/consultant paediatrician with training and expertise in the management of diabetic ketoacidosis should direct management. The child should also be cared for in a unit that has:

- Experienced nursing staff trained in monitoring and management of diabetic ketoacidosis.
- Clear written guidelines for managing diabetic ketoacidosis.
- Access to laboratories that can provide frequent and accurate measurement of biochemical variables.

Children with signs of severe diabetic ketoacidosis (long duration of symptoms, circulatory compromise, depressed level of consciousness) or those who may be at increased risk for cerebral oedema (<5 years of age, new onset, high blood urea, low pCO₂) should be considered for immediate treatment in an intensive care unit (paediatric if available) or a children’s ward specialising in diabetes care with equivalent resources and supervision.

It may be possible to manage children with ketosis and hyperglycaemia at home or in an ambulatory health care setting (such as an emergency ward) if they are not vomiting. The response to treatment should be evaluated frequently (2-4 hourly). If ketosis is not corrected by oral hydration and subcutaneous insulin within 12 hours, the child should be re-evaluated and the need for IV fluids, insulin and admission to hospital should be reviewed.

Steps in the Assessment and Management of Diabetic Ketoacidosis

The following steps are involved in the management of diabetic ketoacidosis:

- Clinical assessment.
- Resuscitation.
- Investigation.
- Monitoring.
- Rehydration.
- Sodium replacement.
- Potassium replacement.
- Insulin treatment.
- Management of cerebral oedema if present.
- Management of the recovery phase.
Algorithm for the Management of Diabetic Ketoacidosis

**IMMEDIATE ASSESSMENT**

**Clinical History**
- Polyuria, polydipsia
- Weight loss (weigh patient)
- Abdominal pain
- Tiredness
- Vomiting
- Confusion

**Clinical Assessment**
- Assess hydration, perfusion, BP, GCS
- Deep sighing respiration (Kussmaul)
- Smell of ketones
- Lethargy/drowsiness ± vomiting

**Investigations**
- Venous blood gas, FBC, electrolytes, urea, creatinine, other investigations as indicated
- Biochemical signs of DKA include:
  - Ketonuria/ketonaemia
  - Blood glucose level >11mol/L
  - pH <7.25, Bicarb <15 mmol/L

**CONFIRMED DIAGNOSIS OF DIABETIC KETOACIDOSES**
- Contact Senior Staff

**Resuscitation**
- Airway ± insert NG tube
- Breathing (100% O2)
- Circulation (Saline 0.9% 10-20 ml/kg over 1-2 hours (may need to repeat until circulation restored)

**IV Therapy**
- Calculate fluid requirements
- Correct over 48 hours
- Use Saline 0.9% as initial fluid
- Monitor ECG for elevated T-waves
- Add KCL 40 mmol per litre fluid

**Low-dose continuous INSULIN INFUSION**
- 0.1 unit/kg/hour
- (consider 0.05 U/kg/h for young child)

**Critical Observations**
- Hourly blood glucose level, RR, HR, BP
- Hourly accurate fluid input & output (insert urinary catheter if conscious state impaired)
- Neurological status at least hourly
- Electrolytes and blood gas 2-4 hourly after start of IV therapy
- Monitor ECG for T-wave changes

**Re-evaluate**
- IV fluid calculations
- Insulin delivery systems & dose
- Need for additional resuscitation
- Consider sepsis

**IV Therapy**
- Change to Saline 0.45% + Glucose 5%
- Adjust insulin infusion (not <0.05 U/kg/h)
- Adjust sodium infusion to promote an increase in serum sodium

**Transition to SC Insulin**
- Start SC Insulin then
- Stop IV insulin 90 mins later

**Source:** adapted from ISPAD guidelines

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Chapter 9: Diabetic Ketoacidosis
Australian Clinical Practice Guidelines: Type 1 Diabetes in Children and Adolescents
Clinical Assessment

The diagnosis and clinical assessment of diabetic ketoacidosis should be confirmed with the following:

- Characteristic history of polydipsia and polyuria, which may be absent in the young child.
- Full physical examination, including weight (where possible), BP, assessment for evidence of acidosis (hyperventilation), assessment of conscious level (Glasgow Coma Score) and severity of dehydration.
  - 5% (reduced skin turgor, dry mucous membranes, tachycardia, tachypnoea).
  - 10% (capillary return 3 seconds or more, sunken eyes).
  - >10% (shock, poor peripheral pulses, hypotension, oliguria).

Note: Volume deficit is difficult to assess accurately in diabetic ketoacidosis, particularly in the young child, and may be overestimated because of the subjective criteria used. Shock with haemodynamic compromise is uncommon in childhood diabetic ketoacidosis.

- Biochemical confirmation: glycosuria, ketonuria, capillary BG level (which may be inaccurate in the setting of circulatory compromise and acidosis) and acid-base status.

Resuscitation

The following aspects need to be considered in the resuscitation of a child or adolescent with diabetic ketoacidosis:

- Assess and maintain airway patency and breathing.
- In severely shocked patients give 100% oxygen by facial mask.
- If shocked initiate IV fluid administration and volume expansion immediately with an isotonic solution (0.9% saline). The volume and rate of administration depends on circulatory status; where necessary the volume is typically 10-20 ml/kg over 1-2 hours, which may be repeated as required.
- Use crystalloid and not colloid. There are no data to support the use of colloids in preference to crystalloids in the treatment of diabetic ketoacidosis.
- Insert a nasogastric tube in patients with impaired consciousness or recurrent vomiting to prevent aspiration of gastric contents.

Investigation

The following urgent baseline laboratory measurements should be ordered:

- Blood glucose.
- Blood electrolytes (calculate corrected sodium) (see correction formula for sodium replacement) and osmolality (calculate by 2 [Na$^+$ + K$^-$] + glucose).
- Venous pH and acid base status (arterial blood gas if signs of shock are present).
- Full blood count and haematocrit (the white blood cell count may be elevated due to stress and cannot be interpreted as a sign of infection).
- Blood urea and creatinine (creatinine measurements may be spuriously raised by assay interference from ketones).
- Urine microscopy and culture.
- Blood cultures and chest x-ray if indicated.
- Urinalysis for ketones (and/or blood ketones).
Monitoring

The management of diabetic ketoacidosis in childhood is dependent on careful clinical observation of progress. Throughout treatment, hourly clinical observations, IV and oral medication, fluids and electrolytes, and laboratory results must be documented.

Signs of severe diabetic ketoacidosis (long duration of symptoms, cardiovascular compromise, depressed level of consciousness) or increased risk for cerebral oedema (including <5 years of age, new onset) should prompt immediate consideration of treatment in an intensive care unit (paediatric if available) or in a children’s ward specialising in diabetes care with equivalent resources and supervision.47

Monitoring includes:

- Hourly heart rate, respiratory rate, blood pressure.
- 2nd to 4th hourly temperature.
- Hourly accurate fluid input and output. If the level of consciousness is impaired, a urinary catheter may be necessary. Fluid balance should be reassessed regularly (at least 2nd hourly) because continuing polyuria may worsen dehydration.
- Hourly or more frequent neurological observations for warning signs and symptoms of cerebral oedema.
  - Headache.
  - Inappropriate slowing of heart rate.
  - Recurrence of vomiting.
  - Change in neurological status (restlessness, irritability, increased drowsiness, incontinence) or specific neurological signs (such as cranial nerve palsies, pupillary response).
  - Rising blood pressure, decreased oxygen saturation.
  Note: it may be difficult clinically to discriminate cerebral oedema from other causes of altered mental status.
- Hourly capillary BG level measurement. Laboratory confirmation with venous glucose should be performed every 2 to 4 hours because capillary methods may be inaccurate in the presence of poor peripheral circulation and acidosis.
- Laboratory investigations: 2 to 4 hourly electrolytes, urea, haematocrit, venous BG level and blood gases. In severe diabetic ketoacidosis it may be necessary to monitor electrolytes hourly.
- In severe diabetic ketoacidosis, ECG monitoring may be helpful to assess T-waves for evidence of hyperkalaemia or hypokalaemia.
- Urinalysis for ketones until negative.

Rehydration

Diabetic ketoacidosis is characterised by loss of water and electrolytes. The high effective osmolality of the extracellular fluid (ECF) compartment results in a shift of water from the intracellular fluid compartment (ICF) to the ECF. Elevated serum urea nitrogen and haematocrit may be useful markers of severe ECF contraction. Dehydration is associated with a reduction in glomerular filtration rate (GFR), leading to reduced glucose and ketone clearance, which potentiate diabetic ketoacidosis.

Administration of IV fluid prior to insulin results in substantial falls in blood glucose, because the resultant increase in GFR leads to increased urinary glucose excretion.50;51

The aims of fluid and sodium replacement therapy in diabetic ketoacidosis are:
• Restoration of circulating volume.
• Replacement of sodium and water deficits over at least 36-48 hours.
• Restoration of GFR with enhanced clearance of glucose and ketones from the blood.
• Avoidance of cerebral oedema, which may be caused by fluid shifts from the ECF to the ICF compartment.

Following initial resuscitation, subsequent fluid management should be with 0.9% saline. If hypernatraemia is present consider the use of 0.45% saline.

• As the severity of dehydration is difficult to determine and may be overestimated, daily fluid infusion rates should rarely exceed 1.5-2 times the usual daily requirement based on age, weight, or body surface area.
• IV or oral fluids that were given before the initiation of hospital management should be included in calculations of deficit and replacement. Urinary losses should not be added to the initial calculation of replacement fluids.
• The patient should remain ‘nil by mouth’ except for ice to suck.
• Calculation of effective osmolality may be useful to guide ongoing fluid and electrolyte therapy.

Sodium Replacement

Measurement of serum sodium is an unreliable measure of the degree of ECF contraction and may be depressed due to the dilutional effect of hyperglycaemia and fluid shift from the ICF to the ECF.

Corrected sodium concentration can be calculated as:

\[
\text{corrected sodium} = \text{sodium} + \frac{2 \times (\text{glucose} - 5.5)}{5.5} \quad (\text{all values in mmol/L})
\]

The calculation can be simplified to 2 mmol/L of sodium to be added for every 5.5 mmol/L of glucose above 5.5 mmol/L.

Normal saline is used as the initial rehydration fluid.

Effective osmolality (2 \([\text{Na}^+ + \text{K}^-] + \text{glucose}\)) at the time of presentation is frequently in the range of 300-350 mOsm/L. If the corrected sodium is greater than 150 mmol/L, a hypernatraemic as well as an independent glucose hyperosmolar state exists and correction of dehydration and electrolyte imbalances should be over 48-72 hours. Normal Saline with 40 mmol/L KCl has an osmolality of 390 mOsm/L, which may exacerbate the hyperosmolar state. The continued use of large amounts of 0.9% Saline has also been associated with the development of hyperchloreaemic metabolic acidosis.

The use of hypotonic fluids, however, is associated with greater rises in intracranial pressure compared to isotonic fluids. Therefore, the use of solutions with salt content less than 0.45% NaCl, which contain a large amount of electrolyte free water, is likely to lead to a rapid osmolar change, movement of fluid into the ICF compartment and may increase the risk of cerebral oedema. The failure of the serum sodium to rise or development of hyponatraemia during IV fluid administration has been shown to precede cerebral oedema.

Potassium Replacement

Diabetic ketoacidosis in adults is associated with total body potassium deficits of approximately 3-6 mmol/kg, but data are lacking in children. Hypertonicity, insulin deficiency, and buffering of hydrogen ions within the cell lead to potassium loss. Serum potassium may be reduced, normal or elevated at the time of presentation. Hypokalaemia
may be related to prolonged duration of disease, whereas hyperkalaemia is due to reduced renal function. Administration of insulin and the correction of acidosis will drive potassium back into the cells, decreasing serum levels.

The following issues need to be considered in potassium replacement:

- Potassium should be added after restoring normal circulation, concurrent with starting insulin therapy.
- Replacement therapy should be based on serum potassium measurements.
  - If the patient is anuric (after passage of a catheter) or hyperkalaemic, defer potassium replacement until urine output is documented and electrolytes are available.
  - If the patient is hypokalaemic, start potassium replacement immediately.
- Commence replacement at a dose of 5 mmol/kg/day (40 mmol/L IV fluid).
- Do not exceed a maximal potassium infusion rate of 0.5 mmol/kg/hour without consultation/cardiac monitoring.
- Potassium replacement should continue throughout intravenous fluid therapy.
- Potassium phosphate salts may be used as an alternative or in combination with potassium chloride/acetate to avoid hyperchloraemia; however administration of phosphate may induce hypocalcaemia and prospective studies have failed to show significant clinical benefit from phosphate replacement.

**Bicarbonate Replacement**

Severe acidosis is reversible by fluid and insulin replacement. Insulin administration arrests further synthesis of ketoacids and allows excess ketoacids to be metabolised. The metabolism of keto-anion results in the regeneration of bicarbonate and correction of acidaemia. Furthermore, treatment of hypovolaemia improves poor tissue perfusion and renal function, leading to excretion of organic acids and reversal of lactic acidosis, which may account for up to 25% of the acidaemia.

Prospective controlled trials of sodium bicarbonate in small numbers of children and adults with diabetic ketoacidosis have failed to demonstrate a clinical benefit or harm. Bicarbonate therapy may cause paradoxical CNS acidosis and rapid correction of acidosis may cause hypokalaemia, accentuate sodium load and contribute to serum hypertonicity. Bicarbonate therapy may also increase hepatic ketone production, thus slowing the rate of recovery from the ketosis. No prospective randomised studies of patients with severe diabetic ketoacidosis (pH <6.9) have been reported.

Some patients may benefit from cautious bicarbonate therapy, such as those with severe acidaemia (pH <6.9 ± serum bicarbonate <5 mmol/L), which causes decreased cardiac contractility, peripheral vasodilatation and impaired tissue perfusion, and patients with potentially life-threatening hyperkalaemia. If bicarbonate is given, it should be administered at a dose of 1-2 mmol/kg by an intravenous infusion over 60 minutes. Cardiac monitoring should be performed in these patients due to the risk of inducing hypokalaemia.

**Insulin**

Rehydration alone will decrease the BG level to some extent; however insulin therapy is required to normalise the BG level and to suppress lipolysis and ketogenesis. Insulin therapy offsets insulin resistance and inhibits lipolysis and ketogenesis; causing suppression of glucose production and stimulated peripheral glucose uptake. The resolution of acidaemia usually takes longer than normalisation of blood glucose concentrations. Although different
routes (SC, IM, IV) and doses have been used, there is considerable evidence to support the use of ‘low dose’ intravenous insulin.63-67

Outline of insulin treatment:

- Insulin dose: 0.1 units/kg/hour by IV infusion. Consider 0.05u/kg/hr in the younger child.
- BG level should fall by approximately 4-5 mmol/L per hour, but initial rehydration alone will cause the BG level to fall, so a greater drop in BG level can be accepted in the first few hours of treatment.
- The dose of insulin should remain at 0.1 U/kg/hour at least until resolution of ketoacidosis (pH >7.30, HCO3 >15 mmol/L and/or closure of anion gap).
- When the BG level falls to 15 mmol/L, glucose should be added to the IV fluid to prevent an unduly rapid decrease in plasma glucose concentration and possible development of hypoglycaemia. A solution of 0.45% saline and 5% dextrose (prepared by adding 25 ml of 50% dextrose to 500 ml of 0.45% saline and 2.5% dextrose) is commonly used.
- In cases of hyponatraemia, IV fluid with a higher sodium content (for example, Normal Saline) may be used with dextrose added.
- The insulin infusion rate and/or the dextrose infusion rate should then be adjusted to keep the BG level between 5-10 mmol/L.
- The insulin infusion rate should only be decreased if the BG level remains below the target range despite dextrose supplementation.
- Do not stop insulin infusion or decrease below 0.05 units/kg/hour because continuous supplies of both insulin and glucose substrate are required to promote anabolism and reduce ketosis.
- If IV fluids are required after 24 hours 0.45% saline adjusted to 5% dextrose may be used.
- If biochemical parameters of ketoacidosis (pH, anion gap) do not improve, reassess the patient, review insulin therapy, and consider other possible causes of impaired response to insulin (for example infection, errors in insulin preparation, adhesion of insulin to tubing with very dilute solutions).
- In circumstances where IV administration is not possible, IM or SC insulin administration has been used effectively and has been demonstrated to be safe.68 It should be noted that poor perfusion will impair insulin absorption.69

The insulin infusion can be prepared by adding 50 units of short-acting or rapid-acting insulin to 500 ml of 0.9% saline, resulting in a solution containing 1 unit of insulin per 10 ml. The infusion may be run as a sideline with the rehydrating fluid, providing a volumetric pump is used. Some intensive care units prefer to use a more concentrated solution of insulin and a step syringe pump. If a volumetric pump is not available, a separate IV site may be required for low infusion rates. The insulin infusion and the giving set should be changed every 24 hours, due to the potential for insulin to denature. The insulin infusion must be clearly labelled so that confusion with the rehydrating solution does not occur.

Management of Cerebral Oedema

Treatment should be initiated as soon as the condition is suspected. Management should involve:

- Reduction in the rate of fluid administration.
• Intravenous mannitol should be given (0.25-1.0g/kg over 20 mins) in patients with signs of cerebral oedema before impending respiratory failure. Although mannitol has been shown to have possible beneficial effects in case reports, there has been no definite beneficial or detrimental effect in epidemiological studies.\textsuperscript{37,70} Timing of administration (delayed administration being less effective) may alter the response.
• Repeat mannitol administration in 2 hours if there is no initial response.\textsuperscript{71}
• Hypertonic saline (3%) 5-10 ml/kg over 30 mins may be an alternative to mannitol. Intubation and ventilation may be necessary, but aggressive hyperventilation has been associated with poor outcome in retrospective studies of diabetic ketoacidosis-related cerebral oedema.\textsuperscript{36}
• The patient should be transferred to an intensive care facility and a neurological assessment and MRI or CT scan arranged.

Management of the Recovery Phase

Recovery management involves:
• Transition from IV fluids and ‘nil by mouth’ to oral fluids.
• Transition from continuous insulin infusion to subcutaneous insulin.

Oral fluids
• These should be introduced when the patient is metabolically stable (BG level <12 mmol/L, pH >7.30 and HCO3 >15 mmol/L). Low joule or low calorie fluids may be given by mouth as tolerated and should be included in the fluid balance calculations.

Covering snacks and meals on intravenous insulin infusion
• It is useful to maintain the insulin infusion until the child or adolescent has had at least one meal.
• For snacks the basal infusion rate is doubled at the commencement of the snack and continued for the duration of the snack and 30 minutes afterwards before returning to the basal rate.
• For main meals the basal infusion rate should be doubled at the commencement of the meal and continued at this rate for the duration of the meal and for 60 minutes after the meal. The infusion rate can then be returned to the basal rate.
• The insulin infusion can be discontinued when the patient is alert and metabolically stable and when eating has been established.

Transition from intravenous to subcutaneous insulin
• The most convenient time to change to subcutaneous insulin is just before a mealtime. The subcutaneous insulin should be given 30 minutes before the meal (or immediately if rapid-acting insulin analogues are used). The insulin infusion should be continued throughout the meal for a total of 30-90 minutes after the subcutaneous insulin injection depending on the type of insulin used. The half-life of intravenous insulin is only 4.5 minutes; therefore it is important that the subcutaneous insulin is given before the infusion is ceased.
• Short-acting insulin should be given 4 to 6 hourly, however the dose needs to be individualised on the basis of serial blood glucose levels.
• The total daily dose required is at least 1 units/kg body weight/day, however this may need to be adjusted on the basis of previous insulin dosages.
• Frequent monitoring in the post diabetic ketoacidosis interval is required to avoid hypoglycaemia.\textsuperscript{62}
Various regimens may be used:

- The use of intermediate and short/rapid-acting insulin as a bd, tds or basal bolus regimen will depend on the patient’s age and local practices. Typically for a bd regimen the total insulin dose is approximately 1 unit per kg per day with _ given before breakfast and _ before the evening meal, the ratio being _ intermediate-acting insulin and _ short/rapid-acting (for further details, see Chapter 5).

The Evidence

The evidence for the definition and aetiology of diabetic ketoacidosis is listed in **Evidence Table 9.1**.

- Diabetic ketoacidosis is due to decreased effective circulatory insulin concentration in association with insulin resistance and increased production of counter-regulatory hormones.3-8 (III-2)

The evidence for the frequency of diabetic ketoacidosis is listed in **Evidence Table 9.1**.

- The frequency of diabetic ketoacidosis ranges from 16 to 80% in children newly diagnosed with diabetes, depending on geographic location.13;32;33 (IV)

The evidence for the factors associated with diabetic ketoacidosis is listed in **Evidence Table 9.1**.

- Factors associated with diabetic ketoacidosis in children with newly diagnosed type 1 diabetes include younger age (those aged less than five years are at greatest risk),11 children without a first degree relative with type 1 diabetes,12 and those from families of lower socioeconomic status.2;11;13 (IV)
- Diabetic ketoacidosis has been reported in at least 25% of children with newly diagnosed type 2 diabetes.17;19 (IV)

The evidence for the most common precipitating factors of diabetic ketoacidosis in established type 1 diabetes is listed in **Evidence Table 9.1**.

- The risk of diabetic ketoacidosis in established type 1 diabetes is increased in children and young people with poor metabolic control or previous episodes of diabetic ketoacidosis.11;15 The most common precipitating factors in the development of diabetic ketoacidosis include infection, often as a result of inadequate insulin therapy during intercurrent illness and insulin omission.10;11;19;20-22 Adolescent girls,23-25 children with psychiatric disorders,25;26 such as eating disorders, and those from families of lower socioeconomic status are also at increased risk.22;27 (IV)
- Diabetic ketoacidosis has been reported in early studies in association with continuous subcutaneous insulin infusion (CSII), as inappropriate interruption of insulin pump therapy can precipitate diabetic ketoacidosis.11;28;29 However, more recent studies have not documented an increased risk of diabetic ketoacidosis in patients treated with CSII.30;31 (III-2)

The evidence for mortality in diabetic ketoacidosis and risk factors for cerebral oedema is listed in **Evidence Table 9.1**.

- Diabetic ketoacidosis is the most common cause of death in newly diagnosed type 1 diabetes.10;11;22;34 (IV)
- The greatest risk of mortality from diabetic ketoacidosis is from cerebral oedema.10;11;22;35;36 (IV)
- Although poorly understood, the risk factors for cerebral oedema in diabetic ketoacidosis include presentation with new onset type 1 diabetes,35;37;39 younger age,37;38;39 elevated serum urea nitrogen and/or severity of dehydration at presentation, severity of acidosis,36;43 greater hypocapnia at presentation (after adjusting for degree of acidosis), an attenuated
rise in serum sodium during treatment for diabetic ketoacidosis\textsuperscript{36;40-42}, bicarbonate treatment to correct acidosis has also been associated with cerebral oedema.\textsuperscript{36;44} (III/IV) Most studies have not found an association between cerebral oedema and degree of hyperglycaemia at presentation of diabetic ketoacidosis, rate of change of serum glucose during diabetic ketoacidosis treatment or volume or sodium content of intravenous fluids have.\textsuperscript{36;45;46} (III/IV)

The evidence for predictors of need for admission to hospital or ICU for management of diabetic ketoacidosis or ketosis with hyperglycaemia is listed in Evidence Table 9.1.
- Children with signs of severe diabetic ketoacidosis (long duration of symptoms, circulatory compromise, depressed level of consciousness) or those who may be at increased risk for cerebral oedema (<5 years of age, new onset, high blood urea, low \text{pCO}_2) should be considered for immediate treatment in an intensive care unit\textsuperscript{47} (paediatric if available) or a children’s ward specialising in diabetes care with equivalent resources and supervision. (IV)
- It may be possible to manage children with ketosis and hyperglycaemia at home or in an ambulatory health care setting (such as an emergency ward) if they are not vomiting.\textsuperscript{48;73} (IV)

The evidence for difficulties in assessing dehydration in diabetic ketoacidosis is listed in Evidence Table 9.1.
- Volume deficit is difficult to assess accurately in diabetic ketoacidosis, particularly in the young child, and may be overestimated because of the subjective criteria used.\textsuperscript{49} (III-3)

The evidence for issues in the management of diabetic ketoacidosis is listed in Evidence Table 9.1.
- Hyperchloraemic acidosis and Sodium replacement.\textsuperscript{53} (III-2)
- Potassium phosphate salts may be used as an alternative or in combination with potassium chloride/acetate to avoid hyperchloraemia; however administration of phosphate may induce hypocalcaemia\textsuperscript{54;55} (IV) and prospective studies have failed to show significant clinical benefit from phosphate replacement.\textsuperscript{56-58} (III-1)
- Prospective controlled trials of sodium bicarbonate in small numbers of children and adults with diabetic ketoacidosis have failed to demonstrate a clinical benefit or harm.\textsuperscript{36;59;60} Furthermore, bicarbonate therapy may cause paradoxical CNS acidosis and rapid correction of acidosis may cause hypokalaemia, accentuate sodium load and contribute to serum hypertonicity. Bicarbonate therapy may also increase hepatic ketone production, thus slowing the rate of recovery from the ketosis.\textsuperscript{61} (III-1)
- Although different routes (SC, IM, IV) and doses have been used, there is considerable evidence to support the use of ‘low dose’ intravenous insulin.\textsuperscript{63-67} (II)
- In circumstances where IV administration is not possible, IM or SC insulin administration has been used effectively and has been demonstrated to be safe.\textsuperscript{68} It should be noted that poor perfusion will impair insulin absorption.\textsuperscript{69} (II)

The evidence for the management of cerebral oedema in diabetic ketoacidosis is listed in Evidence Table 9.1.
- Intravenous mannitol should be given (0.25-1.0g/kg over 20 mins) in patients with signs of cerebral oedema before impending respiratory failure. Although mannitol has been shown to have possible beneficial effects in case reports, there has been no definite beneficial or detrimental effect in epidemiological studies.\textsuperscript{32;70} (IV)
- Repeat mannitol administration in 2 hours if there is no initial response.\textsuperscript{71} (IV)
• Hypertonic saline (3%) 5-10 ml/kg over 30 mins may be an alternative to mannitol. Intubation and ventilation may be necessary, but aggressive hyperventilation has been associated with poor outcome in retrospective studies of diabetic ketoacidosis-related cerebral oedema.10 (III-3)

Additional Technical Reports and Consensus Statements used to formulate the recommendations and principles of clinical practice are listed in Evidence table 9.2.

• The guidelines for the management of diabetic ketoacidosis take into account the conclusions of a consensus statement resulting from a workshop that took place in the United Kingdom involving the European Society for Paediatric Endocrinology (ESPE) and the Lawson Wilkins Pediatric Endocrine Society (LWPES). The Consensus statement was developed with close partnership between the ESPE and LWPES and the International Society for Pediatric and Adolescent Diabetes (ISPAD), all three organisations being represented by members who participated in the writing process. The statement was also endorsed by and contributed to by related organisations; the Juvenile Diabetes Research Foundation International (JDRFI), the World Federation of Pediatric Intensive and Critical Care Societies, the European Society for Pediatric Critical Care, the European Society of Paediatric and Neonatal Intensive Care (ESPNIC) and the Australian Pediatric Endocrine Group (APEG).1

• The American Diabetes Association has produced a position statement on hyperglycaemic crises in patients with diabetes mellitus.10

Recommendations and Principles

• The guidelines for the management of diabetic ketoacidosis should take into account the conclusions of a consensus statement resulting from a workshop that took place in the United Kingdom in June 2003 involving the European Society for Paediatric Endocrinology (ESPE), the Lawson Wilkins Pediatric Endocrine Society (LWPES) and other societies including the Australasian Paediatric Endocrine group (APEG).1 (C)

• The most common precipitating factors in the development of diabetic ketoacidosis include infection, often as a result of inadequate insulin therapy during intercurrent illness and insulin omission.10;11;19;20-22 (IV)

• Diabetic ketoacidosis is the most common cause of death in newly diagnosed type 1 diabetes.10;11;22;34 (IV)

• The greatest risk of mortality from diabetic ketoacidosis is from cerebral oedema.10;11;22;35;36 (IV)

• Although poorly understood, the risk factors for cerebral oedema in diabetic ketoacidosis include presentation with new onset type 1 diabetes,35;37;39 younger age,37;38;39 elevated serum urea nitrogen and/or severity of dehydration at presentation, severity of acidosis,36;43 greater hypocapnia at presentation (after adjusting for degree of acidosis), an attenuated rise in serum sodium during treatment for diabetic ketoacidosis36;40-42; bicarbonate treatment to correct acidosis has also been associated with cerebral oedema.36;44 (III,IV)

• Immediate assessment for diabetic ketoacidosis should consist of clinical history, assessment and biochemical confirmation (see algorithm).72 (C)

• ‘Low dose’ intravenous insulin is recommended for the treatment of moderate to severe diabetic ketoacidosis.1 (C)

• A specialist/consultant paediatrician with training and expertise in the management of diabetic ketoacidosis should direct management.1 (C)

• The child should be cared for in a unit that has experienced nursing staff trained in monitoring and management of diabetic ketoacidosis, clear written guidelines for
managing diabetic ketoacidosis and access to laboratories that can provide frequent and accurate measurement of biochemical variables.\(^1\)(C)

- Children with ketosis and hyperglycaemia, but who are not vomiting, may be managed at home or in an ambulatory care setting (such as an emergency ward).\(^{48,73}\)(IV)
- Children with signs of severe diabetic ketoacidosis or those who may be at increased risk for cerebral oedema should be considered for immediate treatment in an intensive care unit (paediatric if possible) or a children’s ward specialising in diabetes care.(C)
- The management of cerebral oedema in diabetic ketoacidosis is a medical emergency and treatment (fluid restriction, mannitol, neurological assessment) should be initiated in an intensive care facility as soon as the condition is suspected.\(^{37,70}\)(IV)

**Reference List**


72. International Society for Pediatric and Adolescent Diabetes: *ISPAD Consensus Guidelines for the Management of Type 1 Diabetes Mellitus in Children and Adolescents*. Zeist, Netherlands, Medforum, 2000

Chapter 10: Surgery and Fasting

Surgery on children with diabetes should only be undertaken in hospitals with dedicated paediatric facilities for the care of children with diabetes and expert staff (medical, anaesthetic, surgical and nursing).

Children with diabetes requiring a surgical procedure need insulin, even if fasting, to avoid ketoacidosis. They may have increased insulin requirements peri-operatively due to physiological stress and increased counter-regulatory hormones.\textsuperscript{1-3}

When fasting before an anaesthetic an intravenous glucose infusion should be commenced to prevent hypoglycaemia. Paediatric patients particularly those under the age of 5 years old may be prone to hypoglycaemia during anaesthesia and surgery.\textsuperscript{4,5}

Emergency Surgery

Unless it is absolutely clinically indicated, emergency surgery should be delayed in any patient with ketoacidosis until diabetes control has improved and the diabetes stabilised. Diabetic ketoacidosis may by itself cause an acute abdomen, which resolves with treatment of the ketoacidosis.

Elective Surgery

Elective surgery should only be performed in a child or adolescent whose diabetes is under good control.

If glycaemic control is uncertain or poor:
- The child or adolescent should enter hospital beforehand for assessment and stabilisation of metabolic control.
- If control remains poor, surgery should be cancelled and re-booked.

Scheduling of Surgery

Operations should be scheduled early in the morning if possible. If surgery cannot be scheduled for the morning, the patient with diabetes should be first on the afternoon list. This will allow post-operative stabilisation during the day shift.

Maintaining Metabolic Control

Any patient with diabetes who is undergoing prolonged fasting requires:
- Continuous intravenous glucose.
- Hourly blood glucose monitoring in order to maintain blood glucose levels of 5-10 mmol/L.
- Adequate insulin replacement.

The management of diabetes during surgery or procedures that require fasting is complex and exacting. There are different approaches and each case must be judged on its own merits. The suggested protocols below have been shown to be efficacious but do not imply that other protocols when carried out by physicians expert in the care of childhood and adolescent diabetes cannot be used or are in any way less efficacious.

In children and adolescents with type 1 diabetes the optimal method of maintaining metabolic control during major surgery or prolonged post-operative fasting is by an insulin infusion,\textsuperscript{3}
which should be started in association with a maintenance saline/dextrose infusion when fasting commences.

Blood glucose levels must be done hourly whilst on an insulin infusion. Other tests such as electrolytes, blood gases and additional parameters will be determined by the underlying clinical condition.

### Intravenous Fluids

Intravenous fluid should commence at maintenance rates (see Table 9.1) when fasting begins. The intravenous fluids should contain 5 percent dextrose (50 gm/L) initially. This can be made by adding 25 ml of 50% dextrose to 500 ml of N/2 Saline + 2.5% dextrose, or by adding 12.5 ml of 50% dextrose to 500 ml of N/4 + 3.75% dextrose. The glucose concentration of the fluids can be increased if required. An alternative fluid schedule, which does not vary with age, is to use 1500 ml/m²/24 hours.

<table>
<thead>
<tr>
<th>Table 10.1: Maintenance Fluid Volume for Different Age Groups</th>
</tr>
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<tbody>
<tr>
<td><strong>Age Group</strong></td>
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<tr>
<td>Up to 9 months</td>
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<tr>
<td>12 months</td>
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<td>2 years</td>
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<tr>
<td>8 years</td>
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<tr>
<td>12 years</td>
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### Management of Short or Minor Procedures Involving Sedation or Anaesthesia

**Patients on twice or three times daily insulin regimens**

**Procedure first on morning list**

For short procedures involving sedation or anaesthesia, it may be possible to simplify the management of the diabetes by strategies such as:

**Option 1:**
- Arrange for the procedure to be performed at 8 am and delaying the morning insulin (and giving a reduced dose) until food is allowed (providing food is tolerated before 10 am).
- Hourly monitoring of the blood glucose levels is still required.
- Intravenous glucose will usually be required but may not be required if the procedure is short and the blood glucose is maintained.
- If food is not tolerated by 10 am, short/rapid-acting insulin will need to be started by infusion or subcutaneous injections, in addition to the glucose infusion and frequent monitoring.

**Option 2:**
- Give a reduced morning insulin dose at about 7am (50-60% of the usual intermediate insulin dose, no short/rapid-acting unless blood glucose level is high).
- Commence IV fluids at the same time (N/2 Saline + 5% dextrose, or N/4 + 5% dextrose).
- Perform hourly blood glucose readings and increase glucose concentration of IV fluids to 7.5% or 10% if required.
- Extra mid-morning short/rapid-acting insulin may be given if required (10-25% of total daily dose).
Cease IV fluids once oral intake resumes. The usual doses of evening insulin can be given if eating normally.6

**Procedures first on afternoon list**
- If breakfast is not allowed follow the advice below for ‘major surgery where oral intake is not possible for prolonged period’.
- If breakfast is allowed give a reduced morning insulin dose prior to breakfast (30-40% of usual intermediate-acting insulin and 50% of usual short/rapid-acting insulin, depending on BG level).
- Commence IV fluids 2 hours after breakfast (N/2 Saline + 5% dextrose, or N/4 + 5% dextrose) at maintenance rates.
- Perform hourly blood glucose readings and increase glucose concentration of IV fluids to 7.5% or 10% if required.6
- Extra mid-morning short/rapid-acting insulin may be given if required (10-25% of total daily dose).6
- Post-operatively, IV fluids can be ceased once oral intake resumes and additional doses of short/rapid-acting insulin given if required.
- The usual dose of evening insulin can be given if eating normally. Otherwise a reduced dose should be given.6

**Patients on basal-bolus insulin regimens**

**Procedures first on morning list**
- Consider the need for reduction (by 20-30%) of evening intermediate acting insulin if there is a pattern of low blood glucose in the morning.6
- At 7am give 40-50% of the usual short/rapid-acting insulin and commence IV fluids (containing 5% dextrose).6
- Perform hourly blood glucose readings and increase glucose concentration of IV fluids to 7.5% or 10% if required.6
- Extra mid-morning short/rapid-acting insulin may be given if required (10-25% of total daily dose).6
- Usually resume normal food and insulin from lunch.6

**Procedures first on afternoon list**
- The patient is usually allowed breakfast.6
- At 7am give 50-60% of the usual short/rapid-acting insulin.6
- Commence IV fluids (containing 5% dextrose) at maintenance rates 2 hours after breakfast.6
- At 12noon give about 10% of the total daily dose of short/rapid-acting insulin.6
- Perform hourly blood glucose readings and increase glucose concentration of IV fluids to 7.5% or 10% if required.6
- Postoperatively, additional short/rapid-acting insulin may be required (usually 10% of the total daily dose as needed 4-hourly),6 until normal eating is resumed.
- Give the usual insulin and food at dinner and supper.6

**Patients on insulin pumps**
The diabetes team will determine the approach depending on the individual patient and procedure
- Minor procedures: The pump can be continued at the basal rate, keeping glucose infusion to a minimum. Monitor blood glucose levels hourly. Correction doses can be given preoperatively and postoperatively as needed and carbohydrate boluses when the
patient is ready to eat. Alternatively the pump can be discontinued preoperatively and a basal-bolus regimen instituted with adjustment as above.6

- Major procedures: The subcutaneous insulin pump is discontinued and an IV insulin infusion used.6

**Major Surgery or Surgery where Oral Intake is not Possible for a Prolonged Period**

- Commence insulin infusion (see below) and intravenous fluids (containing 5% dextrose) at maintenance rate.
- Hourly BG levels must be done while on an insulin infusion.
- Maintain BG level between 5-10 mmol/L by adjusting the rate of the insulin infusion by 10% increments as required.6

**Insulin Infusion Rates**

Short-acting insulin should be administered as a separate intravenous infusion and diluted in 0.9 percent Saline solution (50 units of insulin in 500 ml of 0.9 percent Saline - equivalent to 1 unit of insulin per 10 ml Saline). The insulin infusion should be run through a volumetric pump at an initial maintenance rate of 0.02 unit/kg/hr in a line separate from the hydration fluid.6 Another protocol is to infuse the insulin at a rate of 0.15 unit/gram of glucose in the maintenance fluids per hour.6 However, whatever the protocol used, the insulin dosage must be adjusted according to individual requirements.

The blood glucose levels are maintained between 5-10 mmol/L by adjusting the rate of the insulin infusion by increments of 10 percent.

The insulin infusion therapy is continued until oral food intake has been established and subcutaneous insulin therapy is possible. The subcutaneous insulin should be given 30 minutes before the meal (or immediately if rapid-acting insulin analogues are used). The insulin infusion should be continued throughout the meal for a total of 30-90 minutes after the subcutaneous insulin injection depending on the type of insulin used.6

**The Evidence**

The evidence for the management of surgery and fasting in children and adolescents with type 1 diabetes is listed in Evidence Table 10.1.

- Children and adolescents with type 1 diabetes have increased insulin requirements peri-operatively.3(III-3)
- In children and adolescents with type 1 diabetes peri-operative management with an insulin infusion results in better blood glucose control than subcutaneous insulin injection.3 (III-3)

Additional Consensus Statements used to formulate the recommendations and principles of clinical practice are listed in Evidence Table 10.2.

**Recommendations and Principles**

- Surgery on children with diabetes should only be undertaken in hospitals with dedicated paediatric facilities for the care of children with diabetes and expert staff (medical, anaesthetic, surgical and nursing).7,8(C)
- When fasting before an anaesthetic an intravenous glucose infusion should be commenced to prevent hypoglycaemia.7,8(C)
• Children with type 1 diabetes requiring a surgical procedure should receive insulin, even if fasting, to avoid ketoacidosis. There may be increased insulin requirements peri-operatively due to physiological stress and increased counter-regulatory hormones.\textsuperscript{3}(III-3)
• In children and adolescents with type 1 diabetes the optimal method of maintaining metabolic control during major surgery or prolonged post-operative fasting is by an insulin infusion.\textsuperscript{3}(III-3)

III-3 = Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group
C = Consensus statement endorsed by professional organisations

Reference List
8. International Society for Pediatric and Adolescent Diabetes: \textit{ISPAD Consensus Guidelines for the Management of Type 1 Diabetes Mellitus in Children and Adolescents}. Zeist, Netherlands, Medforum, 2000
Chapter 11: Sick Day Management

Sick day management is the term used to describe the management of a child or adolescent with diabetes who develops an intercurrent illness.

**Diabetes and Infectious Illnesses**

Children and adolescents with well-controlled diabetes have no greater risk of acquiring infections than the general population, but having diabetes does introduce the need for extra caution in the management of sick days.

While there are no epidemiological studies in children looking at independent risk factors for infection in diabetes, many in vitro models have suggested altered immunity affecting neutrophil function, although the exact relationship with glycaemic control remains unclear. An association with glycaemic control is suggested by studies in diabetic adults showing that more aggressive insulin therapy and blood glucose control post operatively can improve neutrophil function in vitro, and decrease the incidence of wound infection post operatively. Another study in critically ill adults (non diabetic) showed that intensive insulin therapy to maintain blood glucose (BG) between 4.4 and 6.1 mmol/L compared with conventional therapy (BG 10 – 11 mmol/L) reduced the mortality due to multi-organ failure with a proven septic focus. The incidence of bacteraemia was decreased by 46% in the intensive insulin therapy group.

Those with poorly controlled diabetes may have decreased immune defences against infections resulting in:

- Increased risk of acquiring infections.
- Increased chance of infections spreading quickly.
- Increased risk of unusual infections (eg tuberculosis).
- Increased risk of infections from organisms that are not normally pathogenic.
- Poor response to antibiotics.

Diabetes may influence responses to the treatment of coexisting illnesses.

**Impact of Illnesses on Diabetes**

In general, children and adolescents with well-controlled diabetes cope with illnesses very well.

Illnesses vary in their impact on the diabetes. Illnesses may cause:

- Little effect on blood glucose levels.
- Low blood glucose levels.
- High blood glucose levels.

**Infections Causing Little Effect on Blood Glucose Levels**

The key feature of these infections seems to be the lack of systemic upset and they often cause no significant alteration in the metabolic status, eg intercurrent infections such as upper respiratory tract infections, mild infectious mononucleosis or rubella. The transient fever associated with immunisations is usually not associated with any problems with the diabetes.
Infections Causing Low Blood Glucose levels

Such illnesses are usually marked by nausea, vomiting and diarrhoea, but are not accompanied by a fever or systemic features, and there is no increase in insulin resistance or requirement. The problem seems to be mainly the inability to absorb or retain food. Common causes are viral illnesses associated with mild gastritis (nausea and vomiting only) or a mild gastroenteritis (vomiting and diarrhoea). Food poisoning may lead to a similar picture and often the child may complain of abdominal discomfort or pain.

Infections Causing High Blood Glucose Levels

More commonly illnesses in childhood and adolescence raise blood glucose levels. Illnesses associated with fever tend to raise blood glucose because of higher levels of stress hormones and cytokines increasing gluconeogenesis and insulin resistance. In addition, ketones may appear in the urine. Many of these infections have a silent prodromal phase which may cause unexplained high glucose levels for several days before the illness declares itself.

Illnesses that cause raised blood glucose levels are usually those associated with general malaise (lethargy, weakness, irritability, muscle aches, headache), fever and obvious signs of an infection. The child or adolescent may feel nauseous, not feel like eating or drinking, and may vomit.

Typical infections likely to be associated with increased insulin resistance:
- Viral illnesses associated with fever and systemic features, especially if associated with vomiting. Common causes are viral pharyngitis, influenza, and the childhood illnesses such as measles and varicella.
- Bacterial infections, especially if associated with fever. Common causes are tonsillitis, ear infections, lower respiratory tract infections and urinary tract infections associated with fever.

It is important for the child or adolescent to be seen by his/her doctor as bacterial illnesses require antibiotic therapy or other specific therapy and the sooner these are started the better.

The combination of a high blood glucose level and ketones in the urine during illness is a warning sign of a serious lack of insulin action in the body and is due to development of insulin resistance. Treatment is urgent as without extra insulin this state may progress to ketoacidosis.

General Principles of Sick Day Management

No studies were identified addressing insulin adjustment and sick day management in children and adolescents with type 1 diabetes. However, current insulin regimens for sick day management have stood the test of time.

The essential principles in sick day management are:
- *Treat the underlying illness*
  The treatment of the underlying illness is no different in the child or adolescent with diabetes, the only proviso being that medical assessment should be sought earlier in case antibiotic or other therapies are required.
- *Symptomatic relief*
  If a fever, headache or aches and pains are present, give regular paracetamol or ibuprofen in recommended doses and make the child or adolescent comfortable.
- **Rest**  
  Encourage bedrest and keep the child or adolescent at home if unwell.

- **Sugar-free medications**  
  It is important for the child or adolescent to take the medications as prescribed. For young children, many syrups are available in sugar-free forms (antibiotics, paracetamol, ibuprofen) and those not sugar-free are usually satisfactory as the amount of sugar present in each dose is not large enough to cause a problem. For older children and adolescents, most medications are available in tablet or capsule form and these are sugar-free.

- **Hydration**  
  Encourage plenty of fluids. A child or adolescent with a fever loses more fluid due to the increased body temperature. There may be continuing losses of quite large volumes of fluid because of glycosuria causing an osmotic diuresis. It is important to remember that because of the osmotic diuresis even markedly dehydrated children or adolescents with diabetes can progress to more severe dehydration if the blood glucose remains high. If the blood glucose is >15 mmol/L water or low joule drinks should be offered so as not to raise the blood glucose further.

- **Preparation for sick days**  
  Each family should have a sick day kit prepared and ready to use (see Table 11.1).

### Table 11.1: Emergency Kit for Sick Day Management at Home

<table>
<thead>
<tr>
<th>Item</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid-acting insulin or short-acting insulin.</td>
</tr>
<tr>
<td>Glucose test strips, meters and lancets/finger pricking devices.</td>
</tr>
<tr>
<td>Urine test strips for glucose and ketone estimation or blood ketone meter and strips.</td>
</tr>
<tr>
<td>Doctor’s/hospital’s phone number.</td>
</tr>
<tr>
<td>Sweet cordial/fruit juice/lemonade or other soft drinks (caffeine is not recommended).</td>
</tr>
<tr>
<td>Low joule (diet drinks) or water.</td>
</tr>
<tr>
<td>Glucagon.</td>
</tr>
<tr>
<td>Diabetes manual or emergency guidelines, including sick day foods.</td>
</tr>
<tr>
<td>Thermometer.</td>
</tr>
<tr>
<td>Diary.</td>
</tr>
<tr>
<td>Paracetamol or ibuprofen - sugar-free syrup or tablets.</td>
</tr>
</tbody>
</table>

- **Education on sick day management**  
  There are several key concepts that must be taught to all families:
  - Insulin must never be omitted.
  - Glucose levels during illness may rise, even in the absence of any ingested food due to gluconeogenesis.
  - Vomiting is a serious sign.
  - The presence of ketones in the urine or blood with high blood glucose is a serious sign.

Families must be aware of the signs that indicate the condition is too serious to treat at home (see Table 11.2).

- **General nutrition**  
  If the child or adolescent is anorexic, encourage oral intake by tempting with fluids and foods that may appeal (see Table 11.3).
Table 11.2: Indicators for Patient to be Transferred to Hospital

Sick day management at home should be abandoned and transfer to hospital arranged if:

- Vomiting persists, especially if it is frequent or becomes bile-stained.
- Hyperventilation occurs suggestive of Kussmaul respiration.
- Ketones are present and are increasing.
- Blood glucose continues to rise despite treatment.
- The child or adolescent becomes more unwell, drowsy, disoriented or confused.
- The nature of the illness is not understood.
- Abdominal pain is severe or localised.
- The caregivers are uncertain about how to handle the situation.
- Other diseases coexist (e.g. cystic fibrosis).
- The patient is very young (e.g. under 2 years).

Table 11.3: Sick Day Foods and Fluids

The following quantities are approximately 1 exchange (15 gm of carbohydrate)

**Fluids:**
- 1 _ cup orange, apple or pineapple juice.
- 1 cup tea/water with 1 tablespoon of sugar or 1 _ tablespoons of honey.
- 1 cup of milk (170 ml) with 1 tablespoon of sweet drinking powder.
- 1 cup of sweet soft drink.

**Foods:**
- Slice of bread or toast.
- 1 _ cup potato or 1 medium size potato.
- 1 _ cup boiled rice.
- 1 English muffin.
- 2-3 plain dry biscuits.
- 2 scoops of ice-cream.
- 200 gm unsweetened yoghurt or _ carton (100 gm) sweetened yoghurt.
- 1 _ cup unsweetened tinned fruit.
- 1 _ cup sweet jelly.
- 1 small banana.
- 1 medium orange.
- 7 small jelly beans.

Insulin Regimens in Infections associated with Hyperglycaemia and Ketosis

**Management at home**

Additional insulin given at home can frequently avert hospitalisation in illnesses associated with hyperglycaemia and ketosis.

The additional insulin used is short-acting or rapid-acting insulin given every 2-4 hours as additional injections equal to 10-20 percent of the total insulin daily dosage.

The dosage, the frequency and the route of injection will vary according to the particular circumstances for the particular patient.

The factors that have to be taken into account are:

- The degree of elevation of the blood glucose level.
- The length of time the blood glucose levels have been elevated.
- The patient’s age (extra caution in the very young).
- The total insulin dosage during a normal day.
Presence or absence of urinary ketones.

The response to the previous dose of insulin.

In general, 20 percent of total daily dosage is used for the additional injections if the patient is very sick, has blood glucose in excess of 15 mmol/L and has moderate or larger amounts of ketones in the urine. An acceptable regimen is shown below in Table 11.4.

### Table 11.4: How to Calculate the Amount of Extra Insulin on Sick Days

<table>
<thead>
<tr>
<th>Blood glucose (mmol/L)</th>
<th>Urine ketones</th>
<th>Blood ketones (mmol/L)*</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤15</td>
<td>Negative</td>
<td>&lt;1*</td>
<td>Do not give extra insulin. Check blood glucose and ketones again in two hours.</td>
</tr>
<tr>
<td>&gt;15</td>
<td>Negative</td>
<td>&lt;1*</td>
<td>Re-check blood glucose in two hours. Blood glucose may fall without extra insulin. If persistently elevated consider an extra 5% of TDD (total daily dose) of insulin.</td>
</tr>
<tr>
<td>&gt;15</td>
<td>Trace or small</td>
<td>1.0-1.4*</td>
<td>Give an extra 5 to 10% of TDD every 2-4 hours. Check blood glucose and ketones again in two hours.</td>
</tr>
<tr>
<td>&gt;15</td>
<td>Moderate or large</td>
<td>≥1.5*</td>
<td>Give an extra 10 to 20% of TDD every 2-4 hours. Check blood glucose and ketones every hour.</td>
</tr>
</tbody>
</table>

Note: Extra insulin may be given as rapid-acting insulin or short-acting insulin analogues. To calculate the Total Daily Dose (TDD) add up all the insulin given on a usual day (ie. Rapid-acting + intermediate/long-acting). Do not include additional boluses given for unexpected hyperglycaemia.

*Adapted from sample algorithm*, no data available from clinical trials.

If a rapid response is required, the short-acting insulin can be given intramuscularly every 2 hours (Note: syringes with 8mm needles may not reach the muscle compartment). This should be only under the direction of an endocrinologist and is outside the usual protocols supervised by diabetes educators. Normally the condition is less urgent and the injections are given subcutaneously at 4-hourly intervals until there is improvement.

Once the blood glucose is less than 15 mmol/L but above 12 mmol/L, repeated doses are usually 10 percent of the total daily dose given every 4 hours (in addition to the usual insulin).

#### Management in hospital

If the patient requires transfer to hospital for any reason (see Table 11.2) the management should include the following:

- If blood glucose level is >15 mmol/L and there are moderate or large ketones, but with no or only mild ketoacidosis (venous pH >7.20).
  - IV fluids should be commenced (0.9% Saline initially at maintenance plus replacement of estimated deficits over 24-48 hours).
  - Extra doses of short/rapid-acting sub-cutaneous insulin (10-20% of the total daily dose given as short/rapid acting) are given every 2-4 hours until BG level <15 mmol/L and ketones have cleared.
- Once BG level falls below 15 mmol/L, dextrose should be added to the IV fluids. The recommended dextrose containing fluid is N/2 Saline + 5% dextrose. This can be made by adding 25 ml of 50% dextrose to 500 ml of N/2 Saline + 2.5% dextrose.
- Grade to oral intake when possible.
Insulin Regimens in Infections Associated with Persistent Hypoglycaemia

Management at home
These illnesses are marked by semi-starvation due to extreme anorexia, often associated with vomiting and diarrhoea. The need is for frequent blood glucose testing, frequent sips of sugar- or glucose-containing drinks or small portions of easily absorbed carbohydrate foods. Insulin doses should be reduced but must not be suspended. In twice-daily insulin regimens the short/rapid-acting insulin can be greatly reduced or possibly even omitted. The intermediate insulin dosage may need reductions of 20-50 percent.

In basal-bolus regimens the short/rapid-acting doses may need to be reduced by 20-50 percent and the intermediate insulin by 20-50 percent.

Management in hospital
If the blood glucose level cannot be maintained by oral intake:

- IV fluids should be commenced with N/2 Saline + 5% dextrose.
- The BG level should be checked every 1-2 hours.
- Insulin doses should be reduced as described above.

Glucagon
For severe hypoglycaemia, in the hospital setting, the preferred treatment is intravenous glucose (bolus dose 2-5 ml/kg of 10% dextrose over a few minutes) followed by dextrose-containing maintenance fluids (see also severe hypoglycaemia). Intravenous dextrose raises the blood glucose level faster than intramuscular glucagon.10,11 When intravenous access is difficult or outside the hospital setting, severe hypoglycaemia should be treated with intramuscular glucagon injection. The recommended dose is 0.5 units (or mg) for children <25kg or <8 years old and 1.0 units (mg) for older children or those weighing >25kg).12 Remember that glucagon may make the child or adolescent vomit.

Minidose Glucagon
Under the supervision of a doctor or diabetes educator it is possible to prevent or treat ongoing mild hypoglycaemia in a child unwilling to eat or drink in an ambulatory setting with small doses of subcutaneous glucagon.13 If hypoglycaemia is mild, ongoing or is impending (ie blood glucose <4.4 mmol/L associated with gastroenteritis or food refusal),13 an injection of a small dose of glucagon may reverse the hypoglycaemia without causing nausea and vomiting and enable oral fluids to be re-established. This may prevent hospitalisation in some cases. The recommended dose regimen is detailed below. Following the use of mini-dose glucagon continued monitoring is imperative.

Table 11.5: Recommended Dose for Mini-dose Glucagon13

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>mcg (µg)</th>
<th>mg</th>
<th>ml</th>
<th>Units on insulin syringe</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2</td>
<td>20</td>
<td>0.02</td>
<td>0.02</td>
<td>2</td>
</tr>
<tr>
<td>2 – 15</td>
<td>10 per year of age</td>
<td>0.01 per year of age</td>
<td>0.01 per year of age</td>
<td>1 per year of age</td>
</tr>
<tr>
<td>&gt;15</td>
<td>150</td>
<td>0.15</td>
<td>0.15</td>
<td>15</td>
</tr>
</tbody>
</table>
Insulin Pump Sick Day Management

The key points in the management of sick days are the same for insulin pump users as for those on insulin injections. As people on pumps use only rapid-acting insulin and do not have any injected depot of long-acting insulin, diabetic ketoacidosis can develop rapidly and therefore hyperglycaemia must be taken very seriously.

If the blood glucose level is 15 mmol/L or above, the following steps should be taken:

- Immediately check for problems with the pump or delivery system.
- Check for ketones in the blood or urine.
- Proceed as directed in Table 11.6 depending on ketone result.
- To overcome insulin resistance, the basal rate and/or correction boluses may need to be increased during the period of illness.

Table 11.6: Management of Sick Days with Insulin Pump

<table>
<thead>
<tr>
<th>If urine ketones are negative or small or blood ketones less than 0.6 mmol/L.</th>
<th>If urine ketones are moderate or high or blood ketones more than 0.6 mmol/L, or you don’t think the pump is working.</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Give a correction bolus with the pump (see Insulin pump adjustments – Chapter 5).</td>
<td>• There may be a pump delivery problem or a significant illness developing.</td>
</tr>
<tr>
<td>• Test the BG hourly.</td>
<td>• Liaise with diabetes pump team.</td>
</tr>
<tr>
<td>• Drink extra low joule fluids.</td>
<td>• Use injected insulin given with a syringe or pen to deliver the correction bolus dose (see Insulin pump adjustments - Chapter 5).</td>
</tr>
<tr>
<td>• If BG is lower after 1 hour, recheck again in 1 to 2 hours and decide if another correction bolus dose is needed (use the unused bolus rule, see Insulin pump adjustments - Chapter 5).</td>
<td>• Drink extra unsweetened (low joule) ‘diet’ fluids.</td>
</tr>
<tr>
<td>• If the BG is not lower after the first bolus proceed to give an injection with a syringe or pen (see column 2).</td>
<td>• Test the BG hourly.</td>
</tr>
<tr>
<td></td>
<td>• Replace the insulin in the pump, and the infusion set and cannula. Do not use the pump again until the situation is under control.</td>
</tr>
<tr>
<td></td>
<td>• If after 2 hours there is no improvement, liaise with diabetes pump team.</td>
</tr>
<tr>
<td></td>
<td>• If after 2 hours the BG is improved, use the unused bolus rule to decide if an additional bolus is needed (see Insulin pump adjustments - Chapter 5). Pump use can be resumed.</td>
</tr>
<tr>
<td></td>
<td>• If BG remains high, ketones persist, or nausea, vomiting or abdominal pain develop, liaise with diabetes pump team or immediate hospital assessment recommended.</td>
</tr>
</tbody>
</table>

Table adapted from Walsh and Roberts: Pumping insulin. Everything you need for success with an insulin pump.15

When patients are eating less their meal boluses should be decreased; however as food absorption may be poor during the illness, it may be necessary to decrease insulin boluses to even less than the usual ratio. The basal insulin rate may also need to be decreased if the blood glucose still tends to be low.

Hypoglycaemia should be treated in the usual way.
The Evidence
No studies were identified addressing insulin adjustment and sick day management in children and adolescents with type 1 diabetes.

The evidence for the management of severe hypoglycaemia (intravenous glucose versus intramuscular or intravenous glucagon) is listed in Evidence Table 11.1.
- Intravenous dextrose raises the blood glucose level faster than intramuscular glucagon.10;11 (II)

The evidence for the management of mild or impending hypoglycaemia using minidose glucagon is listed in Evidence Table 11.1.
- In a small case series, 28/33 children with type 1 diabetes who had gastroenteritis with impending hypoglycaemia, were effectively managed at home with small doses of intramuscular glucagon.13 (IV)

Additional Technical Reports and Consensus Statements used to formulate the recommendations and principles of clinical practice are listed in Evidence Table 11.2.

Recommendations and Principles
- Families should be informed that intercurrent illnesses can cause high or low blood glucose levels.7;16;17 (C)
- All families should receive education about the management of sick days and have a sick day kit at home containing rapid-acting or short-acting insulin, glucose test strips, meters, lancets/finger pricking devices, urine test strips for glucose and ketone estimation or blood ketone meter and strips, doctor’s/hospital’s phone number, sweet cordial/fruit juice/lemonade or other soft drinks, low joule (diet drinks) or water, glucagon, diabetes manual or emergency guidelines, sick day foods, thermometer, paracetamol or ibuprofen (sugar-free syrup or tablets).7;16;17 (C)
- Insulin should never be omitted even if unable to eat.7;16;17 (C)
- Blood glucose and ketones should be monitored frequently.7;16;17 (C)
- Any underlying illness should be treated promptly.7;16;17 (C)
- Extra oral fluids should be encouraged especially if the blood glucose is high or ketones are present.7;16;17 (C)
- Additional boluses of short/rapid-acting insulin equal to 10-20 percent of the total insulin daily dosage should be given every 2-4 hours if the blood glucose is high and ketones are present.7;16;17 (C)
- Patients/carers should seek assistance immediately if, after extra insulin boluses, the blood glucose remains high, ketones persist, or nausea, vomiting or abdominal pain develop.7;16;17 (C)
- Severe hypoglycaemia should be treated with intravenous dextrose (in the hospital setting).10;11 (II)
- If venous access is difficult or outside the hospital setting, intramuscular glucagon should be used to treat severe hypoglycaemia.7;16;17 (C)
- Under the supervision of a doctor or diabetes educator, small doses of subcutaneous glucagon may be used to prevent or treat mild hypoglycaemia in an ambulatory setting.13 (IV)

II = Evidence from at least one properly-designed RCT
IV = Evidence obtained from case series, either post-test or pre-test and post-test
C = Consensus statement endorsed by professional organisations
Reference List
12. MediMedia Australia Pty Limited: MIMS Australia. 2003
Chapter 12: Hypoglycaemia

Hypoglycaemia is the most frequent acute complication of type 1 diabetes. It is the major factor limiting intensified regimens aiming for near-normoglycaemia. Severe hypoglycaemia is rated as the most anxiety-promoting feature of diabetes by both children and parents and may lead to loss of self-esteem and social isolation. Hypoglycaemia does not appear to cause permanent neuro-psychological impairment in adults but may do so in younger children. Hypoglycaemia should be avoided in children, especially in those under 5 years of age.

Definition

There is no agreed definition of hypoglycaemia. The blood glucose level at which hypoglycaemic clinical features occur varies considerably between individuals and even within the same individual.

Hypoglycaemia may be symptomatic or asymptomatic (hypo unawareness). The level at which hypoglycaemia is recognised by the individual is influenced by preceding hypoglycaemic episodes and also by preceding hyperglycaemia. The individual’s recognition of hypoglycaemia is predominantly due to the autonomic features (see below). Recognition of neuroglycopenic features varies considerably but may be improved in adults by specific blood glucose awareness training programmes. Young children may not be able to recognise the clinical features of hypoglycaemia.

Counter-regulatory hormone and symptom responses to falling glucose levels develop at higher levels in children than adults and may be detected at plasma glucose values between 3.5 and 4.0 mmol/L. Children and adolescents with poor glycaemic control may experience symptoms and hormonal responses at even higher, sometimes normal, glycaemic levels.

Whilst the precise definition of what constitutes hypoglycaemia remains controversial parents and children need to know what levels of glucose to respond to. The brain needs a constant supply of glucose, and cognitive defects in children and adolescents with diabetes have been found at glucose values between 3.3 and 3.6 mmol/L. As a result, it is advisable to maintain blood glucose values above 4.0 mmol/L in children with diabetes.

Symptoms and Signs

As in adults, symptom responses to hypoglycaemia in children or adolescents may be divided into those described as autonomic or neuroglycopenic.

The autonomic symptoms and signs may be:
- Cholinergic (sweating, hunger, tingling around the mouth).
- Adrenergic (tremor, tachycardia, pallor, palpitations and anxiety).

Neuroglycopenic symptoms and signs include:
- Weakness.
- Headache.
- Visual disturbance.
- Slurred speech.
- Vertigo and dizziness.
- Difficulty in thinking.
- Tiredness.
- Drowsiness.
• Change in affect (eg depressed, angry, argumentative).
• Mental confusion.
• Coma.
• Convulsions.

Usually autonomic responses occur before neuroglycopenic features however in hypoglycaemia unawareness, neuroglycopenic features occur before autonomic features (which may be absent).

Parents and caregivers usually recognise symptoms of hypoglycaemia in younger children who show behavioural changes such as irritability or show changes in appearance such as pallor and sweatiness.

The symptoms of hypoglycaemia may not always be the same for a given blood glucose level and parents and caregivers need to be aware of the protean nature of the clinical features possible during hypoglycaemia.

### Table 12.1: Symptoms of Hypoglycaemia in Diabetic Children and Recommendations for its Treatment

<table>
<thead>
<tr>
<th>Severity</th>
<th>Clinical Features</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Mild autonomic features (adrenergic and cholinergic) - hunger, shakiness, tremor, nervousness, anxiety, sweatiness, pallor, palpitations and tachycardia. Mild neuroglycopenia – decreased attention and cognitive performance.</td>
<td>Juice, sweet lemonade, cordial, snack. If the hypoglycaemia is very mild it may be possible to bring forward the scheduled meal if episode occurs within 15-30 minutes of a planned meal.</td>
</tr>
<tr>
<td>Moderate</td>
<td>Moderate neuroglycopenic and autonomic features - headache, abdominal pain, behaviour changes, aggressiveness, impaired or double vision, confusion, drowsiness, weakness, difficulty in talking, tachycardia, dilated pupils, pallor, sweatiness.</td>
<td>10-20 gm of easily absorbed carbohydrate followed by a snack with carbohydrate foods.</td>
</tr>
<tr>
<td>Severe</td>
<td>Severe neuroglycopenic features - extreme disorientation, loss of consciousness, focal or generalised seizures.</td>
<td>Outside hospital: Glucagon by injection (s.c., i.m. or i.v.) 0.5 mg &lt;8 years of age or &lt;25kg, 1.0 mg &gt;8 years of age or &gt;25kg. If no response in 10 minutes, check blood glucose. If still low repeat once. Follow-up with carbohydrate foods and frequent monitoring. In hospital: intravenous dextrose (2-5 ml/kg body weight of 10% dextrose) followed by 5-10% dextrose infusion to maintain blood glucose level between 5-10 mmol/L.</td>
</tr>
</tbody>
</table>
Grading

Hypoglycaemia may be symptomatic or asymptomatic.\textsuperscript{22}

Symptomatic hypoglycaemia can usefully be divided into three grades on the following clinical criteria:

- Grade 1 or mild when the child or adolescent with diabetes is able to detect and treat the hypoglycaemia himself/herself. Hypoglycaemia occurring in children under the age of 5 years can not be classified as grade 1 or mild because young children are not able to treat themselves.
- Grade 2 or moderate hypoglycaemia occurs when someone else has to go to the aid of the child or adolescent with diabetes, but treatment is possible orally.
- Grade 3 or severe hypoglycaemia occurs when the child or adolescent is unconscious, convulsion or unable to take oral glucose because of extreme disorientation and the only therapy is either glucagon by injection or intravenous glucose.

Frequency

In the Diabetes Control and Complications Trial, adolescents receiving intensive therapy had 86 episodes of hypoglycaemia per 100 patient-years requiring assistance and 27 episodes of hypoglycaemic coma or seizures per 100 patient-years. Adolescents on conventional therapy had 28 and 10 episodes per 100 patient-years respectively.\textsuperscript{23}

In the UK, a national audit of children aged less than 17 years with type 1 diabetes reported that 4\% experienced one or more episodes of severe hypoglycaemia per year.\textsuperscript{24}

In a recent audit of glycaemic control in NSW and ACT, the prevalence of severe hypoglycaemia (coma or convulsion) was 36 episodes per 100 patient-years.\textsuperscript{25,26} In Western Australia (in 1995), the incidence of severe hypoglycaemia (coma or convulsion) was 15.6 per 100 patient-years.\textsuperscript{27}

Adolescents have a higher incidence of moderate and severe hypoglycaemia despite having higher HbA\textsubscript{1c} levels than adults.\textsuperscript{23,28,29} The increased risk of hypoglycaemia in adolescence may be related to:

- The need for larger insulin doses during the phase of rapid growth.
- Irregular diet.
- Irregular activity levels.

Nocturnal Hypoglycaemia

Nocturnal hypoglycaemia is frequent, often prolonged and may be asymptomatic.\textsuperscript{30} Nocturnal hypoglycaemia does not necessarily disturb sleep patterns. It may be suspected if pre-breakfast blood glucose is low, confusional states, nightmares or seizures occur during the night or impaired thinking, lethargy, altered mood\textsuperscript{31} or headaches are experienced on waking. Counter-regulatory responses may be impaired during sleep.\textsuperscript{32,33}

Nocturnal hypoglycaemia is not reliably predictable on the basis of a bedtime blood glucose level;\textsuperscript{34} therefore, blood glucose monitoring with regular measurements after midnight is essential to detect nocturnal hypoglycaemia.

Nocturnal hypoglycaemia may be reduced by careful attention to the dose and type of insulin used. The 11pm blood glucose level does not accurately predict the 2am blood glucose level.\textsuperscript{34} Periodic early morning blood glucose levels are recommended.
Consequences

The adverse consequences of hypoglycaemia include:

- Injury or accident during a hypoglycaemic episode. A recent international multicentre survey of drivers with type 1 diabetes found that they are at increased risk for driving mishaps than drivers who do not have type 1 diabetes.\textsuperscript{35}

- Death.  
  Hypoglycaemia was implicated in 8% of diabetes related deaths in children <20 years old.\textsuperscript{36}

- Fear of hypoglycaemia by the parents of a young child. This often interferes with any attempts to improve control.\textsuperscript{37} Similarly, for an adolescent, an unexpected hypoglycaemic episode is an embarrassment that he/she may seek to avoid, even at the expense of hyperglycaemia and poorer control.

- Direct effects of hypoglycaemia on the brain.  
  Although no adverse neuropsychological effects have been demonstrated in adults following severe hypoglycaemia,\textsuperscript{3,5,38} there are greater concerns about the consequences of hypoglycaemia in young children because of the continued growth and development of the brain. Cognitive deficits have been reported in children who have developed diabetes before the age of five years, or if the child has had hypoglycaemia induced seizures.\textsuperscript{6-9,39,40} Both inadequate glycaemic control and the sensitivity of the young brain to hypoglycaemia may account for these findings. In children who have developed diabetes after the age of 5 years, this difference has not been found.

- In a recent cost-of-illness study hypoglycaemia was found to have significant socioeconomic costs.\textsuperscript{41}

Counter-Regulatory Responses to Hypoglycaemia and Hypoglycaemia Unawareness

In non-diabetic individuals, a number of responses are generated by insulin-induced hypoglycaemia. Initially, endogenous insulin secretion is suppressed at an early stage. Secondly, glucagon and adrenaline, the rapid-acting counter-regulatory hormones, are promptly released.\textsuperscript{42} This results in glycogenolysis, but if hypoglycaemia is prolonged, gluconeogenesis is also stimulated. Adrenaline has additional effects on peripheral glucose utilisation and stimulates lipolysis. Finally, when hypoglycaemia is prolonged, growth hormone and cortisol responses increase hepatic glucose production and suppress glucose use in peripheral tissues.\textsuperscript{42}

The integrity of glucose counter-regulation is disturbed by type 1 diabetes.\textsuperscript{12,43} In diabetic subjects receiving insulin by injection, insulin levels cannot therefore be suppressed and in addition glucagon responses to insulin-induced hypoglycaemia are characteristically lost. Unfortunately adrenaline responses may also be disrupted.

The reduction in adrenaline responses may be:

- Permanent.
- Reversible and be the result of hypoglycaemia per se, i.e. hypoglycaemia-associated autonomic failure.

Hypoglycaemia-associated autonomic failure is often associated with loss of symptomatic responses.\textsuperscript{14,16,21} It may be reversible by prevention of hypoglycaemia.

The development of hypoglycaemia unawareness in childhood should lead to suspicion of previous episodes of undiagnosed hypoglycaemia (often nocturnal).\textsuperscript{44}
Prevention

Hypoglycaemia in children is largely preventable. However there is a significant proportion of severe hypoglycaemic episodes in which no obvious cause can be determined. The most common causes of hypoglycaemia are:

- Inadequate or missed meals or snacks.
- Physical activity (unplanned or more prolonged than usual) without appropriate food intake.
- Insulin administration errors (eg inadvertent reversal of morning and evening doses or of the short/rapid- and intermediate-acting insulins).
- Alcohol ingestion (resulting in impaired hepatic gluconeogenesis).
- Idiopathic (no obvious cause discernible). It is likely that some of these are related to variations in insulin absorption.

All children and adolescents with diabetes should carry glucose tablets or readily absorbed carbohydrate foods (preferably in waterproof sealed wrap) on their person and have glucagon available at home (and in boarding schools where there is a nurse on staff).

Children and adolescents with type 1 diabetes should be encouraged to wear a Medic-Alert37;45 (or similar warning information), and people rendering first aid should be made aware to look for such warning devices.

Adequate parental education and support should be available so that proper insulin and dietary adjustments can be made to reduce the risk of hypoglycaemia. For example, parents and children should be taught how to deal with unusual exercise and events such as school camps.

Confirmation

Although it is useful to have the hypoglycaemia confirmed by a blood glucose measurement, treatment is urgent and should not be withheld if undue delay is likely.

Treatment

Mild to moderate hypoglycaemia

Treatment involves immediate consumption of 10-20 gm of an easily absorbed form of carbohydrate, followed by a snack of carbohydrate foods to maintain normoglycaemia until the next meal or snack.45

Glucose cannot be absorbed from the oral cavity therefore massaging the outside of the cheek against the gum is not effective.46

In adults, a RCT crossover study compared the rises in blood glucose levels after various therapies for hypoglycaemia. After 10 gm oral glucose, peak BG level reached 5.4 ± 0.4 mmol/L, after 20 gm oral glucose peak BG level reached 6.8 ± 0.7 mmol/L and after 1 mg glucagon peak BG level reached 11.8 ± 0.8 mmol/L.47

Lemonade and glucose tablets (which must be easily chewable) are examples of appropriate foods for the treatment of mild to moderate hypoglycaemia.

If giving a drink to a hypoglycaemic child, it is useful to put the child’s hands around the cup and to guide the cup to the mouth. This minimises the natural reaction of rejecting the drink. Insulin and dietary adjustments should be made to prevent further hypoglycaemia when appropriate.
Severe hypoglycaemia

For severe hypoglycaemia therapy is urgent. People who are either unconscious or fitting are unable to swallow. Nothing should be given by mouth. The airway should be checked to ensure that respiration is unhampered, the person should be placed on their side (resuscitation position) to prevent aspiration of material into the lungs and emergency services (dial 000) called.

Parents are taught to administer glucagon by injection according to the manufacturer’s instructions. The recommended dose is 0.5 units (or mg) for children who are <25kg or ≤8 years old, and 1.0 units (mg) for older children or those weighing >25kg. All children and adolescents with diabetes should have glucagon at home and their families shown (by ‘hands on’ practice during diabetes education sessions) how to administer it in times of severe hypoglycaemia. Following treatment with IM glucagon, further treatment with intravenous dextrose by emergency services may occasionally be required if hypoglycaemia persists.

Glucagon is normally administered intramuscularly or subcutaneously but can also be given intravenously in the hospital setting. Glucagon frequently causes nausea and vomiting.48

Figure 12.1: Glucagon Kit for Treatment of Hypoglycaemia

Intravenous glucose (dextrose) is more rapid at reversing hypoglycaemia than IM49 or IV50 glucagon. However, intravenous glucose can only be administered by doctors or specially trained health care professionals such as paramedics or intensive care ambulance officers. The dose is 0.2-0.5 gm/kg body weight. This can be given as 2-5 ml/kg of 10 percent dextrose. If 25 percent dextrose is used, the dose is 1.0-1.5 ml per kg body weight, but care must be taken not to exceed this because of the danger of causing severe hyperglycaemia rapidly. The dextrose should be given slowly over a few minutes. Care should be taken to avoid extravasation because its hyperosmolality may cause local tissue irritation or necrosis. 50% dextrose should not be used.

Intramuscular epinephrine (0.3 mg) has been shown to be less effective than IM glucagon (1.0 mg) in raising the blood glucose at 15 minutes (2.6 ± 0.2 versus 0.5 ± 0.3 mmol/L).51 Other therapies which have been shown to have effect in adult studies include oral terbutaline (5.0 mg), subcutaneous terbutaline (0.25 mg) and oral alanine (40 gm).47 Glucagon remains the drug of choice if intravenous dextrose is not readily available.

Follow-Up of Treatment of Hypoglycaemia

The initial treatment for hypoglycaemia may need to be repeated if follow-up blood glucose testing indicates a recurrence or continuation of the hypoglycaemia.
Many children vomit persistently after severe hypoglycaemia, especially after glucagon.

After the emergency treatment of the hypoglycaemia, it is necessary to ensure that the hypoglycaemia does not recur and hence the following actions are needed:

- Frequent measurement of blood glucose levels.
- Ensuring that food is tolerated (either as frequent small amounts of sugary drinks or an adequate amount of easily absorbed carbohydrate).
- Supervision by a relative or friend who should accompany the person home.
- Arranging an early appointment with the doctor for review of diabetes management.
- If food is not tolerated, then hospitalisation for a continuous infusion of 5-10 percent dextrose and frequent monitoring is necessary.

**Hypoglycaemia and Physical Activity**

Hypoglycaemia may occur during, immediately after or many hours after physical activity. Special attention should be given to children and adolescents performing intensive sports, especially those involving endurance training, due to the association with delayed hypoglycaemic reactions which may occur in the middle of the night or before breakfast the next day. Advice should be sought from a dietitian for foods suitable for those undertaking endurance sports.

Most sports days can be readily managed by increasing caloric intake during and after the sport. A general recommendation is that an extra serve of easily absorbable carbohydrate be taken for every half hour of sport. Requirements for extra carbohydrate with physical activity are very individual.

Intensive sports need to have appropriate reductions made in dosages of the insulin acting during and for the following 12-24 hours after the physical activity.

Blood glucose levels need to be measured before, during and after intensive sport. Experience and blood glucose monitoring help determine the most appropriate strategies.

All children and adolescents participating in sport should have access to help in case of hypoglycaemia. Participating in physical activity in isolation should be discouraged. Those involved in strenuous and potentially dangerous sports should have a ‘buddy’ able to offer assistance.

If weight gain is an issue, decreasing insulin before exercise lessens the need for extra food.

**Somogyi Phenomenon**

The concept of hypoglycaemia causing rebound hyperglycaemia was generally referred to as the Somogyi phenomenon or effect. Fasting hyperglycaemia was thought to be due to a counter-regulatory overshoot of the blood glucose following unrecognised nocturnal hypoglycaemia. Whilst the Somogyi phenomenon has been shown to exist, the dawn phenomenon and the waning of insulin levels are more likely causes of prebreakfast hyperglycaemia.

**Hypoglycaemia in School**

Teachers and carers at schools should be informed as to the symptoms of hypoglycaemia and appropriate treatment. They should also have access to advice when necessary.

It may be useful for a member of the diabetes team to visit the school and provide this education to the teacher.
Children should not be restricted in activities at school but extra carbohydrate should be given prior to sports or physical education activities. Easily absorbed carbohydrate should be available at school.

**Foods for Management of Hypoglycaemia**

Examples of the foods suitable for the management of hypoglycaemia are indicated below. Easily absorbed carbohydrate should be followed within 15-20 minutes by a choice of carbohydrate foods to maintain blood glucose levels.

Easily absorbed carbohydrate to begin with:
- 125-200 ml ordinary soft drink or diluted cordial.
- 4 large jelly beans, 7 small jelly beans.
- 2-3 teaspoons of sugar.
- Glucose tablets (10-20 gm).

Carbohydrate foods to follow up with (equivalent to 15 gm carbohydrate or 1 exchange):
- 1 slice of bread.
- 1 banana or apple.
- 200 gm unsweetened yoghurt or 100 gm sweetened yoghurt.
- 1 glass of milk (300 ml).

**The Evidence**

The evidence for the effect of intensive diabetes management on the incidence of hypoglycaemia in type 1 diabetes is listed in Evidence Table 12.1.

- In the Diabetes Control and Complications Trial, adolescents receiving intensive therapy had 86 episodes of hypoglycaemia per 100 patient-years requiring assistance and 27 episodes of hypoglycaemic coma or seizures per 100 patient-years. Adolescents on conventional therapy had 28 and 10 episodes per 100 patient-years respectively.23(II)
- In NSW and ACT, the prevalence of severe hypoglycaemia (coma or convulsion) was 36 episodes per 100 patient years.25;26(IV)
- A prospective study in Western Australia found that the incidence of severe hypoglycaemia (coma or convulsion) increased from 4.8 to 15.6 per 100 patient-years in parallel with a decrease in HbA1c from 10.2% in 1992 to 8.8% in 1995. This increase was particularly marked in younger children (<6 years) in whom severe hypoglycaemia increased from 14.9 to 42.1 episodes/100 patient-years.27(IV)
- Adolescents have a higher incidence of moderate and severe hypoglycaemia than adults despite having higher HbA1c levels than adults.23;29(II)

The evidence for the management of severe hypoglycaemia (intravenous glucose versus intramuscular or intravenous glucagon) is listed in Evidence Table 12.2.

- RCT’s have found that intravenous glucose (dextrose) is more rapid at reversing hypoglycaemia than IM49 or IV50 glucagon.(II)

The evidence for the effects of hypoglycaemia on cognitive function in children and adolescents with type 1 diabetes is listed in Evidence Table 12.3.

- Hypoglycaemia has been associated with neurocognitive dysfunction in children especially if there is a history of hypoglycaemic seizures or if the child had early onset of diabetes.6-10,39;40(II, III, IV)
The Consensus Statements used to formulate the recommendations and principles of clinical practice are listed in Evidence Table 12.4.

Recommendations and Principles

- Hypoglycaemia is the most frequent acute complication of type 1 diabetes.\(^{23,25,26,27,29}\)\(^{\text{II}}\)
- Hypoglycaemia is the major factor limiting intensified regimens aiming for near-normoglycaemia.\(^{23,25,26,27,29}\)\(^{\text{II}}\)
- Severe hypoglycaemia should be avoided in children, especially in those less than 5 years old.\(^{\text{6,10,39,40}}\)\(^{\text{II, III, IV}}\)
- Blood glucose values should be maintained above 4.0 mmol/L in children and adolescents with diabetes.\(^{37,56,57}\)\(^{\text{C}}\)
- Children and adolescents with diabetes should wear some form of identification or warning of their diabetes.\(^{37,56,57}\)\(^{\text{C}}\)
- All children and adolescents with diabetes should carry glucose tablets or readily absorbed carbohydrate (preferably in waterproof sealed wrap) on their person and have glucagon available at home (and in boarding schools where there is a nurse on staff).\(^{37,56,57}\)\(^{\text{C}}\)
- Hypoglycaemia in children is largely preventable; however there is a significant proportion of severe hypoglycaemic episodes in which no obvious cause can be determined.\(^{56,57}\)\(^{\text{C}}\)
- School teachers and carers at schools should be informed of the symptoms and appropriate treatment of hypoglycaemia and should have access to advice when necessary.\(^{37,56,57}\)\(^{\text{C}}\)
- In the hospital setting severe hypoglycaemia should be treated with intravenous dextrose as this is the most rapid way of treating severe hypoglycaemia.\(^{49,50}\)\(^{\text{II}}\)
- The recommended dose of intravenous dextrose is 2-5ml/kg of 10% dextrose. 50% dextrose should not be used because of dangers of tissue necrosis associated with extravasation.\(^{\text{C}}\)
- Intramuscular or subcutaneous glucagon is an effective way of treating severe hypoglycaemia in a home-care setting or if intravenous dextrose is not possible.\(^{49,50}\)\(^{\text{II}}\)

II = Evidence from at least one properly-designed RCT  
IV = Evidence from case series, either post-test or pre-test and post-test  
C = Consensus statement endorsed by professional organisations

Reference List

32. Porter PA, Byrne G, Stick S, Jones TW: Nocturnal hypoglycaemia and sleep disturbances in young teenagers with insulin dependent diabetes mellitus. Archives of Disease in Childhood 75:120-123, 1999
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Chapter 13: Psychosocial Aspects

Impact on Child

Type 1 diabetes in childhood imposes a number of psychological stresses on both the child and the family. Fluctuations in blood glucose levels may contribute directly to alterations in behaviour and mood, with increased restlessness and irritability and reduced capacity to concentrate.

A social worker and a clinical psychologist should be part of the multidisciplinary team involved in the management of children and adolescents with diabetes. Psychological morbidity is increased in children with diabetes as it is in children with other chronic illnesses.

Initial adjustment to diabetes is characterised by sadness, anxiety, withdrawal, depression, and dependency. Such difficulties often resolve within the first year, but poor adaptation in this initial phase has been found to place children at risk for later emotional difficulties.

Diabetes treatment routines may:

- Impose a lack of spontaneity in lifestyles.
- Engender passivity and inappropriate dependence upon adults for decision-making and self-care.
- Foster feelings of rebellion in some young people.
- Engender a loss of confidence.

Treatment regimens may be difficult to accept and may lead to some children and adolescents struggling with developmentally appropriate issues of independence and autonomy. Adolescents develop an increasingly sophisticated understanding of the implications of chronic illness for future wellbeing, life opportunities, and career choices. This may cause a sense of being ‘damaged’ at a time when a strong sense of self and an unlimited future are of key importance for psychological well being.

An Australian prospective study of neuropsychological and psychosocial functioning followed 133 children from diagnosis of type 1 diabetes. At ten years 36 percent of an adolescent subset met the criterion for one or more DSM-IV diagnoses, approximately double the prevalence reported in a recent Australian community sample of similar-aged peers.

Impact on Family

The diagnosis of type 1 diabetes itself is experienced as a significant psychological crisis in which the parents grieve the loss of the idealised child. Family adaptation to illness is not a static process, but must change to take account of the child’s developing maturity and capacity for self-management of their condition.

Frequently expressed parental feelings include:

- Anxiety over the ever-present possibility of hypoglycaemia.
- Frustration over failure to achieve perfect glycaemic control.
- Concern over long term complications.
- Guilt and responsibility for transmitting the genetic components of diabetes.
- Diminished enjoyment of the parental role as parents struggle to balance the psychological needs of the child with the restrictions and treatment requirements imposed by the illness.
• Higher parenting stress levels.\textsuperscript{7}
• Feeling less cohesive and more rigidly organised than control families.\textsuperscript{7}

Other family members are also affected by the presence of a child with diabetes:

• Siblings may resent the extra parental time directed to the child with diabetes.
• Siblings may resent that family activities are curtailed to take account of the demands of the diabetes regimen.
• Siblings may be fearful that they have caused the illness in their sibling.
• Family members may fear that they may themselves develop diabetes.
• Grandparents may be fearful of their ability to look after their grandchild.
• Grandparent\’s desire to compensate the child may undermine parental management, especially in regard to issues around food.

Type 1 diabetes in children and adolescents is associated with higher rates of psychiatric disorders including adjustment disorders, major depression, anxiety disorders\textsuperscript{9} and eating disorders.\textsuperscript{12} Psychiatric disorders in childhood increase the risk of subsequent psychiatric disorders in adolescence and adulthood.\textsuperscript{13}

Serious problems with self management in childhood diabetes tend to arise about 3.5 years after diagnosis or in early adolescence and are difficult to treat.\textsuperscript{14} The optimal time for interventions to address later problems with compliance in early adolescence appears to be in the initial period following diagnosis when compliance tends to be high.\textsuperscript{14}

Mild cognitive deficits have been observed to occur more frequently in children with type 1 diabetes; especially in those children who were first diagnosed under two years of age.\textsuperscript{15} Such deficits are associated with learning difficulties which may require specialist recommendations and remediation for academic problems.

Clinical psychology assessment and early intervention for psychological problems in children with type 1 diabetes and their families are essential to maximise health outcomes

**Psychosocial Factors and Metabolic Control**

Relationships between psychological factors (child adjustment, parental mental health, family functioning) and metabolic control are of great interest in type 1 diabetes. Psychological distress in siblings and adult family members may impair their relationship with the child with type 1 diabetes, reducing opportunities for effective family support.

A number of studies have found an association between psychological difficulties in the child and chronic poor metabolic control.\textsuperscript{10,16-19} Causality is unproven but it is assumed that troubled children are less likely to adhere to treatment regimens, leaving them at ‘double jeopardy’ for adverse physical and mental health outcomes.

In contrast, associations between mood disorders and family conflict and very ‘tight’ or good metabolic control have also been reported,\textsuperscript{20-22} raising the possibility that neurotic symptoms may either contribute to, or result from, obsessive pre-occupation with the demands of the diabetes regimen.

In the Australian longitudinal study, adolescents were divided into three groups on the basis of their metabolic control history.\textsuperscript{10} Fifty percent of the mixed poor control group (HbA\textsubscript{1c} >9.5\% for more than one third the time since diagnosis) had a psychiatric diagnosis compared with twenty five percent of the well controlled group (no hyper- or hypoglycaemia), with the hypoglycaemia group (no severe hypoglycaemia) falling between these two extremes.\textsuperscript{10}
Relationships between parameters of family functioning and metabolic control in the child have shown:

- Rigidly organised, inflexible families have been associated with both better\(^{23,24}\) and poorer\(^{25}\) metabolic control in the child.
- Strict parental supervision was associated with better health outcomes but greater psychological dependency in the child.\(^{23}\)

Metabolic control and psychological outcomes do not always coincide. Over-zealous adherence with treatment regimens may have a psychological cost for some children. Psychological dependency on parents exerting strict control may lead to failure of the child to develop age appropriate competencies and self management strategies necessary for effective metabolic control in adolescence and early adulthood.

**Adherence to Therapy**

Non-adherence to therapy should be considered in children and particularly adolescents with poor metabolic control, especially in those presenting with recurrent diabetic ketoacidosis.

Medical regimens that are long-term, complex and that encroach considerably upon daily living are less likely to elicit adherence.\(^{26}\)

Higher levels of education in parents of children with diabetes and in adolescents with type 1 diabetes are associated with improved adherence to therapy.\(^{27,28}\)

Most children administer insulin assiduously. However, recommendations for diet, physical activity, and self-monitoring of blood glucose (and hence self-adjustment of insulin doses) are relatively neglected.\(^{29-33}\)

Non-adherence is associated with deterioration in glycaemic control and increases the risk of complications; however, the consequences of non-adherence are not sufficient to motivate self-care behaviour.\(^{16,34}\)

The NICE Guidelines for the Diagnosis and Management of Type 1 Diabetes in Children and Young People have systematically reviewed the literature on non-adherence in diabetes management.\(^{35}\) Non-adherence has typically been associated with adolescence\(^{36-39}\) as the responsibility for maintaining an adequate diabetic regimen in younger children is often the responsibility of parents.\(^{40}\)

In a longitudinal study of school-age children with diabetes, serious non-adherence with the medical regimen over nine years occurred in 45%.\(^{41}\) The initial episode of non-adherence occurred at an average age of 14.8 years, while time spent being non-adherent was greatest when the patients were aged between 17 and 19 years.\(^{41}\)

At a time of increasing desire for autonomy, there may be conflict between parents and an adolescent who desires independence and a sense of self-normality within peer groups.\(^{36,42}\)

There appears to be a fine balance involved in the transfer of responsibility, with significant problems in diabetes management occurring when self-care autonomy is promoted or impeded at an inappropriate time.\(^{43}\)

Psychiatric disorders may impact on blood glucose control by decreasing adherence with medical requirements.\(^{17,41,44}\) In depression, the lack of motivation, loss of interest in daily activities, and hopelessness may undermine the motivation to carry out tasks necessary to maintain good glycaemic control.

Kovacs and colleagues (1992) found that 56% of children with psychiatric illnesses failed to comply with their medical regimen, as compared to 17% of those without psychiatric disorders.\(^{41}\)

Psychological factors, such as low self-esteem, self-efficacy, and depressive symptoms, have been found to account for 50% of the variance in treatment adherence.\(^{34}\)
Intentional non-adherence, as opposed to non-adherence secondary to motivational or attentional difficulties, is an area that is particularly problematic in individuals with type 1 diabetes exhibiting suicidal ideation or eating disorders. The rate of non-adherence to treatment, which may be a form of self-destructive behaviour, rises from 25% to 63.3% when suicidal ideation has been present in the past year.45

Adolescents with eating disorders are more likely to neglect the glycaemic monitoring, and diet components of their treatment,46 and have also been found to omit or reduce insulin dose in order to produce glycosuria as a method of weight control.46,47,48

Risk Factors

Not all children with type 1 diabetes develop psychological difficulties. The following factors have been studied for their impact on the development of psychological difficulties in children with diabetes:

- Some studies report that females with diabetes are at greater risk,3,10 while others have failed to identify gender as a risk factor for psychiatric disorder.2,45
- Socioeconomic status is not predictive of psychological difficulties.9,45,49
- Maternal psychopathology,5 conflictual or dysfunctional family environments50 and avoidance coping behaviours5 have all been associated with poor psychological adjustment to diabetes.
- Poor initial adaptation to diabetes is predictive of ongoing psychological difficulties.8,9,51
- In the Australian longitudinal cohort study, children with behaviour problems at the time of diagnosis were significantly more likely to have a DSM-IV psychiatric diagnosis ten years later and to have had a history of chronic poor metabolic control.10
- A Victorian study on clinical and quality of life outcomes demonstrated lower quality of life measures in rural youth with diabetes despite glycaemic control.

Treatments and Interventions

Effective care of children and adolescents with diabetes involves not only optimised medical management, but also sensitive attention to psychological well being. The treatment regimen should as simple and non-disruptive to lifestyle as possible, consistent with glycaemic targets.

Effective intervention with ‘at risk’ children is essential to prevent adverse physical and mental health outcomes.

A Health Technology Assessment systematic review on the effects of educational and psychosocial interventions for adolescents with diabetes found an overall small but positive effect of interventions on HbA1c and psychosocial outcomes. However, as many of the studies were small and different interventions were used, the need for larger high quality RCT’s in this area is identified.52

Wysocki et al (2001)53 used Behavioral Family Systems Therapy (BFST) to teach problem-solving and communication skills to adolescents and parents. When compared to adolescents receiving standard, physician-directed treatment or those whose families had attended groups focusing on education and social support, families involved in BFST showed some improved parent-adolescent relations, and reduction in the amount and intensity of family conflict.

Diabetes-specific conflict also decreased in the BFST group compared to the two control groups. Interestingly, total glycated haemoglobin values increased throughout the study but there were no significant between group or interaction effects on GHb at any measurement point..
Several other groups have studied interventions promoting and maintaining family involvement in diabetes management.54,55

- Anderson et al (1999)54 reported greater parental involvement in diabetes care and significantly decreased diabetes-related conflict over time but no improvement in glycaemic control.
- In contrast Laffel et al (2003)55 observed significantly improved diabetes control in the treatment group compared to controls, but no improvement in health-related quality of life or diabetes-related family conflict at one-year follow-up. Maintenance of, or an increase in family involvement in diabetes management were comparable to those found by Anderson et al (1999).54

Early research into promotion of personal and social coping skills reported promising results for children and adolescents with diabetes.56,57

In a more recent and methodologically rigorous piece of research, group Coping Skills Training (CST) was implemented as an adjunct to intensive diabetes management in adolescents.58 The treatment group used role-plays focused on social situations that are challenging for adolescents with diabetes, to develop social problem solving and conflict resolution skills using cognitive behaviour modification principles. All groups reported a decrease in HbA1c. Adolescents receiving intensive therapy plus CST reported better self-efficacy, less distress or difficulty in coping, and less impact of diabetes on quality of life in comparison to the control group. One-year later both physiological and psychological functioning had actually improved further.59 The level of distress or difficulty in coping was the only factor where between-group differences dissipated over time.

Other studies also reported that diabetes-specific stress decreased over time in response to the intervention, but metabolic control, regimen adherence, coping styles, and self-efficacy about diabetes were unchanged.50,51

It is clear that no single intervention trialled to date results in improvement across all the variables of interest, nor do psychological and physical health parameters always respond in tandem. Further research is clearly needed, particularly with younger children and their families.

The Evidence

The evidence for the incidence and risk factors for non-adherence in children and adolescents with type 1 diabetes is listed in Evidence Table 13.1.

- Non-adherence with treatment regimens is common in children and adolescents with type 1 diabetes.16,27,28,30-34,36-39,41,45 (IV)
- Non-adherence with treatment regimens is common especially during teenage years,36-39 when an underlying psychiatric disorder is present,34,41,45 when the parents or child have a low level of education,27,28 when self-care autonomy is promoted or impeded at an inappropriate time,45 and when there is low level of cohesion within the family.27 (IV)
- Adolescents have also been found to omit or reduce insulin doses in order to produce glycosuria as a method of weight control.46,47,48 (IV)

The evidence for the effects of psychosocial interventions on metabolic and psychological outcomes in children and adolescents with type 1 diabetes is listed in Evidence Table 13.2.

- A Health Technology Assessment systematic review on the effects of educational and psychosocial interventions for adolescents with diabetes found an overall small but positive effect on HbA1c and psychosocial outcomes. However, as many of the studies were small and different interventions were used, the need for larger high quality RCT’s in this area is identified.52 (I)
• An RCT (n=119) comparing Behavioral Family Systems Therapy (BFST) with standard treatment showed that BFST improved parent-adolescent relations and reduced family conflict, but effects on glycaemic control were mixed.53(II)

• Another RCT (n=77) found the Coping Skills Training resulted in lower HbA1c and better diabetes and medical self-efficacy, and less impact of diabetes on their quality of life (P =0.005) than those receiving conventional management alone after 1 year.59(II)

• An RCT comparing family focused teamwork with standard care found significantly improved diabetes control in the treatment group compared to controls, but no improvement in health-related quality of life or diabetes-related family conflict was found at one-year follow-up.55(II)

Additional Technical Reports and Consensus Statements used to formulate the recommendations and principles of clinical practice are listed in Evidence Table 13.3.

Recommendations and Principles
• Type 1 diabetes in childhood imposes a number of psychological stresses on both the child and the family.1,135,60,61(C)

• Non-adherence with treatment regimens is common in children and adolescents with type 1 diabetes.16,27,28,30-34,36-39,41,45(IV)

• Non-adherence with treatment regimens is common especially during teenage years,36-39 when an underlying psychiatric disorder is present,34,41,45 when the parents or child have a low level of education,27,28 when self-care autonomy is promoted or impeded at an inappropriate time,43 and when there is low level of cohesion within the family.77(IV)

• Health care professionals should be aware that adolescents may omit or reduce insulin doses in order to produce glycosuria as a method of weight control.46,47,48(IV)

• Psychological interventions have been shown to improve HbA1c and psychosocial outcomes.52,53,55,59(I)

| I = Evidence from a systemic review of all relevant RCT’s |
| II = Evidence from at least one properly-designed RCT |
| IV = Evidence from case series, either post-test or pre-test and post-test |
| C = Consensus statement endorsed by professional organisations |

Reference List
1. International Society for Pediatric and Adolescent Diabetes: ISPAD Consensus Guidelines for the Management of Type 1 Diabetes Mellitus in Children and Adolescents. Zeist, Netherlands, Medforum, 2000


Chapter 14: Diabetes Complications

Long-term microvascular complications of diabetes can cause:
- Blindness due to diabetic retinopathy.
- Renal failure due to diabetic nephropathy.
- Disabling pain due to diabetic neuropathy.

Early microvascular changes are subclinical but can be detected by sensitive testing methods. The most important antecedents for the development of microvascular complications in children and adolescents are:
- Longer duration of diabetes.¹
- Older age.¹
- Poor glycaemic control.²
- Family history of diabetes complications.³

The pubertal years accelerate the progression of microvascular complications of diabetes (retinopathy, nephropathy and neuropathy). Hypertension,⁴-⁹ dyslipidaemia¹⁰-¹³ and smoking¹⁴-¹⁹ influence the development of microvascular complications as well as macrovascular complications.²⁰

Discussing Complications

Families with a child or adolescent with diabetes should be made aware of the potential long-term complications of diabetes as part of their diabetes education.

This information should also be made gradually known to the adolescent at a rate appropriate to his/her maturity and developmental stage.²¹

Young people need positive encouragement and education about complications during the adolescent period.²¹

Improvements in diabetes control, no matter how small, all reduce the risk for the development of microvascular complications.²²,²³

It is essential to emphasise that:
- Long-term good metabolic control reduces the risk of development and progress of complications.²
- Outside of the normal range, there is no HbA₁c threshold below which diabetes complications will not occur.²²,²³
- For every degree of improvement in diabetes control a benefit is obtained.²²,²³

These important facts can be used to motivate persons with diabetes to aim for gradual improvements, no matter how small, in their diabetes control.

Screening for diabetes complications during adolescence reinforces this education process. The threat of complications should not be made in trying to motivate adolescents or the family to improve diabetes control.

Diabetic Retinopathy

Diabetic retinopathy is the fifth commonest cause of all blindness in Australia after congenital causes.²⁴ Diabetes is estimated to be the commonest cause of new blindness in working age adults.²⁵
The features of background retinopathy are:\(^{26}\)
- Microaneurysms (the only specific feature of diabetic retinopathy).
- Haemorrhages (intraretinal and preretinal).
- Soft exudates (microinfarctions).
- Hard exudates (protein and lipid leakage).
- Intra-retinal microvascular abnormalities (IRMA).
- Dilatation, constriction and tortuosity of vessels.

Background retinopathy is not vision-threatening and may remain stable for years. It is an almost universal finding in individuals with diabetes of over 20 years duration. Microaneurysms are specific to diabetes and are not found in nondiabetic adolescents.\(^{27}\) They may be transient, lasting from months to years.\(^{28}\)

In some cases background retinopathy can progress to vision-threatening retinopathy which includes:\(^{1,26,29,30}\)
- Pre-proliferative retinopathy.
- Proliferative retinopathy.
- Maculopathy.

Pre-proliferative retinopathy is characterised by vascular obstruction, progressive IRMA and infarctions of the retinal nerve fibre layer causing ‘cotton wool’ spots.

Proliferative retinopathy is characterised by the formation of new blood vessels (neovascularisation) in the retina and/or vitreous posterior surface and is vision-threatening. The vessels may rupture or bleed into the vitreoretinal space. Encasement in connective tissue results in adhesions, which can cause haemorrhage and retinal detachment. High-risk characteristics for visual loss are the location and extent of neovascularisation and signs of vitreous or preretinal haemorrhage.\(^{31}\)

In diabetic maculopathy, decreased vascular competence and microaneurysm formation produce exudation and swelling in the central retina that can significantly decrease visual acuity.

The most sensitive detection methods for retinopathy are:
- Stereoscopic fundal photography.
- Fluorescein angiography.

Stereoscopic fundal photography is at least twice as sensitive as direct ophthalmoscopy for the less severe disease.\(^{32,33}\) Fundal photography (7-field) is comparable to two-field fluorescein angiography in detecting retinopathy,\(^{54}\) however the latter requires intravenous injection of fluorescein. Fluorescein commonly causes nausea and may cause anaphylactic reactions.\(^{35}\) Fluorescein angiography reveals functional abnormalities (vascular permeability) as well as structural abnormalities in the blood vessels whereas fundal photography reveals only structural abnormalities. Both methods produce a recording (hard copy or electronic), which can be referred to in subsequent assessments and can be shown to the adolescent.

**Prevalence and association studies of retinopathy**
The largest epidemiological study of diabetic retinopathy revealed the prevalence of any grade of retinopathy to be:\(^{6}\)
- 17% in those with less than five years diabetes duration.
- 50% after 5-6 years diabetes duration.
- 98% after 15 or more years duration.
Proliferative retinopathy was present in:  
- 4% after 10 years duration.
- 25% after 15 years.
- 67% after 35 years.

The frequency and severity of retinopathy were strongly associated with increasing diabetes duration. The severity of retinopathy was also independently associated with increasing age. Children less than 13 years of age had a lower prevalence of background retinopathy (9 percent) than those over 13 years (34 percent) with the same mean duration.

In 1994, an Australian study of adolescents with type 1 diabetes showed that background retinopathy was found in 42 percent (using stereoscopic fundal photography), with highly significant associations with both total diabetes duration and glycaemic control. At a median follow-up of 1.3 years, progression had occurred in 11% and regression in 5%.

High blood pressure is a risk factor for the development and progression of retinopathy even after controlling for microalbuminuria.

The evidence for an association of smoking with retinopathy is inconsistent. Higher cholesterol has been correlated with hard exudates and macular oedema and lower HDL-cholesterol is associated with more retinopathy.

Proliferative retinopathy is rare before 10 years of diabetes. In the Wisconsin study, proliferative retinopathy, though rare, did occur in patients less than 20 years of age and, in a few, as early as five years after diabetes.

**Screening for retinopathy**

There is no evidence available to determine the optimal frequency for screening for retinopathy in the paediatric and adolescent age group. One study is currently underway using 7-field stereoscopic fundal photography and thus data to answer this question may be available soon. The current ISPAD recommendation is to screen for retinopathy annually in adolescents after 2 years of diabetes and after 5 years of diabetes in those who are prepubertal. The Canadian Guidelines 2003 recommend annual screening in those >15 years of age and after 5 years of diabetes. The NICE Guidelines do not offer a recommendation for children and adolescents and recognise there is a diversity of views but indicate that for adults with type 1 diabetes screening should start at diagnosis and be performed annually.

If stereoscopic fundal photography is used then biennial assessment may be appropriate for those with minimal background retinopathy, diabetes duration of less than 10 years and if the HbA1c is not significantly elevated. If significant retinopathy is present then more frequent review is necessary.

Immediate expert ophthalmological management should be sought if any of the following are noted:
- Progression of retinopathy to more than 10 microaneurysms.
- Moderate non-proliferative or preproliferative retinopathy.
- Visual change or deterioration, macular oedema or proliferative changes.

The ISPAD Consensus Guidelines 2000 recommend that assessment as a minimum should be by ophthalmoscopy through dilated pupils by an observer with special expertise in diabetic eye disease (pupil dilation by Cyclopentolate 1% + Phenylephrine 2.5% or Tropicamide 1% ± Phenylephrine 10%). Whilst the preferred method is by stereofundal retinal photography through dilated pupils, the need for mydriasis is being investigated. Nonmydriatic retinal photography may have a place in retinal screening in type 2 diabetes in which maculopathy is
a commoner form of sight-threatening disease. However, its place is not clear in type 1 diabetes which is characterised by proliferative, often peripheral, retinopathy as a cause of sight-threatening disease. The Health Technology Board for Scotland assessment report states that there is no clear evidence that mydriasis or the routine use of more than one image significantly alters the sensitivity or specificity of screening for the detection of sight-threatening retinopathy in adults. Comparable screening accuracy is achieved with digital cameras, with or without mydriasis, however direct comparisons suggest that mydriasis may occasionally result in a successful image when non-mydriatic imaging fails.

**Interventions to prevent or delay progression of diabetic retinopathy**

The Diabetes Control and Complications Trial showed that intensive diabetes management reduced the risk and progression of background retinopathy by 53% in adolescents. In the adolescent cohort, vision-threatening retinopathy was too infrequent to allow comparison between the intensive and conventionally managed groups.

In the subsequent four year follow-up after completion of the DCCT (EDIC-Epidemiology of Diabetes Interventions and Complications), the intensive group continued to have a reduction in significant progression despite a narrowing of the HbA1c difference between intensively and conventionally treated groups (median 6.5 years of intervention).

Laser intervention was needed in 6% of the conventional group compared with 1% of the formerly treated intensive group.

Improved metabolic control may initially worsen diabetic retinopathy, however within 1.5 to 3 years; definite advantages of intensive treatment in these patients are evident.

Intervention to improve glycaemic control is currently the only established therapy to retard the progression of early retinopathy in adolescents. A randomised controlled trial in adults showed reduction in progression of retinopathy with lisinopril (angiotensin converting enzyme inhibitor) over a 2-year period in normotensive adults with type 1 diabetes. Randomised controlled trials using the older lipid-lowering drugs have shown a reduction in retinal hard exudates.

Large multicentre randomised trials in adults have shown that laser therapy reduces visual loss from proliferative retinopathy. In at-risk eyes, timely laser intervention halves the risk of blindness. Focal laser photocoagulation is beneficial in eyes with macular oedema. Intervention needs to occur before clinical symptoms of visual loss.

**Cataracts**

The lens should be assessed, preferably by slit lamp examination, as specific stellate cataracts can be seen in children after relatively short diabetes duration. On close questioning these children often have symptoms suggestive of a prolonged antecedent history. The cataracts can be vision-threatening and therefore may need excision.

Clinical examination of the eyes for the presence of cataracts should be performed soon after diagnosis, especially if there has been a slow/prolonged onset of diabetes.

**Refractive Errors**

Changes in blood glucose levels (e.g. during prolonged hyperglycaemia or more commonly following stabilisation or initiation of treatment on diagnosis) can cause transient accommodative problems. If there have been changes in glycaemic control, it is preferable to delay the prescription of spectacles for 3 months.
Diabetic Nephropathy

Diabetic nephropathy is the second most common cause of end-stage renal disease in Australia (after glomerulonephritis) and the commonest in New Zealand.56 Diabetic nephropathy is also associated with premature death, generally due to associated macrovascular disease.56;57 Persistent microalbuminuria has been shown to predict the development of clinical diabetic nephropathy marked by gross proteinuria 6-14 years later.58-60 This progresses to end-stage renal failure and is associated with increased risk of macrovascular disease.56;57 Albumin excretion rate can vary by as much as 40% for an individual so more than a single sample is recommended when screening for renal disease.61

The definitions of microalbuminuria vary from centre to centre and include:
- Albumin excretion rate (AER) greater than 20 µg/min but less than 200 µg/min on a minimum of two of three consecutive timed overnight urine collections.62
- Albumin/creatinine ratio (ACR) 2.5 - 25 mg/mmol (spot urine).62
- (3.5 – 25 has been proposed in females because of lower creatinine excretion)
- Albumin/creatinine ratio (ACR) 30-300 mg/gm (spot urine).62
- Albumin concentration (AC) 30-300 mg/L (early morning urine).62
- In the DCCT microalbuminuria was defined as urinary albumin excretion greater or equal to 40 mg per 24 hours (or 27.8 µg/min) and less than 300 mg per 24 hours.63

Some groups have found that elevation at even lower levels predicts progression.64 In a collaborative Australian study, a mean AER of 7.2 to 20µg/min predicted progression to microalbuminuria (four of six overnight urine specimens greater than 20µg/min) compared with adolescents with a mean AER less than 7.2 µg/min.65

Regression of microalbuminuria was documented in the DCCT and other studies. In an 8 year follow-up study of patients aged 15-44 years with microalbuminuria (defined as a mean albumin excretion rate of 30-299 µg/min determined over the first two years), the six year regression rate was 58% with progression to proteinuria only in 15%.66

Even using a definition of two of three abnormal timed collections for persistent microalbuminuria, it has been recognised that regression back to normal can occur.67;68 Although an effect of duration has not always been demonstrated,69 the Oxford Regional Prospective Study Group found that the cumulative probability for developing microalbuminuria in children was 40% after 11 years of diabetes duration.70 Hypertension is generally established by the time of overt nephropathy. It remains controversial whether blood pressure actually starts to rise during the transition from normoalbuminuria to microalbuminuria or once microalbuminuria occurs. High blood pressure is clearly associated with microalbuminuria. Mathiesen found the blood pressure to rise only after microalbuminuria had occurred.71 In contrast, others have found that blood pressure rose in parallel with the rise in AER.72 A cross sectional Australian study of adolescents showed that ambulatory blood pressure measurements were already higher during the phase of intermittent microalbuminuria compared to measurements in normoalbuminuric adolescents.73 Longitudinal studies have shown that nocturnal hypertension74 and increased ambulatory blood pressure75;76 precedes microalbuminuria.

Screening for nephropathy

The current ISPAD recommendation is to screen for microalbuminuria annually in:21
- Adolescents after 2 years of diabetes.
- Prepubertal children after 5 years of diabetes.
Screening should be by either:\(^{21}\)
- Timed urine collections (preferably overnight).
  or
- A spot urinary albumin/creatinine ratio.

The Canadian Guidelines 2003 recommend annual screening in postpubertal adolescents with a duration of diabetes >5 years or at the commencement of puberty and having a duration of diabetes >5 years.\(^{40}\) The NICE guidelines recognise the above diversity of views.\(^{41}\)

Overnight timed collections are regarded as preferable as they avoid orthostatic and post-exercise proteinuria. The spot or random albumin/creatinine ratios have the convenience of ease of collection but are less sensitive for detecting rises within the normal range of albumin excretion.

If microalbuminuria is found then screening should be more frequent, and other renal investigations undertaken and specific focus should be placed on blood pressure measurements.\(^{21}\) Implications of persistent microalbuminuria should be discussed with the adolescent and the family.

Other factors that can cause microalbuminuria or lead to the false diagnosis of microalbuminuria are:
- Glomerulonephritis.
- Urinary tract infection.
- Intercurrent infections.
- Menstrual bleeding.
- Vaginal discharge.
- Orthostatic proteinuria.
- Strenuous exercise.

**Interventions to prevent or delay progression of diabetic nephropathy**

The Diabetes Control and Complications Trial showed that intensive diabetes management reduced the risk of developing microalbuminuria by 55% in adolescents in the secondary intervention arm (with diabetes duration >5 years at entry).\(^{2}\) In the adolescent primary prevention cohort, intensive diabetes management reduced the risk of developing microalbuminuria by 10 percent. In the EDIC Study (the subsequent 4 year follow-up after completion of the strict two treatment arms), the intensive group continued to have a reduction in significant reduction in development of microalbuminuria (53%) and proteinuria (86%).\(^{44}\)

Effective antihypertensive therapy in patients with nephropathy (protein excretion >500 mg/24 hours or AER >200 ug/min) has dramatically prolonged the time to end-stage renal disease from 7 to 21 years. Angiotensin Converting Enzyme Inhibitors (ACEI) slows the decline in renal function more effectively than other antihypertensive agents.\(^{77,78}\) The introduction of ACEI must be combined with monitoring of serum potassium and creatinine concentrations. ACEIs are not licensed for use in pregnancy. If hypertension is not treated effectively with ACEI alone, additional antihypertensives should be considered.

In normotensive patients with microalbuminuria, ACEI reduce urinary albumin excretion;\(^{79}\) however a delay in progression to clinically overt nephropathy has not been shown. They may in fact only mask the signs of the disease. Cessation of therapy has led to a rapid increase in albuminuria similar to those in the placebo treated group.

The angiotensin II receptor antagonists are a relatively new class of drugs that are promising and have a more specific effect on renoprotection than ACEI although to date most large studies have been in adults with type 2 diabetes and nephropathy.\(^{80-82}\) Some reviews
Chapter 14: Diabetes Complications

Australian Clinical Practice Guidelines: Type 1 Diabetes in Children and Adolescents

156

indicate that they may also have a role in paediatric patients with diabetes and renal disease although published studies are still awaited.83

Close attention to improving glycaemic control,2 cessation of smoking,16 care in prescribing of OCP’s (see Chapter 18)14 and monitoring of lipids are important aspects in the management of the patient with microalbuminuria.11

Lowering of the nutritional protein intake to decrease protein excretion in growing children is not recommended, however excessive nutritional protein intake should be discouraged (recommended maximum of 1.0-1.2 gm/kg body weight/day).21

Diabetic Neuropathy

Although clinical symptoms and signs of nerve disease in children and adolescents with type 1 diabetes are rare, studies have now demonstrated the presence of subclinical abnormalities. The natural history of these subclinical findings is not yet clear; in particular, which patients from this group progress to having more significant clinical abnormalities.

The presence of reduced sensation in the feet places the adolescent at increased risk of foot problems and a referral for podiatric assessment is indicated.

Neuropathy needs to be considered in such situations as a child with recurrent vomiting (possibly due to autonomic neuropathy) or persistent pain syndromes (possibly due to peripheral neuropathy). The prepubertal child is not necessarily protected from risk.84 Peripheral neuropathy predisposes to foot ulceration and amputation. Painful peripheral neuropathy can be disabling in young adults with childhood-onset diabetes85.

Autonomic neuropathy has been associated with an increased risk of sudden death (due to hypoglycaemic unawareness or arrhythmia) and increased mortality.86

Screening for neuropathy

In adults with type 1 diabetes the consensus recommendation is for annual clinical evaluation for the presence of peripheral nerve function. Clinical neuropathy is rare in children and adolescents with type 1 diabetes even though prospective nerve conduction studies and autonomic neuropathy assessment studies have demonstrated increased prevalence of abnormal findings with greater duration of diabetes.21,87-90 Persistence of such abnormalities is an inconsistent finding.87 With the exception of intensifying diabetes management no other treatment is available. In the presence of poor diabetes control the following clinical assessment should be undertaken:

• History, especially of numbness, pain, paraesthesia.
• Assessment of vibration sensation (by tuning fork or biothesiometer).
• Assessment of ankle reflexes.
• Assessment of sensation (by conventional neurologic examination or by graduated filaments).

In addition, non-invasive tests of subclinical nerve function are available in some major paediatric diabetes centres. These tests include:

• Autonomic nerve tests:
  ➔ Heart rate response to deep breathing.
  ➔ Heart rate response to standing.
  ➔ Heart rate response to Valsalva manoeuvre.
  ➔ Postural change in blood pressure.
  ➔ Pupillary responses (dark adapted pupil size, rate of constriction and dilatation following a flash of light).
• Peripheral nerve tests:
→ Vibration sensation threshold (using a biothesiometer).
→ Thermal discrimination thresholds.
→ Nerve conduction.

With all of the above tests of subclinical nerve function it is important that age- and gender-specific normal ranges are applied when interpreting results. The long-term implications of finding early neuropathy are not yet established and apart from recommending improved glycaemic control there is no proven specific therapy available.

**Interventions to prevent or delay diabetic neuropathy**

In the Primary Prevention Cohort of the DCCT, intensive therapy caused a 69% reduction in the development of clinical neuropathy and in the Secondary Intervention Cohort a 56% reduction.\(^6\) Clinical neuropathy was not sufficiently common for a significant effect to be seen in the combined Adolescent Cohort (7/103 in the conventional group and 3/92 in the intensive group).\(^2\)

Aldose reductase inhibitors may have a place in the treatment of neuropathy\(^9\) but are not yet available for clinical use.

**Macrovascular Disease**

Cardiovascular disease is the major cause of mortality in adults with type 1 diabetes. Clinical macrovascular disease is rare under the age of 30 years. However, increased aortic and carotid intima-media thickness has been detected by ultra-sensitive ultrasound in adolescents with type 1 diabetes.\(^9\)-\(^9\) Intensive therapy during the DCCT resulted in decreased progression of intima-media thickness six years after the end of the trial.\(^9\)

Even though macrovascular disease is not seen in type 1 diabetes in the childhood or adolescent years, risk factors that predispose to it are frequently present, and adolescents and their families should be aware of these:

- Hypertension.
- Dyslipidaemia.
- Smoking.
- Obesity.
- Microalbuminuria and diabetic nephropathy.
- Hypercoagulability.
- Family history of cardiovascular disease.

**Hypertension**

**Blood pressure assessment in children and adolescents**

Due to the pivotal role that blood pressure (BP) plays in the evolution of the microvascular complications of diabetes, early and accurate diagnosis of hypertension is important to enable early initiation of treatment where indicated.

**Method for BP measurement**

Blood pressure measurement needs to be accurate and reproducible. A variety of methods exist to measure blood pressure, each of which has its strengths and weaknesses.

Irrespective of the method used, standardisation of the method of measurement is important to reduce interobserver error. These include:

- **Position of patient**: for static measurement of BP, the patient should be seated quietly for at least 5 minutes.
• **Blood Pressure Cuff Size**: An appropriate selection of cuff sizes is required to ensure that the bladder spans the circumference of the arm and covers at least 75% of the upper arm without obscuring the antecubital fossa.

*Sphygmomanometer*

The sphygmomanometer is the most frequently used and least expensive method of BP measurement. It is also the method most likely to result in readings with significant intraindividual and interobserver variability. To reduce this problem the method of recording BP should be standardised by:

- Readings should be taken in the right arm.
- The arm should be held at the level of the heart.
- The manometer should be positioned at the eye level of the person performing the measurement to avoid parallax error.
- Initial cuff inflation should occur while manually palpating the radial pulse to estimate systolic BP.
- The stethoscope should then be placed lightly over the brachial artery (excessive pressure may create turbulence and confound results) and the cuff inflated to 20 mm Hg above systolic pressure.
- Deflation should be at 2-3 mm Hg per second.
- Systolic blood pressure corresponds with the onset of the audible sound (K1 - the first Korotkoff sound).
- As deflation of the cuff continues, the sounds will become muffled (K4) before eventually disappearing (K5).
- Diastolic BP was previously taken as K4 in children less 13 years of age, and as K5 in children greater than 13 years of age. The update on the 1987 taskforce report on high blood pressure in children and adolescents, published in 1996 recommends the use of K5 in all age groups even if Korotkoff sounds are audible down to 0 mm Hg.\(^96\)
- 2 measurements should be made per visit with the mean systolic and diastolic BP taken.
- Results should be interpreted in light of age, gender and height specific centiles (Table 14.1).\(^96\)

*Dinamap*

Static oscillometric blood pressure measurement devices are being used in increasing numbers in the clinical setting. Although more expensive than the sphygmomanometer, they provide reliable, reproducible readings and require minimal training. Issues of standardisation of measurement technique and appropriate equipment use are the same as for measurements with sphygmomanometer.

Studies that have compared this method of measurement with conventional sphygmomanometry have obtained reasonable, although not perfect correlation\(^97\) for population. Comparison for individuals may not correlate as well, although this will be influenced by the degree of inter- and intraindividual variability that occurs with sphygmomanometer measurements.

Single BP measurements with Dinamap can not differentiate ‘white coat hypertension’ (transient elevation of BP in a clinic setting) from persistent hypertension. The use of multiple supine values is more effective because BP frequently falls with repeated measurement. There are practical issues with this approach in the busy clinic setting.

**Paediatric reference values**

There are no studies that establish paediatric reference values using Dinamap. Studies that employ static oscillometric devices frequently use reference data from the second taskforce
on BP in children, which may not be valid, given that systolic BP is higher and diastolic BP lower with Dinamap measurements when compared with BP measurement using sphygmomanometer.\textsuperscript{98,99}

**Ambulatory blood pressure monitoring**

Ambulatory blood pressure monitoring provides more information than any other method of BP measurement, and correlates best with the risk of hypertension-induced target organ damage.\textsuperscript{100} Ambulatory blood pressure monitors use either an auscultatory or an oscillometric method to measure blood pressure. The auscultatory method requires the use of a microphone to detect the Korotkoff sounds. This method directly measures systolic and diastolic BP and is more prone to false positive readings due to interference from environmental noise or damage to the microphone. Oscillometric monitors are simpler, more robust, and not as prone to false positive readings. They measure systolic and mean blood pressures directly and calculate diastolic pressure. They are prone to the same variation as the Dinamap when compared with sphygmomanometer readings. Most of the studies that have developed reference ranges for ambulatory BP monitoring in children have used oscillometric monitors.

Advantages of ambulatory BP monitoring over other methods of BP measurement include:
- Ability to differentiate ‘white coat hypertension’, which may not pose the same risk of morbidity as persistent hypertension.
- Ability to evaluate diurnal blood pressure variability - lack of nocturnal fall in BP is a predictor of progression of diabetes complications.\textsuperscript{74}
- Ability to determine blood pressure burden and more effectively determine effectiveness of interventions.
- Better correlation with end organ damage.
- Simultaneous evaluation of heart rate variability, which may be an early marker of autonomic dysfunction.

Disadvantages of ambulatory BP monitoring over other methods of BP measurement include:
- Cost - average ambulatory blood pressure monitors costs $2000-$4000 to purchase.
- Time consuming to staff and patient - which limits its usefulness as a screening tool.
- Monitoring disturbs sleep in some adolescents.

**Paediatric reference values**

Several large studies have established paediatric reference ranges for ambulatory BP monitoring using oscillometric monitors\textsuperscript{101,102} although there are no large studies of this in an Australian paediatric population. Systolic ambulatory BP correlates with height SDS, BMI SDS, and heart rate SDS, whereas diastolic ambulatory BP correlates weakly with BMI SDS only.\textsuperscript{101}

**Summary of blood pressure measurement methods**
- Manual methods of BP measurement are most prone to measurement error although are cheapest and have the most well-established reference ranges.
- Automated methods are simpler to use although values need to be interpreted carefully given that they use a different method of measuring blood pressure.
- Ambulatory BP monitoring:
  - Provides the most detail.
  - Is useful for identifying borderline hypertension, and individuals with ‘white coat hypertension’, in addition to establishing treatment effectiveness.
  - Is good at detecting early signs of autonomic neuropathy.
Is expensive and the time required to perform this technique mean that it is frequently not used as a primary screening tool.

**Age of screening for hypertension**

Screening for hypertension should start at 3 years of age, although if the aim is to identify hypertension resulting from non-diabetes related causes, measurement should start at diagnosis of diabetes regardless of age, and continue at least annually if BP is less than 90th centile for age and height.

When blood pressure reaches the 90th-95th centile, BP should be measured at least 6 monthly. If systolic and/or diastolic BP exceeds the 95th centile, measurements should be performed at each visit, given that the diagnosis of hypertension requires persistent elevation on three consecutive occasions.

**Definition of hypertension**

The US Task Force on BP control in children has defined hypertension as the average of systolic and/or diastolic BP readings greater than or equal to the 95th percentile for age and sex based upon measurements obtained on at least three occasions96 (Table 14.1). BP readings between 90th and 95th percentiles are regarded as high normal BP and require close and repeated monitoring.

In addition to height, age and gender, weight and parental hypertension are major influences of BP.103 Family studies of patients with type 1 diabetes who develop nephropathy commonly have non-diabetic parents who have essential hypertension, and also patients with diabetes who have a family history of cardiovascular disease are up to 3 times more likely to develop nephropathy.104

BP readings should be tracked longitudinally since even children without diabetes whose BP is in the upper centiles are more likely to become hypertensive as adults.96 Nomograms, based upon US data, are available for children that take into account age, gender and height.105 Obesity can also result in significant increases in blood pressure.

**Management of hypertension**

All children with type 1 diabetes who are discovered to have hypertension need investigation to establish the cause. There are frequently clinical clues that direct investigations that may include:

- Clinical examination to look for evidence of cardiac murmurs (coarctation) or renal bruits (renal artery stenosis).
- ECG and echocardiographic assessment of left ventricular size and thickness (looking for left ventricular hypertrophy).
- Fundoscopy looking for retinal changes of hypertension.
- Microscopy of urine for sediment and red cell content and morphology.
- Determination of urine protein excretion.
- Measurement of electrolytes, urea and creatinine.
- Other investigations which may be indicated based upon clinical findings may include:
  - Renal ultrasound.
  - DMSA renal scan.
  - Renin and aldosterone measurement.
  - Urinary catecholamine measurement.
- Drug treatment ([see Interventions to prevent or delay progression of diabetic nephropathy](#)).
### Table 14.1: Blood Pressure Ranges for Height Centiles

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<th>Age (yrs)</th>
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Dyslipidaemia

There is no consensus about the optimum age at which screening for lipid abnormalities should commence in children with diabetes.

The natural history of lipid disorders has not been clearly established in children with type 1 diabetes, although the adverse effects of poor glycaemic control and of puberty on the lipid profile are known. Children with diabetes have been shown to have higher levels of total and LDL cholesterol, HDL cholesterol and apolipoproteins A1 and B than their siblings or controls without diabetes.

Even with good glycaemic control and normal or increased HDL-C levels, adult patients with type 1 diabetes are at increased risk of developing accelerated atherosclerosis. Type 1 diabetes is associated with a greater proportion of smaller, more atherogenic LDL particles, than controls without diabetes. Oxidation and non-enzymatic glycation increase the atherogenic risk of LDL particles, by interfering with their clearance.

Hypercholesterolaemia is a risk factor for atherosclerotic vascular disease in all adult groups studied although children and adolescents have not been studied.

In adults with type 1 diabetes, interventions that lower LDL cholesterol to levels <2.8 mmol/l, lower triglycerides and raise HDL cholesterol result in a reduction in the number of cardiovascular events.

The American Diabetes Association recommends screening for lipid disorders on an annual basis in adults and 5 yearly in children >12 years of age if initial values are considered low risk.

Another group recommends screening for dyslipidaemia within 6 months of diagnosis and re-testing mid-puberty.

In most Australian tertiary paediatric diabetes clinics, screening for lipid disorders starts in:
- Prepubertal children after 5 years.
- Pubertal or postpubertal children after 2 years.

Screening should include measurement of:
- Total cholesterol.
- LDL cholesterol.
- HDL cholesterol.
- Triglycerides.

This should ideally be performed following an overnight fast, given that reference values for cholesterol subfractions have been established on fasting samples. For screening purposes, random measurement of lipid levels is acceptable, although triglyceride levels may be higher, which affects calculated LDL cholesterol levels.

Interventions for dyslipidaemia

There are no studies that have determined the age at which treatment should be initiated in adolescents with type 1 diabetes and dyslipidaemia.

Interventions to be considered in adolescents with dyslipidaemia include:
- Intensive glycaemic control.
- Attempts to achieve a more normal weight if obese.
- Regular exercise.
- Low saturated fat intake (<10% of energy intake).
- Low cholesterol diet (step 1 cholesterol intake <300 mg/day, step 2 cholesterol intake <200 mg/day).
- Statins.\textsuperscript{113}
- Nicotinic acid.\textsuperscript{114,115}
- Bile acid sequestrants.\textsuperscript{115}
- Fibroic acid derivatives.

Fibrates have been shown to lower the rate of carotid intima medial thickening in asymptomatic hyperlipidaemic adults with type 1 diabetes.\textsuperscript{116} There is limited experience with their use in children.

Combination of a statin and a fibrate may increase the beneficial effects on lipids but also increases the risk of adverse events including abnormal liver function tests, rhabdomyolysis and myositis.\textsuperscript{110}

Hypercoagulability

Diabetes is associated with hypercoagulability.

Low dose aspirin has been recommended for adults with diabetes. However, the American Diabetes Association guidelines advise against its use in those under age 20 years because of the increased risk of Reye Syndrome.\textsuperscript{110}

Cost Issues

No studies were identified which addressed the costs associated with screening for and treating of microvascular or macrovascular complications of type 1 diabetes in children and adolescents. A few studies were identified that addressed these issues in adults in different health care settings. These results may not be applicable to the Australian health care setting.

In 1996 the Diabetes Control and Complication Research Group (using a Monte Carlo model system) concluded that intensive therapy (compared with conventional therapy) was well within the range of cost-effectiveness considered to represent good value in the American health care system.\textsuperscript{117} This model did not include future costs. Another analysis based on the DCCT model did include future costs and concluded that intensive therapy is even more cost effective when future costs are considered.\textsuperscript{118}

A computer model analysis (from the Swiss health insurance payer perspective) found that screening for microalbuminuria and retinopathy followed by appropriate treatment, were cost saving, with reduction in cumulative incidence of end stage renal disease and blindness respectively and an improvement in life expectancy for those with microalbuminuria.\textsuperscript{119} Whilst other computer model analysis agree that screening for nephropathy is cost effective,\textsuperscript{120} some disagree.\textsuperscript{121}

The Evidence

The evidence on the effect of intensive diabetes management on microvascular and macrovascular complications in adolescents with type 1 diabetes is listed in Evidence Table 14.1.

- The Diabetes Control and Complications Trial confirmed the relationship between good glycaemic control (HbA\textsubscript{1c}) and decreased incidence of microvascular and macrovascular complications in both adults and adolescents.\textsuperscript{2,20,22,63,95} (II)
No studies were identified specifically addressing the optimum frequency of screening for microvascular complications of type 1 diabetes in children and adolescents, therefore the recommendations for screening reflect current consensus guidelines.\textsuperscript{21,122(C)}

No studies were identified specifically addressing the optimum frequency of screening for macrovascular complications of type 1 diabetes in children and adolescents; therefore the recommendations for screening reflect current consensus guidelines.\textsuperscript{110,111,122(C)}

Additional Technical Reports and Consensus Statements used to formulate the recommendations and principles of clinical practice are listed in \textit{Evidence Table 14.2}.

**Recommendations and Principles**

- **Type 1 diabetes confers the risk of long-term diabetes microvascular complications.**\textsuperscript{2,20,63,95(II)}
- **Families with a child or adolescent with diabetes should be made aware of the potential long-term complications of diabetes as part of their diabetes education.** Adolescents should be made aware at a rate appropriate to their maturity.\textsuperscript{21,122(C)}
- **Families with a child or adolescent with diabetes should be made aware that long-term good metabolic control reduces the risk of development and progress of complications.**\textsuperscript{2,63(II)}
- **Families with a child or adolescent with diabetes should be made aware that other modifiable risk factors for diabetic microvascular complications include higher blood pressure, smoking and dyslipidaemia.**\textsuperscript{2,63(II)}
- **Screening for retinopathy should be performed annually in adolescents after 2 years of diabetes and after 5 years of diabetes in those who are prepubertal.**\textsuperscript{21,122(C)}
- **Assessment for retinopathy should be by an observer with special expertise in diabetic eye disease.** If stereoscopic fundal photography is used then biennial assessment may be appropriate for those with minimal background retinopathy, diabetes duration of less than 10 years and if the HbA\textsubscript{1c} is not significantly elevated. If moderately severe retinopathy is present then more frequent review is necessary.\textsuperscript{42,122(C)}
- **Clinical examination of the eyes for cataracts should be performed soon after diagnosis, especially if there has been slow or prolonged onset of diabetes.**\textsuperscript{21,122(C)}
- **Screening for microalbuminuria should be performed annually in adolescents after 2 years of diabetes and after 5 years of diabetes in those who are prepubertal.** Assessment should be either by timed overnight urine collections or a spot urinary albumin/creatinine ratio. If microalbuminuria is found then screening should be more frequent, and other renal investigations undertaken and specific focus should be placed on blood pressure measurements.\textsuperscript{21,122(C)}
- **In the presence of poor diabetes control, clinical evaluation of peripheral nerve function should occur annually and should as a minimum include:**\textsuperscript{122(C)}
  - History (especially of numbness, pain, paraesthesia).
  - Assessment of vibration sensation (by tuning fork or biothesiometer).
  - Assessment of ankle reflexes.
  - Assessment of sensation.
- **Type 1 diabetes frequently results in accelerated atherosclerosis.** Good glycaemic control can decrease this risk.\textsuperscript{20,95(II)}
- **Blood pressure measurements should be recorded at diagnosis and, if normal, annually.** Hypertension should be considered to be present if repeated blood pressure levels are >95th centile for age, gender and height specific normative data.\textsuperscript{122(C)}
Screening for lipid disorders should begin within 6-12 months of diagnosis of diabetes, and if normal should be performed every 5 years in prepubertal children and every second year in pubertal children.\textsuperscript{110,111}(C)

II = Evidence obtained from at least one properly designed RCT  
C = Consensus statement endorsed by professional organisations

Reference List


22. DCCT Research Group: The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. \textit{Diabetes} 44:968-983, 1995


41. National Institute for Clinical Excellence. Type 1 Diabetes (Childhood): Diagnosis and Management of Type 1 Diabetes in Children and Young People. 2004.


Chapter 14: Diabetes Complications

**Australian Clinical Practice Guidelines: Type 1 Diabetes in Children and Adolescents**


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Chapter 15: Other Complications and Associated Conditions

Lipodystrophy (Lipoatrophy and Lipohypertrophy)

Lipoatrophy is now seldom seen with the use of human insulin. Although recent case reports describe lipoatrophy occurring in pump patients treated with lispro insulin, it is still an uncommon side effect.

Lipohypertrophy is a frequent complication of insulin therapy. It is estimated to be present in almost 30% of those with type 1 diabetes.3

Non-rotation of injection sites has been consistently reported as an independent risk factor for lipohypertrophy.5,4 Not only is it unsightly but insulin may be absorbed erratically and unpredictably from these areas.

Necrobiosis Lipoidica Diabeticorum

These are well circumscribed, raised reddish lesions sometimes progressing to central ulceration, usually seen on the pre-tibial region. The reported prevalence in children varies from 0.06% to 10%.6,7 The aetiology is not clearly understood. Necrobiosis lipoidica diabeticorum has been associated with underlying microvascular complications.8,9 A wide variety of treatments in adults have been used over the years including: topical, systemic or intra-lesional steroids, aspirin, cyclosporin, mycophenolate, becaplermin, excision and grafting, laser surgery, hyperbaric oxygen, topical granulocyte-macrophage colony-stimulating factor and photochemotherapy with topical PUVA.10-17 None has been proven useful in controlled clinical trials and many of these treatments have significant side effects.

Limited Joint Mobility

Limited joint mobility is a common complication affecting about 30% of those with type 1 diabetes in childhood and adolescence.18,19 One study describes a decreased prevalence over the last 20 years (from 31% to 7%) which may reflect improved glycaemic control.20

Limited joint mobility is demonstrated by opposing the palms in a ‘praying position’ which demonstrates inability to straighten interphalangeal and metacarpophalangeal joints, sometimes associated with limited mobility of wrists, elbows, neck and spine.

Limited joint mobility is associated with microvascular complications in children and adolescents21,22 as well as in adults.23-25 This condition is sometimes associated with thickening of the skin.

Contractures are seen more often in patients with poor long-term diabetic control.21

Limited joint mobility in the feet may lead to secondary foot problems associated with abnormal pressure areas.26,27,28,29

There is no satisfactory treatment for limited joint mobility.

Osteopenia

Osteopenia (low bone mineral density) may occur in children and adolescents with type 1 diabetes. Decreased bone mineral density has been documented in diabetic children soon after the diagnosis of clinical diabetes30 and in those with longer diabetes duration.31,32 The underlying mechanism is not well understood and the long-term clinical significance of this is uncertain.
Impaired Growth and Development

Monitoring of growth and development and the use of percentile charts is a very important part of ongoing care of children and adolescents with diabetes.

Increased height at diagnosis of type 1 diabetes has been frequently reported. The precise mechanism for this and whether or not this increased height is maintained is unclear. Some studies report that poorly controlled patients show a decrease in height standard deviation score over the next few years, whilst better controlled patients maintain their height advantage. Others have not shown this relationship with diabetic control.

In a recent Australian study, children treated with modern regimens (diagnosed after 1990) maintained their increased height better than children diagnosis before 1991. Although the median HbA1c did not differ significantly, those diagnosed after 1990 had a significantly higher number of insulin injections per day.

Poor gain of height and weight and late pubertal development (Mauriac syndrome) are often seen in children with persistently poorly controlled diabetes. Insulin insufficiency, coeliac disease and other gastrointestinal disorders should be considered in this setting. There is no role for human growth hormone therapy in the poorly growing child with diabetes, unless it is associated with documented growth hormone deficiency.

As the child or adolescent has reached a satisfactory weight after diagnosis, excessive weight gain may indicate excessive energy intake and this may be related to excessive insulin. Excessive weight gain is more common during and after puberty. The Diabetes Control and Complications Trial and other studies have described greater weight gain as a side effect of intensive insulin therapy. As obesity is a modifiable cardiovascular risk factor, careful monitoring and management of weight gain in diabetes should not be overlooked.

As large doses of insulin are required during the adolescent growth spurt, it is important to remember to reduce the dose, if possible, as adult height is approached.

Associated Autoimmune Conditions

Hypothyroidism
Primary hypothyroidism due to autoimmune thyroiditis occurs in approximately 3-5 percent of children and adolescents with diabetes. Antithyroid antibodies have been shown to occur in up to 25% of individuals with diabetes, but are not necessarily associated with hypothyroidism. Screening of thyroid function by Thyroid Stimulating Hormone (TSH) every two years is recommended in asymptomatic individuals without a goitre or in the absence of autoantibodies. More frequent assessment is indicated otherwise.

Clinical features may include the presence of a painless goitre, increased weight gain, decreased growth, tiredness, lethargy, cold intolerance and bradycardia. Diabetic control may not be significantly affected.

Hypothyroidism is confirmed by demonstrating a low free thyroxine and a raised TSH. Compensated hypothyroidism may be detected in an asymptomatic individual with a normal thyroxine level and a modestly raised TSH.

The treatment is oral L-thyroxine (T4) replacement sufficient to normalise TSH levels and usually this allows regression of the goitre if present.

Hyperthyroidism
Hyperthyroidism is less common than hypothyroidism in association with diabetes, but still more common than in the general population. It may be due to Grave’s disease or the hyperthyroid phase of Hashimoto’s thyroiditis.
Hyperthyroidism should be considered if there is unexplained difficulty in maintaining glycaemic control, weight loss without loss of appetite, agitation, tachycardia, tremor, heat intolerance, thyroid enlargement or characteristic eye signs.

Treatment is anti-thyroid drugs such as carbimazole or propylthiouracil. Beta-adrenergic blocking drugs are helpful during the acute phase of thyrotoxicosis to control tachycardia and agitation. Treatment options for persistent or recurrent hyperthyroidism include surgery or radio-active iodine.

Coeliac disease
Coeliac disease occurs in 1-10% of children and adolescents with diabetes. Recent Australian paediatric studies have shown prevalence rates of 2.6-5.7% in diabetes clinic populations. Coeliac disease is often asymptomatic and not necessarily associated with poor growth or poor diabetes control (although it should be considered in these situations). Any child with gastrointestinal signs or symptoms including diarrhoea, abdominal pain, flatulence, dyspeptic symptoms, recurrent aphthous ulceration, unexplained poor growth or anaemia should be investigated. Undiagnosed coeliac disease has also been associated with increased frequency of hypoglycaemic episodes and a progressive reduction of insulin requirement over the 12 months prior to diagnosis.

Screening by immunological tests
At present there are no clear data regarding how frequently coeliac disease should be screened for. Current consensus recommendations suggesting screening (by looking for the presence of antiendomysial antibodies (EMA) or antigliadin antibodies when EMA is not available) should be carried out around the time of diagnosis and every 2-3 years thereafter or if the clinical situation suggests the possibility of coeliac disease. This may need to be revised when more data are available.

IgA deficiency (which is present in 1:500 people) should be excluded when screening for coeliac disease by measuring the total IgA level. EMA IgA may not be detected in IgA deficiency, resulting in a false negative test. If the child is IgA deficient, then IgG antigliadin should be used for screening. It is important to remember that coeliac disease is more common in those with IgA deficiency than in the general population (1.7% compared with 0.25%).

Although experience with a recently introduced assay for tissue transglutaminase (tTG) antibodies suggests that tTG may be more sensitive than EMA (91% vs 86%), the latter is slightly more specific for coeliac disease (100% vs 96%). If EMA or tissue transglutaminase antibodies are not available, then IgA antigliadin or IgG antigliadin (in the <2-year-old child) antibodies are sensitive but less specific screening tests (than EMA) for coeliac disease.

Follow up of positive antibody tests
In the presence of an elevated antibody level, a small bowel biopsy is needed to confirm the diagnosis of coeliac disease (by demonstrating subtotal villus atrophy).

Treatment
A gluten-free diet normalises the bowel mucosa and frequently leads to disappearance of EMA but may not lead to improved diabetic control. In an asymptomatic child with proven coeliac disease the justifications for a gluten-free diet are to reduce the risk of subsequent gastrointestinal malignancy and conditions associated with subclinical malabsorption (osteoporosis and iron deficiency). Whilst this is a prudent recommendation, there is no literature documenting the long-term benefit of a gluten-free diet in asymptomatic children.
diagnosed with coeliac disease by routine screening. One paediatric case series has shown an increase in height-for-weight following the introduction of a gluten-free diet.\textsuperscript{57} Another demonstrated a non-significant increase in BMI and a non-significant reduction in HbA\textsubscript{1c}.\textsuperscript{63} Some studies have demonstrated short term benefits in other patient groups in terms of improved wellbeing and increased bone mineral density.\textsuperscript{64-66} Another study demonstrated that bone mineral density was already significantly decreased at the time of diagnosis of coeliac disease in truly asymptomatic adults.\textsuperscript{67}

A Swiss population based study found the risk of enteropathy associated T-cell lymphoma to be low (0.07/100,000 per year). None of the 10 patients identified suffered from type 1 diabetes.\textsuperscript{68}

Children with proven coeliac disease should be referred to a paediatric gastroenterologist and receive support from a paediatric dietitian with experience in gluten-free diets.

**Vitiligo**

Vitiligo is an acquired, pigmentary disorder characterised by a loss of melanocytes resulting in white spots or leukoderma.\textsuperscript{69} It is a common autoimmune condition associated with type 1 diabetes and is present in about 6% of diabetic children.\textsuperscript{7} Treatment is difficult and multiple therapies have been tried with little success.

**Oedema**

Generalised oedema due to water retention is a rare complication of insulin therapy. Oedema may be seen during establishment of glycaemic control after prolonged periods of poor glycaemic control, particularly if there has been significant omission of insulin.\textsuperscript{70,71} The oedema spontaneously resolves over a period of days to weeks with continued good glycaemic control.

**Primary adrenal insufficiency (Addison's disease)**

Up to 2\% of patients with type 1 diabetes have detectable antiadrenal autoantibodies.\textsuperscript{41,72,73} Addison’s disease is occasionally associated with type 1 diabetes (Autoimmune Polyglandular Syndrome, APS I or II).

The condition is suggested by the clinical picture of:
- Frequent hypoglycaemia.
- Unexplained decrease in insulin requirements.
- Increased skin pigmentation.
- Lassitude.
- Weight loss.
- Hyponatraemia and hyperkalaemia.

Diagnosis is by demonstrating a low cortisol response to a Synacthen test. Treatment with glucocorticoid and mineralocorticoid is urgent and lifelong.

In asymptomatic children with positive adrenal antibodies detected on routine screening, methods of follow up vary. A rising ACTH level suggest a failing adrenal cortex and the development of primary adrenal insufficiency.

**The Evidence**

No studies were identified addressing the optimal frequency of screening for thyroid disease and coeliac disease in children and adolescents with type 1 diabetes. Therefore the recommendations for screening are based on current consensus guidelines.\textsuperscript{45,59}
The evidence for the effect of a gluten-free diet in children and adolescents with type 1 diabetes detected to have coeliac disease on routine screening is listed in Evidence Table 15.1.

- Only two short-term studies were identified describing the effect of a gluten-free diet in asymptomatic children and adolescents with type 1 diabetes who have been detected to have coeliac disease on routine screening. One case series has shown an increase in height-for-weight following the introduction of a gluten-free diet.\textsuperscript{57} Another case series demonstrated a non-significant increase in body mass index and a non-significant reduction in HbA\textsubscript{1c} following a gluten-free diet.\textsuperscript{63(IV)}
- No long-term studies were identified showing the benefits of a gluten-free diet in children and adolescents with type 1 diabetes who do not have symptoms of coeliac disease when detected by routine screening.

Additional Technical Reports and Consensus Statements used to formulate the recommendations and principles of clinical practice are listed in Evidence Table 15.2.

**Recommendations and Principles**

- Monitoring of growth and development and the use of growth charts is a very important part of ongoing care of children and adolescents with type 1 diabetes.\textsuperscript{45,59(C)}
- Screening of thyroid function by Thyroid Stimulating Hormone (TSH) every 2 years is recommended in asymptomatic individuals without a goitre or in the absence of thyroid autoantibodies. More frequent assessment is indicated otherwise.\textsuperscript{45(C)}
- Screening for coeliac disease should be carried out around the time of diagnosis and every 2-3 years thereafter. More frequent assessment is indicated if the clinical situation suggests the possibility of coeliac disease.\textsuperscript{46,59,60(C)}
- Although the benefits of a gluten-free diet have not been proven in those with type 1 diabetes detected to have coeliac disease on routine screening,\textsuperscript{57,63} these children should be referred to a paediatric gastroenterologist and on confirmation of the diagnosis receive support from a paediatric dietitian with experience in gluten-free diets.\textsuperscript{59,74(C)}

C = Consensus statement endorsed by professional organisations

**Reference List**

Chapter 15: Other Complications and Associated Conditions

Australian Clinical Practice Guidelines: Type 1 Diabetes in Children and Adolescents


29. Fernando DJs, Masson EA, Vesse A, Boulton AJM: Relationship of limited joint mobility (LJM) to abnormal foot pressures and diabetic foot ulceration. *Diabetes Care* 14:8-11, 1991


46. Australian Clinical Practice Guidelines: Type 1 Diabetes in Children and Adolescents. 1998

47. NSW Health Department: *Principles of Care and Consensus Guidelines for the Management of Diabetes Mellitus in Children and Adolescents*. 1998


60. National Institute for Clinical Excellence. Type 1 Diabetes (Childhood): Diagnosis and Management of Type 1 Diabetes in Children and Young People. 2004.
Chapter 16: Foot Care

Children and adolescents with diabetes do not display the devastating foot problems seen in older people with diabetes. However, structural and functional abnormalities known to predispose adults with diabetes to plantar ulceration are already present in young people with diabetes.

Young people with diabetes may present with potentially destructive foot changes include deformity, plantar callus and high plantar pressure. Although these abnormalities are not unique to diabetes they have been shown to contribute to soft tissue breakdown, ulceration and even amputation in adults. Other structural changes such as soft tissue thickening and limited joint mobility in the foot are specific complications of diabetes and have been found to alter the mechanics of the foot leading to high plantar pressure and ulceration.

When any of these abnormalities is associated with the macrovascular and/or neuropathic complications of diabetes their effect is potentially devastating.

The identification of potentially destructive foot problems in young people with diabetes is not always simple for the clinician. General foot deformities such as hammer toes, hallux abductovalgus and plantar callus are simple to detect clinically. Superficial skin lesions such as interdigital maceration, heloma durum (corns), onychocryptosis (ingrown toenails) or verrucae (warts) are also simple to detect clinically. However less obvious structural abnormalities require closer inspection by the clinician. The clinical assessment process should include checking for abnormalities, which may indicate that the individual has some form of mechanical imbalance.

Deformity

Any of the following abnormalities may indicate a functional imbalance, which can result in abnormal pressure changes on the plantar surface of the foot or abnormal pressure from footwear:

- A significant leg length discrepancy - greater than 1cm.
- Genuvarum or genuvalgum - genuvarum is normal up to the age of 2, genuvalgum is normal between 2 to 7 year olds.
- Internal or external knee position.
- Varus or valgus foot position - a small degree of valgus alignment is normal up to 7 years old.
- In-toeing or out-toeing.
- Abnormal shoe wear patterns – the heel should wear to the centre or slightly laterally, the sole should show even wear and the upper of the shoe should not be deformed.
- Inadequate shoe fit – either too small or too large.

Studies by Barnett et al\(^1\) and Larsen\(^2\) found that the incidence of foot deformities and skin lesions (including plantar callus) in young people with diabetes is higher than that found in those without diabetes. Both these studies also found that young people with diabetes were more likely to wear shoes that were too small.

Some of the lower limb abnormalities outlined above should lead to examination by a podiatrist, orthopaedic surgeon, paediatrician or physiotherapist with experience in biomechanical evaluation of children.
Plantar Callus

Two studies have shown that the incidence of plantar callus is higher in the young diabetic population.\textsuperscript{1,2} A more recent study\textsuperscript{3} found that there was no significant difference in the number of diabetic subjects who presented with callus compared to age and sex matched controls. Although, in this study, the number of subjects affected with plantar callus was no different, those with callus had significantly higher plantar pressure than those without. Plantar callus and high plantar pressure have been strongly linked to plantar ulceration in adults with diabetes.

Young people presenting with plantar callus should be monitored closely for any indication of soft tissue damage. They should also be advised to see a podiatrist for general foot care and/or possibly some form of orthotic device because:

- Plantar callus may indicate structural or functional abnormality in the foot.
- Plantar callus can increase plantar pressure.
- People with plantar callus should always be regularly monitored for soft tissue change.

High Plantar Pressure

In adults high plantar pressure is a reliable predictor of subsequent ulceration in diabetic people. Although neuropathy is an essential part, it is now believed that high plantar pressures are a major determinant for the development of these lesions.\textsuperscript{4-8} No significant difference in plantar pressure between young people with diabetes and non-diabetic controls has been detected.\textsuperscript{3} However those with plantar pressures two standard deviations above the non-diabetic control mean may be at risk of future foot pathology. Treatment should be instigated when high plantar pressure is detected. Effective and non-invasive pressure reducing treatments have also been investigated. These include simple cushioning insoles, orthoses or both in conjunction.\textsuperscript{3}

Plantar callus may be present in some individuals but there are no clinical signs of high plantar pressure. The only method of evaluating plantar pressure is by using pressure analysis equipment. This equipment should be available at most high-risk foot clinics and diabetes complications assessment clinics.

Plantar pressure is assessed using pressure analysis equipment. High plantar pressure may damage underlying soft tissue. People with diabetes who have high plantar pressure should be encouraged to have regular foot examinations.

Soft Tissue Changes

Skin changes in diabetes are similar to those found in scleroderma and the aging process.\textsuperscript{9,10} In essence these changes result in the loss of elasticity and anchoring fibrils and thickening of the dermis.\textsuperscript{11,12} This predisposes plantar skin to injury from minor trauma.\textsuperscript{12} Qualitative and quantitative examination of the skin has been undertaken in young people with diabetes. Rosenbloom et al\textsuperscript{13} found that the skin on the dorsum of the hands appeared thick, tight and waxy in some young people with diabetes. This prompted investigation of the skin on the sole of the foot using ultrasonography but no thickening of plantar skin was noted when diabetic subjects were compared to non-diabetic controls.\textsuperscript{14}

Thickening of the plantar aponeurosis has been found to be associated with increased forefoot plantar pressure and limited joint mobility in adults with diabetes.\textsuperscript{15,16}
Plantar aponeurosis thickening (greater than two standard deviations above the non-diabetic control mean) has been detected by ultrasound in thirty-two per cent of young people with diabetes.\textsuperscript{14} In this study, thickening of the aponeurosis was associated with limited subtalar joint mobility, but not with high plantar pressure in these younger individuals. It is possible that the soft tissue changes found in these younger patients may not have progressed sufficiently to alter plantar pressure. However, these young people should be closely monitored for any increase in plantar pressure. Features to note include:

- Changes in skin tone which may predispose the foot to damage from minor trauma.
- Reduced adipose tissue on the plantar surface of the foot which increases mechanical stress on plantar skin.
- Increased thickness of the plantar aponeurosis which may be associated with higher plantar pressure.

**Limited Joint Mobility**

Limited joint mobility in the feet of adults with diabetes increases plantar pressure, which in turn leads to tissue breakdown and ulceration.\textsuperscript{4-6,17,18} High plantar pressures in adults with neuropathy are uncommon when joint mobility is within normal range.\textsuperscript{7} The primary determinant of high plantar pressures is limited joint mobility, and neuropathy is a secondary phenomenon.\textsuperscript{4-6}

Limited joint mobility has also been detected in the feet of young people with diabetes.\textsuperscript{1,14,19} The foot joints affected include the ankle, subtalar, 1st metatarsophalangeal and interphalangeal joints. Joint limitation particularly at the 1st metatarsophalangeal joints has been shown to increase plantar pressure under the hallux, an area at great risk of developing a plantar ulcer.\textsuperscript{3}

Limited joint mobility at the 1st metatarsophalangeal joint is relatively simple to detect clinically. Young people with less than 60° of dorsiflexion (in a weightbearing position) should be suspected of having limited joint mobility and more in-depth investigations of other foot joint motion and plantar pressure should be undertaken.

**The Evidence**

The evidence for the effect of type 1 diabetes on joint mobility in the feet of young people is listed in Evidence Table 16.1.

- Reduced joint mobility in the feet has been found in young people with diabetes.\textsuperscript{1,14,19} (IV)

The evidence data for the management of high plantar pressure in adolescents with type 1 diabetes is listed in Evidence Table 16.2.

- The effects of orthosis, cushioning or both in combination were monitored in 17 diabetic subjects with high peak plantar pressure and in 17 diabetic subjects with plantar callus; reductions of up to 63% were achieved. Diabetic subjects who had not received any interventions showed no significant change in peak plantar pressure.\textsuperscript{3} (IV)

No studies were identified addressing the optimal frequency of screening for foot complications in children and adolescents with type 1 diabetes. Therefore the recommendations for screening are based on current consensus guidelines.\textsuperscript{20} (C)

Additional Technical Reports and Consensus Statements used to formulate the recommendations and principles of clinical practice are listed in Evidence Table 16.3.
Recommendations and Principles

- Health care professionals should be aware that the structural and functional abnormalities known to predispose adults with diabetes to plantar ulceration are already present in young people with diabetes.\(^1\)\(^:14\)\(^:19\) (IV)
- Young people presenting with plantar callus, or detected to have high plantar pressures or limited joint mobility need to be monitored closely for foot complications.\(^2\)\(^0\) (C)
- Orthosis, cushioning or both in combination may be used to treat high peak plantar pressure.\(^3\) (IV)

IV = Evidence obtained from case series, either post-test or pre-test and post test
C = Consensus statement endorsed by professional organisations

Reference List

Chapter 17: Dental Health

The maintenance of dental health and the prevention of dental disease is important for children and adolescents with diabetes mellitus.

The assessment of dental health should be a part of the regular medical follow-up. The overall dental management for children and adolescents with diabetes includes:

- Maintaining oral hygiene using all available cleaning techniques (brushing, flossing, and using toothpastes and antibacterial rinses).
- Regular cleaning and scaling of teeth by the dentist.
- Dietary advice.
- In some cases, chlorhexidine rinses.
- In some cases, antibiotics.

Children and adolescents with diabetes should be referred early to a dental specialist, such as a periodontist or paediatric dentist, if there are special periodontal or decay problems.

Assessment of dental health includes not just the teeth, but the whole mouth cavity. It should be remembered that patients with type 1 diabetes, especially those with poor metabolic control, have an increased risk of oral candida carriage. This may also be associated with dryness of the mouth, a burning sensation and painful fissures in the mouth and lips.

Dental Caries

Sugary foods and poor toothbrushing promote formation of dental plaque on the surface of the tooth. Acids made by plaque bacteria become trapped under the plaque and cause tooth decay. Substances released from the surface of the dental plaque (eg bacterial lipopolysaccharides) activate a destructive inflammatory response in the gingivae.

For the child and adolescent with good glycaemic control, dental caries is no more likely than for those without diabetes.

However, dental decay is increased in those with poor glycaemic control and this has been attributed to:

- Reduced amount of saliva in the mouth.
- High glucose content in the saliva.

Periodontal Disease

Diabetes is a risk factor for periodontal disease especially when metabolic control is poor or when diabetes duration is long.

Periodontal disease is a chronic, potentially progressive bacterial infection resulting in inflammation and destruction of tooth-supporting tissues. Diabetes is associated with increased incidence, greater progression and severity of periodontal disease.

The periodontal tissues are made up of the:

- Gingivae (gums).
- Ligament holding the tooth into the bone (periodontal ligament).
- Bone itself.
The point of attachment of the gingival tissues to the tooth is a shallow groove around the neck of the tooth (gingival crevice). The gingival crevice needs to be kept clean if it is to stay healthy. If dental plaque is left on the surface of the teeth adjacent to the dental crevice, inflammation of the gingivae will occur (periodontal disease). In diabetes there are changes in the small blood vessels of the gingiva and changes in the local immune response to plaque, particularly the neutrophil response. These changes can increase the risk of periodontal disease.

Periodontal disease includes:
- Gingivitis.
- Periodontitis.

**In gingivitis:**
- The gingivae become red, swollen and bleed easily.
- The infection damages the attachment between the teeth.
- The infection is typically painless and little attention is usually paid to it.
- Associated smoking is a major risk factor for periodontal disease \(^\text{10}\) and can accelerate the onset of periodontitis in teenagers.

**In periodontitis:**
- Periodontitis is unusual in children and adolescents; gingivitis is far more common.
- Progression to periodontitis occurs when the gum margins lose their tight seal against the surface of the tooth and a pocket is formed between the gum and the tooth. Such pockets provide an ideal spot for the growth of bacteria and are hard to clean out. The bacteria are typically gram-negative anaerobes including Porphyromonas gingivalis, Prevotella intermedia, spirochaetes and occasionally the micro-aerophilic organism Actinobacillus actinomycetemcomitans.\(^\text{11}\)
- Periodontitis is characterised by destruction of the gingiva, periodontal ligament, alveolar bone, cementum and loss of connective tissue attachment.
- The gingivae may recede and the teeth begin to look longer (the recession may become so severe that the teeth get very loose and need to be removed).

Gingivitis or more severe problems can be recognised just by looking and by gently probing the gum margins to see if there is any bleeding or pocketing around the necks of the teeth. Those with poor glycaemic control are more liable to gingivitis. If more detailed assessment of the bone around the teeth is required then dental x-rays are used.

**Prevention and Treatment of Dental Caries and Gingivitis**

Tooth decay and gingivitis can be both prevented and/or reversed by:
- Using low fluoride or ‘Junior’ toothpaste (until 8 years of age), and daily use of a low dose fluoride mouthwash to help repair any surface damage to the teeth.
- Regularly examining (twice yearly) for the presence of gingivitis or periodontal disease.
- Taking extra care with dental hygiene in adolescents with orthodontic bands and wires which make the cleaning of teeth very difficult and can exaggerate the gum response. In this situation, the routine dental team should review more frequently for caries.
- Brushing and flossing teeth at least twice a day to remove the plaque from the surfaces of the teeth and gingivae. Important points to note are:
The best brush is one with soft bristles and a small head and to use small circular movements or short backward and forward vibration strokes.

Children seldom have the ability to perform efficient cleaning before the age 10 years and often the duration of their brushing is too brief.

Children also forget to clean the backs of their teeth and for these reasons parents should brush young children’s teeth routinely.

With older children ‘parental brushing’ as often as possible is important.

The use of a battery-powered automatic toothbrush often improves a child’s acceptance of this and increases the duration of brushing.

The Evidence

The evidence for the effect of type 1 diabetes on dental health in children and adolescents is listed in Evidence Table 17.1.

- Dental decay is increased in those with poor glycaemic control.4(IV)
- Diabetes is a risk factor for periodontal disease especially when metabolic control is poor or when diabetes duration is long.6-9(IV)

No studies were identified specifically addressing the optimum frequency of screening for dental pathology in children and adolescents with type 1 diabetes; therefore the recommendations for screening reflect current consensus guidelines.12(C)

Additional Technical Reports and Consensus Statements used to formulate the recommendations and principles of clinical practice are listed in Evidence Table 17.2.

Recommendations and Principles

- Children and adolescents with type 1 diabetes should be informed that dental decay is increased when glycaemic control is poor.4(IV)
- Health care professionals should be aware that diabetes is a risk factor for periodontal disease especially when metabolic control is poor or when diabetes duration is long.6-9(IV)
- Children and adolescents with type 1 diabetes should be informed that tooth decay and gingivitis can be prevented and/or reversed by brushing and flossing teeth at least twice a day to remove plaque from the surfaces of the teeth and gingivae.12(C)
- The mouth should be examined regularly (twice a year) for the presence of gingivitis or periodontitis.12(C)

IV = Evidence obtained from case series, either post-test or pre-test and post test.
C = Consensus statement endorsed by professional organisations

Reference List


Chapter 18: Adolescent Health

Introduction

Adolescents often struggle to cope with the demands of diabetes care. Adolescence is a time when major physiological changes occur leading to increased insulin resistance. Insulin dosages are typically higher during adolescence and most teenagers need to switch to a multiple injection regimen.\(^1\) The DCCT demonstrated that HbA\(_{1c}\) levels were generally 1\% higher in adolescents, both in the intensively treated and in the conventionally treated groups but despite this had a higher prevalence of severe hypoglycaemia.\(^2,3\) Young people with type 1 diabetes need to maintain and develop self-esteem and independence at a time when diabetes care itself is at its most challenging.

The major risks faced by adolescents with type 1 diabetes include:\(^4\)
- Deterioration of glycaemic control (see chapter 6).
- Risk-taking behaviour.
- Hypoglycaemia (see chapter 12)
- Recurrent diabetic ketoacidosis (see chapter 9).
- Accelerated microvascular complications (see chapter 14).

When managing adolescents with type 1 diabetes the aim is to achieve:
- Normal growth.
- Normal pubertal development.
- Normal psychological development.
- Maintenance of glycaemic control.\(^1\)
- Prevention of acute complications of diabetes (hypoglycaemia,\(^2,3\) diabetic ketoacidosis\(^5,6\))
- Prevention or minimisation of microvascular complications.\(^7\)
- Normal lifestyle.
- Normal education opportunities.
- Avoidance of risk taking behaviours (smoking, substance abuse).
- Regular attendance to medical supervision.
- Comprehensive preparation for and transition to adult care.

An Approach to the Assessment of Adolescents

The HEADSS technique may be used (along with the routine medical history taking) to guide the assessment of any adolescent.\(^8\) This comprehensive technique includes questions about:
- Home
- Education (or employment)
- Activities
- Drugs (also including alcohol and smoking)
- Sexuality (including contraception)
- Suicide (including other mental health issues)

Transition to Adult Care

Adolescents with diabetes have specific health needs relating to the physical, emotional, psychological and socio-cultural stages of adolescence.\(^9\) Adolescents are less likely to adhere to prescribed care and have poor glycaemic control.\(^10-13\) The transition from a paediatric to an
adult service for the adolescent with diabetes is often difficult. The position paper on transition prepared by the Society for Adolescent Medicine outlines principles for successful transition including:14

- The need for services to be appropriate for both chronological age and developmental attainment.
- Transitional programmes to be flexible enough to meet the needs of a wide range of young people, health conditions and circumstances.
- Transitional programmes to be prepared to address common concerns of young people including growth and development, sexuality, mood and other mental health disorders and damaging behaviours.
- Transfer of care to be individualised to meet specific needs.

If the transition is not carefully managed the following consequences may occur:
- Non-adherence to insulin regimens.13
- Lack of follow-up.
- Prolonged period of poor glycaemic control resulting in suboptimal health.
- Acceleration of microvascular complications.
- Loss of access to emergency advice.

Of the 7 studies identified which addressed the issue of transition to adult services for adolescents with type 1 diabetes, 6 were surveys of the patient15-19 or their paediatrician,20 and one was a case series.21

An Australian survey of young people with type 1 diabetes found that 5.7% felt the transfer should occur before the age of 17 years, 48.6% between 17-20 years, and 44.8% at any stage up to 25 years of age.15 Overseas surveys reported the mean ages for transition were:

- Canada 18.5 years.18
- Finland 17.5 years.21
- United Kingdom (Exeter) 15.9 years.16

A study of transition processes in the Oxford region, UK, showed that the 2 year clinic attendance (at least 6 monthly) fell from 98% pre-transfer to 61% post-transfer (p<0.0005) and the attendance rate for the first appointment on transfer was only 79%.17 A Canadian survey of transition mean age 18.5 years) revealed 21% would have preferred earlier transfer whereas 65% felt they would have liked transfer later.18 After transfer 13% had no regular contact with the adult service, 3% maintained contact with a family practitioner only while the remainder had regular contact with either an endocrinologist in private practice or an adult clinic.18 Thirty-three percent reported problems with the transition process. A delay of more than 6 months between the last visit to the paediatric service and the first visit to the adult service occurred in 27% and in 17% the transition process took more than a year.18

As none of the studies compared different models of transition, the following recommendations for transition are largely consensus based.

The formal transition phase should occur at a time of relative stability in the adolescent’s health and may be coordinated with other life transitions. A useful age at which transition should take place is the end of high school or when the adolescent leaves school to join the workforce, however the following factors need to be taken into account:

- The admission policy of the hospital if care is managed through a hospital-based diabetes service (many now incorporate adolescent services allowing care to the age of 18 years, while others have an age limit of 13-14 years).
- The wishes of the adolescent.
• Emotional maturity.
• Physical maturity.
• Presence of any coexisting medical, surgical or psychiatric disorders that may be more appropriately managed through the paediatric service.

Ideally the transfer to an adult service should involve:
• A preparation phase (from 12 years) which should be:
  ➔ Planned well in advance.
  ➔ Organised by a special transition service.
  ➔ Discussed with the adolescent and family progressively over several years and supplemented with written information outlining the transition process and the available options.
• A formal transition phase (16-18 years) which should be:
  ➔ Directed to an adult diabetes specialist or a clinic with a special interest in young adults with type 1 diabetes.
  ➔ Facilitated by a visit to the adult service or by having the adult physician attend the adolescent clinic if care is provided through a paediatric hospital-based diabetes service.
  ➔ Formally arranged with appropriate letters of referral and details of past history.
  ➔ Accompanied by clear directions on which emergency service to contact in the transition period.
• An evaluation phase (18-19 years) to follow-up and confirm that the transition has taken place in a timely fashion and that continuing appointments have been arranged.

Career Options

In previous times, there were a number of career paths which people with diabetes were discouraged from pursuing. However, with improved understanding and management of diabetes there are now few occupations from which people with diabetes are excluded.

In recent years a number of cases of workplace discrimination against people with diabetes mellitus have been successfully challenged in the courts. However, it is still prohibited to enter professions in:
• The Australian defence forces.
• The full-time or volunteer fire brigade.
• The police force (currently under challenge).
• The aviation industry - commercial or private pilot licences.

(Note: An individual already employed in one of the above listed services prior to a diagnosis of diabetes mellitus may be removed from active duties following diagnosis and placed in a more administrative role within the service).

It is not advisable for people with type 1 diabetes to work at heights (because of the risk to themselves and others if they are affected by hypoglycaemia.

Driving

In the first instance, adolescents with diabetes should discuss with their parents and medical team the issue of driving. The importance of having a good knowledge about hypoglycaemia, its treatment and prevention cannot be overemphasised. The adolescent must be made aware that the combination of alcohol, with its potential to cause hypoglycaemia, and diabetes can result in fatal accidents. The main hazard to driving is unexpected hypoglycaemia.
Results from a recent American survey of drivers revealed an increased incidence of driving mishaps in drivers with type 1 diabetes. Driving performance is significantly disrupted at relatively mild hypoglycaemia. A responsible attitude towards driving is therefore essential.

Adolescents should be taught to do a blood glucose estimation immediately before driving a car and to have rapidly absorbed carbohydrate (e.g., glucose tablets) readily accessible and to take these at the first indication of hypoglycaemia.

When considering hypoglycaemia for licensing purposes, the Road and Traffic Authorities are concerned with severe episodes which may impair consciousness, awareness, motor skills or result in abnormal behaviour. Each State and Territory has its own set of regulations governing the issue of licences to people with diabetes and health care professionals should acquaint themselves with the regulations applying in their State or Territory.

The second edition of ‘Assessing fitness to drive: Guidelines and standards for health care professionals in Australia’ produced by Austroads Inc. in 2001, and approved by all Australian Driver Licensing Authorities makes the following statements in relation to suitability of people with diabetes to drive:

- If there is poor management of a diabetic condition, or poor compliance by a patient to their specified treatment, then the patient with diabetes should be advised not to drive.
- Patients with diabetic retinopathy may drive if their vision meets the specified criteria; regular review by an eye practitioner is required.
- Patients with type 1 diabetes may drive providing they meet the other criteria in the book. Two yearly review is required but the physician may recommend a shorter review period.
- Patients newly starting on insulin therapy should be advised to notify the driving licensing authority of the condition and the treatment.
- Patients should not drive after admission to hospital for stabilisation of diabetes until cleared by their primary health physician.
- Patients should not drive after a major hypoglycaemic episode or hypoglycaemic episode whilst driving until cleared by a physician.

Patients should be made aware about the effects of their condition on driving and advised of their legal obligation to notify the driver licensing authority where driving is likely to be affected. As a last resort, practitioners may themselves advise the driver licensing authority.

Individuals who wish to pursue licences other than for cars, light trucks (up to 8 tonnes gross vehicle mass) and motor cycles, should make enquires to their nearest driver licensing authority.

**Risk Taking Behaviour**

**Smoking**

Smoking should be actively discouraged in diabetes and the education process should be commenced in paediatric services. The risk of morbidity and mortality among smokers with type 1 diabetes is increased.

Clinicians working with adolescents should use outpatient office visits as an important ‘teachable moment’ to prevent tobacco use. Brief interventions (taking 1-2 minutes to ask about smoking and make some recommendations) can be effective and should involve the following stages:

- Ask about smoking habit.
- Advise to consider quitting.
• Assess level of addiction and what ‘stage of change’ they are at.
• Assist by providing quitting strategies and supports.
• Arrange follow-up.

Approximately 30 percent of teenagers show evidence of recent nicotine exposure (from screening surveys using urinary cotinine) and the prevalence in adolescents with diabetes does not differ.

Diabetes education needs to address the following issues:
• Smoking is deleterious to the health of all persons at any age. Smokers who have diabetes may have additional medical consequences. 
• Medical evidence indicates that smoking has been implicated as an additional risk factor for the appearance and progression of microvascular disease (retinopathy, nephropathy and neuropathy) and of macrovascular disease.
• Smoking is also associated with:
  ➔ Hypertension.
  ➔ Poorer glycaemic control.
  ➔ Excess general morbidity.
  ➔ Additional risks in pregnancy.
  ➔ Increased risk of periodontal disease.

**Alcohol**

It is illegal for alcohol to be sold to or served to young people under the age of 18 years in Australia. Proof-of-age identity cards are needed by young people wishing to purchase or be served alcohol.

No studies have been reported on the effects of alcohol ingestion on adolescents with type 1 diabetes. Several small studies have reported the effects of moderate amounts of alcohol consumed in the evening in adults with type 1 diabetes (0.5-1.0 gm per kg body weight, equivalent to 3.5-7 standard (10gm alcohol) drinks for a 70 kg person). One study (0.75 gm/kg alcohol) reported lower post-prandial and morning fasting blood glucose to the point of requiring treatment of hypoglycaemia in 5 out of 6 patients, while the other two studies showed no effect. The effects of drinking larger quantities (‘binge drinking’) have not been studied. However, this pattern of drinking is emerging as the dominant form especially for young females.

Alcoholic drinks provide extra kilojoules (important if weight control is a problem) and the potential to cause the following effects:
• May initially increase blood glucose.
• May increase plasma lipids.
• May increase ketone levels.
• May inhibit gluconeogenesis resulting in delayed hypoglycaemia.

The combination of alcohol-induced confusion and hypoglycaemia is a particularly dangerous one. Reaction times during hypoglycaemia have been shown to be reduced during hypoglycaemia.

Adolescents with diabetes need to be warned about the dangers of alcohol as part of their diabetes education. Consensus guidelines relating to alcohol consumption have advised the following:
• Drink in moderation.
• Do not exceed recommended safe intakes (2 standard drinks for adult males, 1 standard drinks for adult females (1 standard drink is equivalent to approx 10gm alcohol)).
• Avoid binge drinking.
• Avoid consuming alcohol on an ‘empty stomach’.
• Drink low-alcohol beers or wine rather than spirits, fortified wines or spirits/soft drink mixes.
• Measure blood glucose levels regularly during and after consuming alcohol.
• Eat carbohydrate foods while consuming alcohol.
• Eat prescribed snacks/meals on time.
• Measure blood glucose before going to bed, eat a bedtime snack and ensure BG is greater than 8 mmol/L.

**Drugs**

The most commonly used substances with the potential for abuse are still tobacco and alcohol. From the limited information available it would appear that adolescents with diabetes are no more likely to experiment with or use drugs. A survey of adolescents (age 10-20 years) in the US found that 10% had used a drug in the past (8% in the previous year). There is little published information on substance misuse and their effects in adolescents with type 1 diabetes. In general substance use has the capacity to:

• Alter perception.
• Alter cognitive ability.
• Alter consciousness.
• Alter sensation.
• Decrease capacity to achieve glycaemic control.
• Decrease interest in achieving glycaemic control.
• Decrease interest in routines, injection and meal schedules.
• Increase risk of hypoglycaemia being ignored or misinterpreted.
• Reduce appetite and interest in food that may potentiate hypoglycaemia.
• In the case of marijuana, stimulate appetite (the ‘munchies’) with a craving for carbohydrate.

A significant percent of adolescent drug use is likely to be intermittent, experimental or recreational, and effects on diabetes and its management may be few. Regular drug use has the potential of causing deterioration in diabetes control. Regular drug use does not generally occur in isolation but in the context of other risk-taking behaviours, psychosocial distress and peer group or family drug usage.

**Sexuality**

**Impotence**

Fear of impotence may be a concern for adolescent boys with diabetes. Impotence may be caused by psychological or organic conditions.

Impotence due to organic reasons may occur in adults with diabetes of long duration as a result of autonomic neuropathy affecting the nerve supply to the corpora cavernosa or as a result of macrovascular disease of the aorta affecting the blood supply to the penis.

Increasing age, duration of diabetes and poor glycaemic control are risk factors for erectile dysfunction. Impotence is rare in the adolescent age group and may well be minimised or prevented by good glycaemic control.

Impotence due to psychological reasons needs to be treated by counselling and reassurance.
Contraceptives
Assessment of sexual activity and the need for contraception should be a routine part of adolescent diabetes care, as young persons may not actively seek contraceptive advice. The clinician should reassure the adolescent that confidentiality will be maintained. Ensuring confidentiality, along with establishing empathy will create a more suitable environment to explore contraception and related issues.

Oral contraceptive pill (OCP)
Low dose oestrogen-containing OCP preparations are not contra-indicated in adolescents with type 1 diabetes but should be used with caution if there is:
- Uncontrolled hypertension.
- Dyslipidaemia (particularly hypertriglyceridaemia).
- Evidence of microvascular disease.
- Evidence of macrovascular disease.

In general OCP use is not advised in young women with micro- or macro-vascular disease.

The best choice of oral contraceptive pill for adolescents with type 1 diabetes is a low dose oestrogenic-containing monophasic or triphasic preparations. The new gestodene-containing OCPs may have some advantages in patients with type 1 diabetes as they have less effect on lipid profiles and carbohydrate metabolism, as well as being less androgenic.

Young women with type 1 diabetes using OCPs should have an annual gynaecological review that should incorporate expert advice on the most appropriate method of contraception.

Intrauterine devices (IUDs)
Although IUDs are not ideal, particularly in a nulliparous female with type 1 diabetes, if this is the only form of contraception that is suitable or tolerated, it is preferable to an unplanned pregnancy. The newer IUDs appear to be effective and well tolerated in diabetic women.

The risk of pelvic infection, while probably low with newer devices, is highest in:
- New users.
- Younger age groups.
- Those at risk of sexually transmitted disease.
- Women with poorly controlled diabetes.

Barrier methods (condom, diaphragm)
Condoms may be used both as a primary contraceptive method and, importantly, should always be advised for additional protection against the risk of sexually transmitted disease even when other contraceptive methods are employed.

Barrier methods may appear to be well suited to young women with diabetes due to their lack of side effects. However, a high degree of motivation and compliance is required as these methods may have higher failure rates.

Progestogen depot/implant
These are extremely effective forms of contraception. Their use is limited in all women by their side effects. Although they are suitable for use in women with diabetes they should be used with caution as lipid profiles may be altered.
Diabetes and Pregnancy

Pregnancy in all women with type 1 diabetes should be monitored from the pre-conception stage by an experienced multidisciplinary team of obstetrician, diabetologist, diabetes educator and dietitian.

Adolescent girls with diabetes should be made aware of the extreme importance of a planned pregnancy. Education should address effective contraception to avoid an unplanned pregnancy. Pregnancy should only occur when the HbA1c is within or close to the nondiabetic range because poor glycaemic control increases the risk of large babies as well as increasing the risk of foetal malformations 2-10 fold with progressive elevation of the HbA1c.41-43 Furthermore pregnancy may accelerate the progression of microvascular complications44 and the risk of hypertensive disease in pregnancy is increased.45,46

Eating Disorders

A systematic review of case-control studies in children and adults showed that the incidence of anorexia nervosa in people with type 1 diabetes is not increased.47 However, adolescent females with type 1 diabetes and anorexia nervosa have a significantly increased mortality rate compared to patients with type 1 diabetes alone.48

A systematic review of case-control studies has shown that the incidence of bulimia nervosa, ED-NOS (Eating Disorder - Not Otherwise Specified) and sub-threshold disorders are significantly increased in female adults and children with type 1 diabetes. 47 Eating disorders in males with diabetes have been less extensively investigated, but some studies suggest that they may display high levels of unhealthy weight control behaviours and high drives for thinness.49,50

Studies have found an increased level of retinopathy in patients with type 1 diabetes and sub-clinical and clinical eating disorders.47,51,52

The diagnostic criterion of the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders criteria) recognises medication manipulation for the purpose of weight loss as a behavioural disturbance associated with eating disorders.53 Intensive glycaemic control is associated with weight gain,2 and this may be unacceptable to many adolescents. Intentional reduction or omission of insulin have been less extensively investigated, but some studies suggest that they may display high levels of unhealthy weight control behaviours and high drives for thinness.54,55

The incidence of insulin omission or misuse in females with type 1 diabetes is 12-15%.54,55 Insulin purging leads to poor glycaemic control and increased risk of medical complications.57

Predictive signs of disordered eating include:58

- Poor glycaemic control.
- Frequent hospital presentations with diabetic ketoacidosis.
- Weight loss or weight cycling.
- Unhealthy attitudes toward weight and/or food.
- Falsification of blood glucose levels.

The co-existence of type 1 diabetes and eating disorders presents difficulties for the management of the diabetes as well as for psychological treatment. One of the goals of cognitive behavioural therapy for bulimia nervosa is to relax control over eating and this can conflict with the nutritional aspect of diabetes management.57 Treatment of eating disorders depends on the type and severity of the disorder, but should include medical, nutritional and psychological therapy by an experienced multi-disciplinary team.58
The Evidence
The evidence comparing glycaemic control in adolescents and adults is listed in Evidence Table 18.1.
- The DCCT demonstrated that HbA1c levels were generally 1% higher in adolescents, both in the intensively treated and in the conventionally treated groups.2,3(II)

The evidence for current transition processes and outcomes for adolescents with type 1 diabetes moving to the adult care system is listed in Evidence Table 18.2.
- Seven studies addressing the issues of transition to adult services identified poor or delayed post-transfer clinic attendance and frequent dissatisfaction with the transition process.15-21(IV)
- A study of transition processes in the Oxford region, UK, showed that the 2 year clinic attendance (at least 6 monthly) fell from 98% pre-transfer to 61% post-transfer (p<0.0005) and the attendance rate for the first appointment on transfer was only 79%.17(IV)

The evidence for the effect of type 1 diabetes on driving performance is listed in Evidence Table 18.3.
- Results from a recent American survey of drivers revealed an increased incidence of driving mishaps in drivers with type 1 diabetes.22(IV)
- Simulated driving performance is significantly disrupted at relatively mild hypoglycaemia.23(IV)

The evidence for eating disorders in type 1 diabetes is listed in Evidence Table 18.4.
- A systematic review of case-control studies has shown that the incidence of Anorexia Nervosa in females with type 1 diabetes is not increased, however the incidence of bulimia nervosa, ED-NOS (Eating Disorder - Not Otherwise Specified) and sub-threshold disorders are significantly increased in female adults and children with type 1 diabetes.47
- Adolescent females with type 1 diabetes and anorexia nervosa have a significantly increased mortality rate compared to patients with type 1 diabetes alone.48(IV)
- Males with diabetes have high levels of unhealthy weight control behaviours and higher drives for thinness than non diabetic controls.49,50
- The incidence of insulin omission or misuse in females with type 1 diabetes is 12-15%.54,55(IV)
- Studies have found an increased level of retinopathy in patients with type 1 diabetes and sub-clinical and clinical eating disorders.47,51,52(IV)

Additional Technical Reports and Consensus Statements used to formulate the recommendations and principles of clinical practice are listed in Evidence Table 18.5.

Recommendations and Principles
- Health care professionals should be aware that glycaemic control is more difficult in adolescents with type 1 diabetes.2,3(II)
- Adolescents with diabetes have specific health needs relating to physical, emotional, psychological and socio-cultural stages of adolescence.4,9(C)
- The major risks faced by adolescents with diabetes include deterioration of glycaemic control, risk-taking behaviour, hypoglycaemia, recurrent diabetic ketoacidosis and accelerated microvascular complications.3(C)
- The transition from a paediatric to an adult service for the adolescent with diabetes is often difficult.15-21(IV)
- Ideally the transfer to an adult service should be comprehensive and should involve:14(C)
A preparation phase which is planned well in advance by a special transition service and the adolescent and family.

A formal transition phase to an adult clinic, with appropriate referral and clear directions for the patient and family (eg in case of emergencies).

An evaluation phase.

- Adolescents should be taught to do a blood glucose estimation immediately before driving a car and to have rapidly absorbed carbohydrate (eg glucose tablets) readily accessible and to take these at the first indication of hypoglycaemia.22;23(IV)
- Smoking should be actively discouraged in diabetes.25(C)
- Adolescents with diabetes need to be warned about the dangers of alcohol as part of their diabetes education.59;60(C)

• Assessment of sexual activity and the need for contraception should be a routine part of adolescent diabetes care.4;59(C)

- Health care professionals should be aware that the incidence of eating disorders is increased in males and females with type 1 diabetes47;49;50 and that adolescent females with type 1 diabetes and anorexia nervosa have a significantly increased mortality rate compared to patients with type 1 diabetes alone.48(IV)
- Health care professionals should be aware that intentional reduction or omission of insulin to achieve weight loss is common (so-called insulin purging).54;55(IV)
- Health care professionals should be aware that increased levels of retinopathy have been found in patients with type 1 diabetes and sub-clinical and clinical eating disorders.47;51;52(IV)
- Treatment of eating disorders should include medical, nutritional and psychological therapy by an experienced multidisciplinary team.57;58(C)

II = Evidence obtained from at least one properly designed randomised controlled trial
IV = Evidence obtained from case series, either post-test or pre-test and post-test
C = Consensus statement endorsed by professional organisations

Reference List


60. National Institute for Clinical Excellence. Type 1 Diabetes (Childhood): Diagnosis and Management of Type 1 Diabetes in Children and Young People. 2004.
Chapter 19: School

School attendance is compulsory for children from 6 to 15 years unless:

- Families lack access to an educational facility if geographically isolated.
- A medical condition or religious conviction prevents attendance.

All children and adolescents with type 1 diabetes should attend school and participate in normal school activities. Diabetes should not be the cause of a child or adolescent being excluded from any school activity. Full participation in all academic, social and sporting activities is possible and should be encouraged. Any discrimination or stigmatisation is unacceptable.

School is a major part of a child’s life and needs to be a rewarding experience. It is important for children to enjoy school and to function well at school because during the school term they spend approximately 40 percent of their waking hours there. School achievement and adjustment to school are important indicators of the child’s general wellbeing. Furthermore, development of self-esteem and confidence in school activities is likely to have positive effects on diabetes management. Conversely, school difficulties are likely to impact negatively on diabetes control. Behavioural problems at school may be totally unrelated to the child’s diabetes and should not be dismissed as due to diabetes alone.

Children with chronic illness are more at risk for school absenteeism and dysfunction than their healthy peers.

School personnel need to be provided with sufficient information to enable them to provide a classroom environment which facilitates the child’s full integration by ensuring or facilitating:

- Safety at all times.
- Attainment of developmental goals (by exposure to normal life experiences).
- Development of self-esteem.
- Freedom from discrimination from staff and students.
- Peer acceptance and understanding.

It is a legal requirement that schools provide a safe environment conducive to learning and social development in all children, including those with special health needs. Students with diabetes may require additional care. The school has a duty of care to all children including those with special needs. Parents and caregivers of children and adolescents with diabetes should work cooperatively with the school system to ensure mutual understanding of the extent of care provided. With appropriate training some teachers may volunteer to supervise or carry out blood glucose testing, insulin administration or glucagon administration.

An individualised Diabetes Health Care Plan, especially for the younger child with diabetes, should be developed by the parents/care-givers, the student’s health care team and the school.

Specific responsibilities in the Care Plan need to be understood and accepted by parents/care-givers as well as the school.

In some states, for very young children with unstable diabetes, an application can be made to the Department of Education for additional supervision (‘integration support’) in the school setting.
The diabetes management should cause as little disruption as possible, provided that metabolic control and avoidance of hypoglycaemia are not compromised.

**General Considerations in the Development of the Care Plan**

Many children’s diabetes centres and some diabetes associations provide school visits by diabetes educators to inform the staff of the details they need to know about diabetes and to answer any specific questions. The value of these visits cannot be over-estimated and all teaching and office staff should attend. Priority should be given to younger children especially those attending long day care and pre-school.

Diabetes Australia in some States provides a ‘Schools Care Line’. This is a telephone service, manned by a paediatric diabetes educator, available to teachers, parents and students. Essential information (for example the IDF School Pack, accessible from www.diabetesnsw.com.au) for school personnel is available from diabetes centres, Diabetes Australia, Juvenile Diabetes Research Foundation (JDRF) and community health centres. All school personnel (including relief staff and after-school care staff) should be informed if a child in their care has type 1 diabetes. It may be helpful for relief staff to have photographic identification of any child with diabetes in their care.

Background information on diabetes provided to schools should include:

- Differences between type 1 and 2 diabetes.
- Provision of basic information on hypoglycaemia including:
  - Recognition of hypoglycaemia symptoms.
  - Treatment protocols for mild to moderate hypoglycaemia. Awareness that repeat treatment may be necessary.
  - Awareness of the transient deterioration in the child’s brain function and behaviour during and following a hypoglycaemic episode.
  - Basic first aid treatment eg coma position.
- Provision of information on hyperglycaemia including:
  - Polyuria and polydipsia.
  - Need for extra toilet privileges and access to water.
- Awareness that infection control protocols must be adhered to during blood glucose monitoring.
- Provision of a suitable environment for glucose monitoring or insulin injections if required during school hours.
- Awareness that some children now use a continuous subcutaneous insulin pump.
- Emergency contact details.

It is useful to have a photo of the child with important contact numbers in the staff room and in each classroom to alert all staff including relief and part time staff. A medical alert information card should be kept in the child’s records. The child should wear a medical identification bracelet or necklace at all times.

**Issues to be Considered in the Individual Care Plan**

Parents/care-givers should meet with the relevant school personnel as soon as practicable to discuss the issues involved in the care of their child at school. An individual care plan should be developed and reviewed regularly. In general, the younger the child, the greater is the supervision required at school. The extent of the individual care plan will vary greatly and
will be influenced by the consideration of the following issues by the school and the parents/care-givers:

- Child’s level of understanding and knowledge of diabetes.
- Child’s developmental stage and ability to accept responsibility.
- Current treatment recommendations for the individual child.
- Any additional medical problems (eg coeliac disease).
- Child’s usual hypoglycaemic symptoms.
- Avoiding delays in meals, snacks.
- Treating hypoglycaemia immediately.
- Providing the school with an emergency supply of rapidly absorbed carbohydrate (eg jellybeans) in the classroom or wherever the school activity is undertaken.
- Providing extra snacks before, during and possibly following exercise.
- Knowing which foods are easily accessible and easy to consume (eg fruit that does not require peeling).
- Not leaving a child unaccompanied during or after a hypoglycaemic episode (eg in sick bay).
- Knowing that the child should not be sent away unaccompanied by an adult from the classroom to test his/her blood glucose during a suspected hypoglycaemic episode.
- Informing parents/care-givers of the time and nature of the hypoglycaemia (a communication book noting unusual occurrences is helpful for teachers and parents).
- Encouraging the child to eat all of his/her meal (mealtime supervision may be necessary for primary school children. Parents need to be informed if meals are not eaten).
- Being aware that birthday parties at preschool and primary school should not exclude the child with diabetes, as this is a ‘special treat’ occasion and should be so for all the children. Any special considerations (eg provision of diet drinks) should be discussed with the child’s parents or caregivers.
- Providing access to the canteen, recognising that this may need some restrictions.
- Encouraging the child to report hypoglycaemia to school personnel. Teachers need to be cognisant of the child’s personality and feelings, and encourage communication.
- Knowing that following a hypoglycaemic episode children usually recover sufficiently to rejoin the class, although cognitive function may be impaired for several hours. However, if the episode occurred during a sports activity, the child should rest for 10 - 15 minutes before recommencing the activity.
- Helping to fit diabetes into the school routine to prevent the child from feeling different (eg they should eat at the same time as the other children, be given privacy to give injections or do blood tests).
- Determining exactly the physical location where in the school glucose testing and insulin injections will take place.
- Assisting and encouraging the child gradually to take on some responsibility for the diabetes tasks eg negotiating how much reminding the child would like in order to remember to eat on time and how much he/she would like to be left alone.
- Allowing extra access to toilets and drinks when blood glucose levels are high.
- Notifying parents in advance of special events, eg excursions, swimming carnivals, changes to meal times.
- Knowing the impact which diabetes may have on the functioning of the child and family (awareness and acknowledgment of parental concerns inspires confidence, reduces anxiety and their tendency to be over-protective).
- Knowing how blood glucose levels can affect concentration and behaviour.
- Knowing that diabetes should not alter the child’s academic potential.
• Encouraging full participation in all school social, sporting and academic activities, including excursions and camps.

Detentions

Teachers should be aware of the need for regular carbohydrate intake and that eating may be necessary during detention to avoid hypoglycaemia.

Travel to and from School by Bus

Students with type 1 diabetes should be allowed to eat on the bus to avoid hypoglycaemia. A ‘bus’ card approved by transport authorities is available for such special provision in some States.

Emergencies at School

If severe hypoglycaemia causes a child to have a seizure, be unconscious or so disorientated that oral treatment is not possible or is dangerous, the school personnel should lay the child in the coma position and call an ambulance, stating that it is a diabetic emergency (dial 000).

School Examinations

If an examination coincides with the child’s or adolescent’s usual meal or snack time, it is advisable for the child to nibble small amounts of bite-sized carbohydrate food, eg nuts and raisins, throughout, rather than risk having hypoglycaemia by waiting to eat until after the examination. Examination candidates need to be aware that their food should not be wrapped in ‘noisy’ packaging.

High School Examinations

The school is required to send an ‘Application for Candidates with Disabilities’ form, accompanied by a medical certificate, to the ‘Special Provisions for Students’ programmes provided by the individual State or Territory authorities responsible for senior examinations some months prior to the examination. Parents in each State or Territory should enquire about the procedures available to children and adolescents who may experience difficulties with their diabetes during examinations from their diabetes centres, schools or Diabetes Australia.

Most States allow the student to:
  • Take in bite-sized starchy food.
  • Have easy access to leave the room as necessary.
  • Take in a glucose meter and test strips.
  • Have extra time to do an initial blood glucose test, to correct a blood glucose reading under 5 mmol/L and to re-test it.

The provisions may be made on an individual basis depending on the recommendations of the medical practitioner. It is advised that the student receives a copy of the provisions made for him or her. It should be noted that students experiencing hypoglycaemia during the Higher School Certificate examinations (or equivalent in other States) should apply to be treated as an ‘illness/misadventure case’. Giving extra time to compensate for the occurrence of a hypoglycaemic episode may not compensate accurately for the time lost nor allow for the
effect of hypoglycaemia on the child’s concentration. Students treated as an illness/misadventure case usually receive a mark based on a school assessment in place of their actual examination mark.

**School Camps**

Students with diabetes can participate fully in school camp programs. Usually students attend camps when they are reliably independent in the care of their diabetes. This includes the ability to:

- Inject.
- Do blood glucose tests.
- Recognise/treat hypos.
- Understand the importance of timed meals.
- Understand a food plan, dietary carbohydrate portions or serves and the need for extra food before, during and after physical activity.

Parents/guardians should meet with the organisers before the camping event. Each camper should have a standardised medical information sheet completed prior to the camp. All members of staff must be aware of the child with diabetes. The student’s friends and room mates should also be aware.

Staff must know about:

- Food planning and the need for carbohydrate with all meals and snacks.
- Blood glucose testing.
- Prevention of hypos.
- Recognition and treatment of hypos.
- Sick-days.
- When to call for medical help and how to arrange medical evacuation.

The extra exercise at camps increases the risk of hypos. The insulin dose may need to be reduced by up to _ of the usual insulin dose.

Carbohydrate should be served regularly with every meal and snack. Additional carbohydrate should be available for prevention and treatment of hypos.

**Short-term Effects of Fluctuations in Glycaemia on Cognitive Function**

In a case series of 47 children with type 1 diabetes cognitive function was found to remain impaired for a variable period of time following a mild hypoglycaemic episode (despite complete resolution of the hypoglycaemic symptoms) therefore confirming that there is a time lag between recovery rate of physical symptoms and cognitive function in children following a mild hypoglycaemic episode. Decreased cognitive function was also found during hyperglycaemia in an RCT in 8 out of 12 subjects. Mood disturbances have been documented the day after nocturnal hypoglycaemia.

**Long-term Effects of Fluctuations in Glycaemia on Cognitive Function**

Studies have shown that cognitive function is decreased among some children with early onset (<7yrs) and longer duration (>5yrs duration) of diabetes.
Children who had experienced hypoglycaemic seizures were significantly more likely to have a decline in verbal IQ score and other cognitive aspects of perception, fine motor, visuomotor, visual memory and attention.12;14;15

Two longitudinal studies found that the expected cognitive developmental gains (especially verbal skills) were smaller than expected when children were followed from diagnosis of type 1 diabetes to one year,16 two years17 and 6 years post diagnosis.18

A prospective study in Switzerland found cognitive impairment was associated with male gender, young age at diagnosis (before age 6 years), more severe metabolic disturbance at diagnosis and chronic poor metabolic control.19

The Evidence
The evidence for the effect of type 1 diabetes on cognitive function in children and adolescents with type 1 diabetes is listed in Evidence Table 19.1.

- A case series showed that cognitive function remained impaired for a variable period of time following a mild hypoglycaemic episode despite complete resolution of the hypoglycaemic symptoms.5(IV)
- Mood disturbances have been documented the day after nocturnal hypoglycaemia.10 (III-2)
- In an RCT decreased cognitive function was found during hyperglycaemia in 8 out of 12 subjects.9(II)
- Studies have shown that cognitive function is decreased in some children who have a history of hypoglycaemic seizures.12;14;15(IV)
- Early age of onset, longer duration of diabetes and prolonged hyperglycaemia and poor metabolic control are also associated with a higher risk of cognitive dysfunction.11-13;19(IV)
- Two longitudinal studies found that the expected cognitive developmental gains (especially verbal skills) were smaller than expected when children were followed one to six years from diagnosis of type 1 diabetes.16;17;18 (IV)

Additional Consensus Statements used to formulate the recommendations and principles of clinical practice are listed in Evidence Table 19.2.

Recommendations and Principles
- Parents/care-givers and teachers should be aware that discrimination or stigmatisation is unacceptable.20(C)
- Parents/care-givers and teachers should be aware that diabetes should not be the cause of non-participation in any school activity.20;21(C)
- Parents/care-givers should meet with the relevant school personnel as soon as practicable to discuss the issues involved in the care of their child at school.20(C)
- An individual care plan should be developed and reviewed regularly.4(C)
- Parents/care-givers and teachers should be aware how to recognise and treat hypoglycaemia.20;21(C)
- An emergency supply of rapidly absorbed carbohydrate should be readily available in the classroom or wherever the school activity is undertaken.20;21 (C)
- During or following hypoglycaemia or suspected hypoglycaemia, a child must not be expected to walk to a ‘medical room’ nor left unaccompanied.20;21(C)
- Parents/care-givers and teachers should be aware that cognitive function and mood may be affected for some hours after hypoglycaemia.5;10 (III-2, IV)
- Parents/care-givers and teachers should be aware that decreased cognitive function may occur when hyperglycaemia is present.5(II)
• Parents/care-givers and teachers should be aware that risk factors for cognitive dysfunction include a history of hypoglycaemic seizures,12,14,15 early age of onset and longer duration of diabetes.11-13,16,17,18(IV)
• Parents/care-givers, teachers and students should be aware that students with diabetes sitting for the higher examinations may apply for special provisions.21(C)

II = Evidence obtained from at least one properly designed RCT
IV = Evidence obtained from case series, either post-test or pre-test and post test
C = Consensus statement endorsed by professional organisations

Reference List
Chapter 20: Diabetes Camps

Diabetes camps are an integral component of overall care and support for diabetic children and adolescents in Australia. Diabetes camps are held annually in most states in a variety of settings. Despite the varying nature of different diabetes camps all have several features in common. These are:

- Camps are primarily recreational and enjoyable.
- Camps provide both overt and subliminal peer support.
- Camps provide a safe environment for children and adolescents to pursue more challenging activities (physical or social) than they would previously have undertaken.
- Camps provide education and assistance in managing type 1 diabetes.

Background

Diabetes camps have been a part of diabetes care for almost as long as insulin therapy has been available. The first diabetes camp was held in Detroit in the US in 1925. In Australia diabetes camps have been held since 1947. Participation in diabetes camps is now recognised as an important aspect of care for children and adolescents with diabetes. Guidelines and standards for diabetes camps have been published for most countries including Australia.

The Need for Diabetes Camps in Australia

Australian and international research has shown that many children and adolescents with diabetes have needs that are inadequately met in the context of traditional clinical encounters with either a medical practitioner or diabetes nurse specialist. These needs include:

- Poor quality of life and functional health (particularly in children and adolescents from regional Australia).
- High rates of depression, anxiety, behavioural, cognitive and mood disorders.
- Feeling isolated.
- Feeling disempowered and helpless.
- Lacking meaningful age-specific diabetes information.
- Significant negative impact on family function.

Meeting these needs is important both in terms of overall outcomes for individuals and also for the associated potential benefits with regard to specific clinical outcomes. Deteriorating metabolic control through adolescence is well documented in young people with diabetes despite the application of substantial health-care resources. Peer-based and role model support, fundamental aspects of diabetes camps, have the potential to improve outcomes in these areas.

Benefits

Diabetes camps provide an environment where having diabetes is the ‘norm’ rather than something that sets children and adolescents apart from their peers. Given that camps are organised around diabetic routines (meal-times, injection times, finger-prick testing times etc) many campers report that being on camp is ‘...like having a holiday from their diabetes’, in that they don’t have to worry about routine- ‘...it just happens’. In most camps not only the campers but also the leaders have diabetes, thus providing a mini-society where both the members (campers) and elders (leaders) all have one common bond. This creates an
environment where there is both peer support and aspirational motivation. Camps often provide the impetus for establishing ongoing social groups, pen pals, internet chat-room groups etc that can provide ongoing, year-round support. Camp staff who also have diabetes can be valuable mentors and role models to the camp participants.

**Goals**

The goals of diabetes camps are:

- To be enjoyable.
- To allow campers to compare experiences with each other and feel less isolated.
- To increase the confidence of campers in both social and physical activities.
- To allow campers to feel less depressed and anxious, and more positive about their future lives.
- To allow campers to feel less depressed and anxious, and more positive about their future lives.
- To allow campers to gain perspective on their own family dynamics.
- To motivate campers to undertake aspects of their own diabetes care (such as self-injecting and finger prick testing) when there has been child or parental resistance preventing this from occurring.
- Improve diabetes-related knowledge of campers.

In short, diabetes camps are about individual empowerment through increased confidence, understanding and motivation.

**Other Benefits**

Diabetes camps also have other non-camper benefits. These include:

- Parental respite.
- Establishment of ongoing peer-support networks.
- Useful postgraduate, reality-based education for training diabetes health care professionals (medical staff, nurse educators dietitians etc).

**Prerequisites**

Above all else diabetes camps must provide a safe environment for both campers and camp staff. This entails subscribing to an agreed set of standards and protocols prior to the establishment of camps. Standards and protocols should specify leader to camper ratios, levels of medical and paramedical support, dietary routines, injection routines, hierarchy and responsibility of camp organisers, leader and camper application processes, emergency and evacuation protocols and indemnity arrangements. Many of these issues are broadly covered in the Diabetes Australia camping standards. However, some issues are regional and need to be specifically organised for individual camps. Diabetes camps require a high level of support from both medical and paramedical staff in order to provide an adequate level of health safety for campers. Camp leaders, however, are the key component to successful diabetes camps.

Camp leaders should:

- Be suitable role models for young people with diabetes.
- Be mature, enthusiastic and positive in their interaction with campers.
- Have a basic knowledge of diabetes.
- Have knowledge of hypoglycaemia prevention, recognition and treatment.
• Know how to use, maintain and adjust the insulin dose as well as doses of pumps (if campers using an insulin pump are attending).
• Have the ability to arrange prompt medical aid when appropriate.
• Have a knowledge of appropriate age-related sports and activities for children and adolescents with diabetes.
• Have a solid grasp of risk-minimisation principles and how these apply to supervision of the various camping activities.

**Medical Management**

A written plan including camp policies and medical management procedures should be available at camp. A standardised medical information form should be completed for each camper (by his/her family and the managing physician) prior to attending diabetes camp.

Multiple blood glucose determinations should be made throughout each 24-hour period. These should be done before meals and at bedtime. Extra test should be done (throughout the day and also overnight if required) following prolonged strenuous activity, prior hypoglycaemia, after extra insulin doses, or if the child has symptoms of hypo/hyperglycaemia or other physical complaints. All blood glucose levels and insulin dosages should be recorded in a format that allows for review and insulin dose alteration if required.

Due to increased physical activity it may be necessary to decrease the home insulin dosage by 10-30% (occasionally more), especially in those children with good control who were not active before the camp. Three meals and three snacks should be given at set times each day. Additional food should be available for the treatment of hypoglycaemia at all times.

Universal precautions for procedures involving blood draws should be followed. Appropriate containers for disposal of sharps should be available.

**Conclusion**

Diabetes camps are a valuable aspect of care for children and adolescents with diabetes. They are highly popular with both campers and leaders (as is evidenced by high camper and leader return rates). Whilst diabetic peer group interventions have been shown to be more effective than traditional clinical encounters in improving outcomes for adolescents, it is difficult to quantify the clinical and psychological benefits of camping per se for young people with diabetes. The anecdotal experience from diabetes health care professionals however is highly positive. The recent adoption of Australian national standards for diabetes camps should further improve the safety and quality of the diabetes camping experience.

**Information on diabetes camps**

Further information regarding diabetes camps may be obtained from Diabetes Australia and major diabetes education centres.

**The Evidence**

No studies were identified specifically demonstrating the benefits of diabetes camps on glycaemic control for children and adolescents with type 1 diabetes.

Additional Consensus Statements used to formulate the recommendations and principles of clinical practice are listed in Evidence Table 20.1.
**Recommendations and Principles**

- Diabetes camps should be an integral component of overall care and support for diabetic children and adolescents in Australia.\(^{19,20}\) (C)
- Diabetes camps must provide a safe environment for both campers and camp staff.\(^3\) (C)
- Camps should be organised using an agreed set of standards and protocols. Standards and protocols should specify leader to camper ratios, levels of medical and paramedical support, dietary routines, injection routines, hierarchy and responsibility of camp organisers, leader and camper application processes, emergency and evacuation protocols and indemnity arrangements.\(^5\) (C)
- A standardised medical information form should be completed for each camper (by his/her family and the managing physician) prior to attending diabetes camp.\(^5\) (C)

\(\text{C = Consensus statement endorsed by professional organisations}\)

**Reference List**

Chapter 21: Travelling and Holidays

Families are encouraged not to restrict their travel plans because of diabetes in the family. However, to make the holiday safe and enjoyable, families do need to consider:

- The length of the journey.
- The possibility of delays.
- The timing between insulin injections and meals.
- The availability of carbohydrate food.
- Access to medical services and diabetes supplies.
- Changes of climate.
- Changes of types of food.
- Changes in activity levels (increases in physical activity may require reduction of insulin dosage).
- Changes in meal and sleep routines (especially when crossing time zones).
- The management of sickness away from home.

Preparation

The child or adolescent with diabetes should have a medical visit and see the diabetes educator a minimum of 4-6 weeks prior to departure in order to:\(^1\)-3

- Arrange necessary immunisations e.g. tetanus booster, malaria prophylaxis.
- Assess glycaemic control and diabetes management.
- Arrange scripts and medications to take (insulin, glucagon, gastrolyte).
- Organise appropriate identity/Medic-Alert bracelet.
- Discuss necessary adjustments to be made to the diabetes regimen for the flight/long coach trip, and holiday activities with the main aim being avoidance of hypoglycaemia (consider notifying the airline of the child’s special needs).
- Learn how to use short-acting insulin.
- Prepare an emergency kit for sick day management.
- Discuss management of illness away from home.
- Arrange a card with emergency commands (eg ‘I need sugar quickly’) in the appropriate language.
- Prepare the following documentation:
  - Introductory letter for an overseas doctor, ie a summary letter of the child’s medical history and current treatment outline (check with the consulate of the country to be visited if they wish to sight these letters prior to departure).
  - Letter for customs stating the need to carry syringes, insulin and other medical supplies.
  - Translated letters in the appropriate language(s).
  - Travel insurance documents.
  - Contact telephone, fax numbers and addresses of diabetes services in area to be visited.
  - Contact details of the child’s physician or diabetes educator in Australia.

Supplies

Families need to arrange:

- Enough insulin, syringes, pen needles, glucometer, blood and urine test strips for duration of the anticipated stay plus an extra supply. The insulin, glucagon, glucometer
need to be protected from extremes of temperature if these are anticipated on the trip (use wide necked thermos/other insulated container or packing).

- Insulin, glucagon and testing equipment to be readily available in hand luggage, and be divided between two bags to avoid complete loss in case one bag is lost.
- Insulin should only be carried in hand luggage and not placed in luggage in the hold.
- Readily available food for treating hypoglycaemia.
- Enough extra carbohydrate food, the equivalent of two meals, in case of unexpected delays or unsuitable food being provided by airline or restaurant (insulin should be given when it is certain that food is about to be served or is readily available). Airlines tend to give diets for type 2 diabetes if contact is made regarding dietary needs. This is usually not appropriate for children with type 1 diabetes as there is little carbohydrate provided. Families should also take food with them when leaving the aircraft as unexpected delays may occur at any time, even at transit stops or the destination itself.
- Readily available bottled drinks and water.
- Loperamide for diarrhoeal illnesses. This medication should not be used in the very young and in general is over-prescribed. If travelling overseas, loperamide may be a useful stand-by in case of severe diarrhoea.
- Antiemetics. These medications are in general not usually used in children but may be of use if adolescents with diabetes are travelling overseas.

Management of Diabetes on Long Flights

The detailed management of the diabetes during flights that are long and involve many time zones should be discussed with the diabetes educator or the physician well before the departure date. The best way of managing the insulin replacement will vary from individual to individual and will depend on the insulin regimen being used.

Generally, no adjustment is required when travelling north or south. Adjustments may be necessary if travelling east or west, especially if six or more time zones are being crossed. For westward travel the shift in time zone means that the day will be much longer therefore extra meals will require extra doses of insulin. For eastward travel the day will be cut short and the time between injections decreases, therefore requiring a lower insulin dose.

For some, it is easiest to have a watch that remains on the time of the place of origin and to keep to the routines that would have been given for those times. This is possible providing the families have their own food supply and do not rely on airline meal times. Following arrival, adjustments need to be made to the insulin regimen to bring it into line with local times.

For others, especially if there is a major variance in the morning and evening doses (e.g., patients taking twice-daily insulin) an acceptable regimen is to change to using pre-meal (approximately 6-hourly) injections of short-acting insulin during the flight. The need to have an independent source of food and perform frequent blood glucose monitoring is still essential.

The Evidence

The evidence on insulin adjustment during travel when crossing time zones is listed in [Evidence Table 21.1](#).

- There are no paediatric studies addressing the issue of glycaemic control and insulin adjustment while travelling.
- During westward travel the day will be much longer therefore extra meals will require extra doses of insulin. A case series of 27 adults with type 1 diabetes found that for...
westward travel extra insulin was required (3.1% of total daily insulin dose per time shift hour).4(IV)

- The same study found that less insulin was required during eastward travel (total daily insulin dose reduced by 2.6% per time shift hour). During eastward travel the day is cut short and the time between injections decreases therefore requiring a lower insulin dose.4(IV)

- A case series (which included some children) found that patients were generally satisfied with a simplified regimen using pre-meal injections of short-acting insulin (approximately 6-hourly) during long haul flights.5(IV)

Additional Consensus Statements used to formulate the recommendations and principles of clinical practice are listed in Evidence Table 21.2.

**Recommendations and Principles**

- The detailed management of diabetes during visits to distant locations or foreign countries should be discussed with the diabetes educator or the physician well before the departure date.1,6(C)

- The detailed management of diabetes on long flights crossing many time zones should be discussed with the diabetes educator or the physician well before the departure date.1,6(C)

- The family should be advised to arrange enough insulin, syringes, pen needles, glucometer, blood and urine test strips for the duration of the anticipated stay plus an extra supply.1,6(C)

- The family should be advised to have insulin, glucagon and testing equipment readily available in hand luggage, and to have essential supplies divided between two bags to avoid complete loss in case one bag is lost.1,6(C)

- The child or adolescent with diabetes should be advised to have his/her own food supply and not rely on airline meal times.1,6(C)

- The family should be advised that no major change to the insulin regimen is required for north-south travel.1(C)

- The family should be advised that extra insulin may be required for westward travel as the day will be much longer and extra meals will require extra doses of insulin.4(IV)

- The family should be advised that less insulin may be required during eastward travel as the day is cut short and the time between injections decreases therefore requiring a lower insulin dose.4(IV)

- Switching to a simplified regimen of pre-meal injections of short-acting insulin during long haul flights should be considered as an option.3(IV)

**Reference List**


IV = Evidence obtained from case series, either post-test or pre-test and post-test
C = Consensus statement endorsed by professional organisations
Chapter 22: Complementary and Alternative Medicine

The National Center for Complementary and Alternative Medicine at the National Institutes of Health (USA) defines CAM as ‘a broad domain of healing resources that encompasses all health systems, modalities, and practices and their accompanying theories and beliefs, other than those intrinsic to the politically dominant health system of a particular society or culture in a given historical period’.\(^1\:\text{1,2}\) It is generally understood to be health care practices that are outside of those used by conventional medicine; however, there may be some overlap.

There is some evidence to support the use of some complementary and alternative medicine therapies for particular conditions. However, for the majority of such therapies there is limited or no information to support their use and there is a lack of information about their safety.

Like any other medications, complementary and alternative medicine therapies have the potential for adverse effects and for interactions with conventional treatments or other complementary and alternative medicine therapies.\(^3\)

Complementary and alternative medicine may include medicinal (herbal remedies, dietary supplements, vitamins and minerals, naturopathic and homeopathic remedies), or non-medicinal remedies (such as chiropractic, osteopathy and naturopathy).

Complementary and Alternative Medicine use in Diabetes

The amount and nature of complementary and alternative medicine used over a twelve-month period in children attending a diabetes clinic at a tertiary referral hospital in Australia was estimated to be:\(^4\)

- 49% (44% medicinal and 16% non-medicinal).
- 18% medicinal, if the use of vitamins and minerals were excluded.

The most commonly used medicinal remedies were multivitamins and minerals, vitamin C, echinacea, other herbal treatments and homeopathic remedies.

There are many complementary and alternative medicine treatments that have been recommended for use in diabetes, but there appears to be little consensus between authors and little evidence to support these recommendations.\(^5\)

- There are no complementary and alternative medicine therapies that have been shown in controlled trials to cure diabetes or improve control. It is important to remember that many complementary and alternative medicine therapies used by children with diabetes may be for treatment of other conditions or for general health reasons. Children with chronic illnesses are, in general, more likely to use complementary and alternative medicine.\(^6\)
  A systematic review of all published prevalence studies (n=10) reporting the use of complementary and alternative medicine in the paediatric population found that the reported prevalence varied from 9% to 70%.\(^6\)(IV)

Ketoacidosis and death have been described when insulin has been omitted as part of an alternative treatment.\(^7\) Parents should be warned that insulin should never be significantly reduced or omitted as part of an alternative treatment.

Clinicians and Complementary and Alternative Medicine

Clinicians have a responsibility to ensure that they are aware of all the forms of therapies that patients are using. In addition, it is important to try to understand different approaches to health and help parents in making informed and safe choices.
Studies consistently show that families rarely tell their treating doctors about complementary and alternative medicine use. Thus asking about their use should always be a part of the routine history taking process.

In order to discuss complementary and alternative medicine effectively, it is important for clinicians to:

- Ask about their use. Specific questions about different types of complementary and alternative medicine may be required; for example:
  - Naturopathic or natural treatments.
  - Herbal remedies.
  - Dietary supplements.
  - Vitamins and minerals.
  - Homeopathic treatments.
- Avoid dismissal of complementary and alternative medicine, which may discourage families from discussing their actual use. Patients may be concerned about a clinician’s response to their use.
- Be prepared to discuss complementary and alternative medicine use and discuss the risks and benefits of different therapies.
- Understand the reasons and motivations for the health care choices that families make.
- Be aware of and explain to patients that the quality of advice available on the Internet is variable and inconsistent. A recent study looking at complementary and alternative medicine websites for treatment of diabetes found that out of 13 websites, one gave definitely harmful advice (by actively discouraging conventional diabetes therapy) and a further five websites were deemed to be potentially harmful.

Discussing complementary and alternative medicine with families may involve trying to obtain appropriate information about the particular treatment, and like other treatments weighing up the potential benefits and risks with the family.

**Management of a Patient using Complementary and Alternative Medicine**

When a child taking complementary and alternative medicine is admitted to hospital the following steps should be taken:

- Consider the possible effects and interactions of the particular substance.
- Phone the local drug or poisons line for information if necessary.
- If the parent wishes for the child to continue taking the remedy whilst in hospital, the drug should have an AUST R or AUST L number (phone drug information to find out).
  - AUST R medicines are assessed for safety, quality and effectiveness. They include all prescription-only medicines and many over-the-counter products such as those for pain relief, coughs and colds and antiseptic creams.
  - AUST L medicines are used for minor health problems and are reviewed for safety and quality. They include sunscreens over SPF4 and many vitamin, mineral, herbal and homoeopathic products.
- If the drug has a valid AUST L or AUST R number, and the admitting consultant approves the use of that particular complementary and alternative medicine in the patient, then this should be documented in the patient notes. The parents may then supply, administer and record the administration of the complementary and alternative medicine whilst in hospital.
- If the drug does not have an AUST L or AUST R number it should not be administered in hospital. If the parents insist on its use, they should be counselled and advised that they cannot administer the drug whilst in hospital. If they still choose to use the drug
they should sign an ‘Against Medical Advice’ statement and supply, administer and record any further administration of the complementary and alternative medicine.

Issues to consider when assessing the risks and benefits of complementary and alternative medicine use include:

- A common misconception that, by being ‘natural’, they are therefore safe. Like all medical treatments, however, complementary and alternative medicine therapies may have beneficial effects but may also have side effects.
- The type of therapies being used – medicinal treatments versus non-medicinal treatments.
- Available information about a particular therapy regarding efficacy, safety and potential harmful effects.
- The source of the complementary and alternative medicine (eg whether purchased over-the-counter, from a naturopath, etc).
- Where the product was manufactured. Products manufactured and registered with the Australian regulatory authority, the Therapeutic Goods Administration (TGA), will have an AUST L or an AUST R number. The ingredients of products without these are less reliably identified.
- The expectations underpinning their use and the reasons for their use.

Complementary and alternative medicine use is common within the community. Understanding their use within the context of the family is an important part of clinical care.

The Evidence

We found no studies addressing complementary and alternative medicine therapies in children or adolescents with diabetes.

- A systematic review of all published prevalence studies (n=10) reporting the use of complementary and alternative medicine in the paediatric population found that the reported prevalence varied from 9% to 70%.6(IV)

Additional Consensus Statements used to formulate the recommendations and principles of clinical practice are listed in Evidence Table 22.1.

Recommendations and Principles

- Complementary and alternative medicine may include medicinal (herbal remedies, dietary supplements, vitamins and minerals, naturopathic and homeopathic remedies), or non-medicinal remedies (such as chiropractic, osteopathy and naturopathy).1(C)
- Complementary and alternative medicine use is common within the community.1;6(IV)
- In order to improve clinical care health care professionals should aim to understand the use of complementary and alternative medicine within the family context.10;13(C)
- Families should be advised that no complementary and alternative medicine therapies have been shown to cure diabetes or improve control.10(C)
- Ketoacidosis and death have been described when insulin has been omitted as part of an alternative treatment.7 Parents should be warned that insulin should never be significantly reduced or omitted as part of an alternative treatment.(IV)
- Families should be advised that complementary and alternative medicine therapies have the potential for adverse effects and for interactions with conventional treatments or other complementary and alternative medicine therapies.10(C)
- Health care professionals are able to determine the constituents of any complementary or alternative medicine by enquiries to poisons centres and quoting the medicine’s AUST L or
AUST R numbers. Drugs without an AUST L or AUST R number should not be considered for use in hospital. (C)

IV = Evidence obtained from case series, either post-test or pre-test and post-test.
C = Consensus statement endorsed by professional organisations

Reference List
Resources

The full version of these guidelines are available in pdf format on the NHMRC and Australasian Paediatric Endocrine Group websites (http://www.racp.edu.au/apeg/).

Diabetes Australia (DA)

Diabetes Australia provides a wide variety of booklets/fact sheets on food and general issues pertaining to management of type 1 diabetes. The range of services available in each State or Territory can be obtained by contacting local DA offices. Internet access to the various Diabetes Australia State and Territory Offices is available through links at www.diabetesaustralia.com.au

Contact Details for Diabetes Australia States & Territories

DA-NSW (02) 9552 9912
DA-Victoria (03) 9667 1777
DA- Queensland (07) 3846 4600
DA- Northern Territory (08) 8927 8488
DA – Tasmania (03) 6234 5223
DA- South Australia (08) 8234 1977
DA – Western Australia (08) 9325 7699
DA – ACT (02) 6288 9830

Juvenile Diabetes Research Foundation (JDRF)

JDRF provides a variety of brochures on the management of type 1 diabetes in children and adolescents. Details may be obtained from the JDRF office (1300 363 126), or from the JDRF website www.info@jdrf.org.au

Health Care Card

The Health Care Card is a benefit provided by the Commonwealth Government. It is not means tested on assets or income criteria. To qualify for the Health Care Card ‘the child, because of their disability, requires substantially more care and attention than another child of the same age, without the disability’.

The Health Care Card assists families with the cost of prescriptions under the Pharmaceutical Benefits Scheme (PBS) and National Diabetes Services Scheme (NDSS) and with some other concessions. With the Health Care Card the holder can purchase medications on the prescribed list at a reduced cost.

Applications for the Health Care Card are made through Centrelink. Eligibility for the Health Care Card is determined on criteria based on the Treating Doctor’s Report (TDR).
Details regarding the Health Care Card may be obtained from any Centrelink office.

**Carer Allowance (CA)**

The Carer Allowance is an additional benefit to the HCC provided by the Commonwealth Government. A submission may be made to obtain the Carer Allowance from Centrelink. It is not means tested on income or assets criteria.

Applications for the Carer Allowance are made through Centrelink. Eligibility for the CA is determined on criteria based on the Treating Doctor’s Report (TDR).

**International Diabetes Federation (IDF) School Information Pack**

The IDF School Information Pack provides guidance for teachers and other school staff on type 1 diabetes in children and adolescents. The pack consists of:

- Medical alert information card.
- Diabetes information for schools.
- Diabetes Information about schools for parents.
- Management of hypoglycaemia poster.
- An information flipchart.
- Emergency card.
- Management plan.


**Other Resources**

A wide variety of educational resources for health professionals and consumers is available through large tertiary paediatric diabetes services.
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## Appendix 2: Evidence Tables

### Chapter 1: Definition, Epidemiology and Classification

#### 1.1 Prevalence/incidence of type 1 diabetes in children in Australia/worldwide.

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref No</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Comments</th>
<th>Design</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internation al Diabetes Federation (IDF) Atlas</td>
<td>5</td>
<td>Children aged 0-14 yrs with T1D</td>
<td>N/A</td>
<td>T1D incidence</td>
<td>Australia incidence rate 17.8 per 100,000. New Zealand incidence rate 15.2 per 100,000. Fiji incidence rate 0.1 per 100,000. Finland incidence rate 37.4 per 100,000.</td>
<td>Medline and Pubmed were searched from 1980 -2003</td>
<td>Systematic review of all relevant population based studies</td>
<td>IV</td>
</tr>
<tr>
<td>Karvonen 2000</td>
<td>6</td>
<td>WHO DiaMond Project (Multinational Project for Childhood Diabetes). Incidence of T1D from 1990 to 1994 determined in children ≤14 yrs old from 100 centers in 50 countries</td>
<td>N/A</td>
<td>T1D incidence</td>
<td>T1D incidence varied from 0.1/100,000 per year in China and Venezuela to 36.8/100,000 per year in Sardinia and 36.5/100,000 per year in Finland. In most populations, the incidence increased with age and was the highest among children 10-14 years of age</td>
<td>Well-defined population based registry; Capture-recapture method used</td>
<td>Well designed representative cohort study</td>
<td>IV</td>
</tr>
<tr>
<td>Craig 2000</td>
<td>8</td>
<td>Children aged 0-14 years resident in New South Wales, Australia over the period 1992-1996</td>
<td>N/A</td>
<td>T1D incidence</td>
<td>Incidence of T1D from 1990-1996 was 17.8 per 100,000. There was a statistically significant rise in incidence of T1D over this period ( (p=0.0003) ). Seasonal variation (more cases occur in late autumn/winter) Peak incidence at age 11 (girls), and 13 (boys)</td>
<td>Primary ascertainment using a prospective incidence register established in 1990. Secondary source of ascertainment from National Diabetes Supply Scheme (government subsidised scheme for diabetic supplies) Capture-recapture method, ascertainment estimated to be 99% complete Australian NSW data</td>
<td>Well designed representative cohort study</td>
<td>IV</td>
</tr>
<tr>
<td>Verge 1994</td>
<td>16</td>
<td>Children aged 0-14 years in New South Wales, Australia (1990-1991)</td>
<td>N/A</td>
<td>Patients newly diagnosed with T1D by physicians and diabetes educators.</td>
<td>Age-standardized incidence rate of T1D was 14.5 per 100,000 person-yrs</td>
<td>Prospective register, with two independent sources of case ascertainment. The primary source was reporting of newly diagnosed patients by physicians and diabetes educators. The secondary source was National Diabetes Supply Scheme Australian NSW data</td>
<td>Well designed representative cohort study</td>
<td>IV</td>
</tr>
</tbody>
</table>
1.2 Technical Reports and Consensus Statements used to formulate the recommendations and principles of clinical practice.

<table>
<thead>
<tr>
<th>Ref No</th>
<th>Technical Reports/Consensus Statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>31</td>
<td>American Diabetes Association: Screening for Type 2 Diabetes. Diabetes Care 26:21-24, 2003</td>
</tr>
</tbody>
</table>

Chapter 2: Phases of Diabetes

2.1 Intervention trials to delay or prevent the onset of type 1 diabetes.

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref No</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Comments</th>
<th>Design</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPT (Diabetes Prevention Trial) 2002</td>
<td>4</td>
<td>Relative of patients with T1D 84,228 screened Of 372 with 5 year risk of &gt;50% of developing T1D, 339 were randomised, (169 to the intervention and 170 to the observation arm) Adults and children included Multicentre international study</td>
<td>Close observation or low dose s.c. ultralente insulin twice daily (0.25 u/kg/day), plus annual 4 day IV insulin infusion treatment.</td>
<td>Development of diabetes. Median follow up 3.7 years</td>
<td>Diabetes diagnosed in 69 in the intervention group and 70 in the observation group. The majority were asymptomatic (102/139, 73.4%). The annualised rate of progression to diabetes was 15.1% in the intervention group and 14.6% in the observation group (relative risk 0.96, 95% CI 0.69-1.34, p=0.80). In people at high risk for diabetes, insulin in the dose described here does not prevent or delay T1D.</td>
<td><strong>Randomisation:</strong> Participants allocated to intervention or control groups by a centralised computer system, and were stratified by baseline glucose tolerance and clinical centre <strong>Blinding:</strong> No blinding of participants and investigators; control group did not receive placebo because intervention involved injections or infusions and some participants were children <strong>Losses to follow-up:</strong> Annual rate of loss to follow-up was 1.3% <strong>Compliance:</strong> Annual non-compliance rate in intervention group was 5.5%, and 1% in control group Data analysed according to intention-to-treat principle, and</td>
<td>RCT</td>
<td>II</td>
</tr>
<tr>
<td>Ref No</td>
<td>Technical Reports/Consensus Statements</td>
<td></td>
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</tr>
</tbody>
</table>

**2.2 Technical Reports and Consensus Statements used to formulate the recommendations and principles of clinical practice.**

<table>
<thead>
<tr>
<th>ENDIT 2004</th>
<th>8</th>
<th>&gt;30,000 first degree relatives of T1D patients screened</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>552 fulfilled criteria of having confirmed islet cell antibody levels &gt;20 JDFU</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adults and children included (3 to 40 years)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multicentre international study in Europe and America</td>
</tr>
<tr>
<td></td>
<td>552 randomised to receive either nicotinamide (1.2gm/m2) or placebo.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Development of T1D</td>
<td>No sig. diff. between nicotinamide and placebo in development of T1D. Of 159 participants who developed diabetes within 5 years, 82 (30%) were on nicotinamide and 77 (28%) were on placebo.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Concluded that nicotinamide (in the dose described) does not delay or prevent the onset of diabetes in high risk individuals.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Monitor by an independent data and safety monitoring board, with predefined stopping rules.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Study abandoned by NIH at interim analysis.</td>
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<tr>
<td></td>
<td></td>
<td><strong>Pseudorandomisation:</strong> (computer generated codes allocated sequentially by national coordinator)</td>
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<tr>
<td></td>
<td></td>
<td><strong>Blinding:</strong> All study personnel blinded to participants’ treatment allocation; emergency unblinding done for 4 participants</td>
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<tr>
<td></td>
<td></td>
<td><strong>Losses to follow-up:</strong> 1 from each group withdrew consent after randomisation. 549/552 participants began their trial medication. Primary variable (diabetes status) obtained for 447/549 (87%) of patients.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo group: 48 discontinued treatment, 35 lost to follow-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment group: 47 discontinued treatment, 38 lost to follow-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Analysis by intention-to-treat</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Study abandoned at interim analysis after 5 years.</td>
</tr>
</tbody>
</table>

**Quasi-RCT** | **III-1**
### Chapter 3: Medical Management

#### 3.1 Benefits of ambulatory care versus hospital in-patient care of patient with newly diagnosed type 1 diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref No.</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Comments</th>
<th>Design</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clar 2003 (Cochrane Systematic Review)</td>
<td>5</td>
<td>Children with newly diagnosed type 1 diabetes</td>
<td>6 comparative studies of initial hospitalisation compared with home based or outpatient mx. (Simineiro 99 Dougherty 98 Simell 95 Chase 92 Galatzer 82 Spaulding 76)</td>
<td>Metabolic control</td>
<td>No sig. diff.</td>
<td>Rigorous search strategy with appropriate inclusion criteria</td>
<td>Systematic Review (Cochrane)</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Admissions to hospital in first 2 years</td>
<td>No sig. diff.</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Acute complications</td>
<td>No sig. diff.</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Others: no. of hosp. contacts, psychosocial effect on child and parents, other adverse events, cost</td>
<td>No sig diff</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Design Level</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Srinivasan 2004</td>
<td>6</td>
<td>Introduction of new day care programme (DDCP) for newly diagnosed T1D.</td>
<td>The pre-DDCP cohort comprised all children newly diagnosed with type 1 diabetes from March 2000 to November 2000 (n = 49). The post-DDCP cohort were those diagnosed from November 2000 to August 2001 (n = 61).</td>
<td>Hospital stay</td>
<td>Decreased from 5.14 days to 1.70 days (range, 0-10)</td>
<td>Ambulatory stabilisation of children with type 1 diabetes provides similar metabolic outcomes for the child, and comparable levels of diabetes knowledge and similar psychosocial outcomes for the family, to inpatient stabilisation programs.</td>
<td>Comparative study with historical controls</td>
<td>III-3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Insulin requirement</td>
<td>No sig. diff. between the two cohorts in insulin requirement at 12 months</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(pre-DDCP: 0.9 U/kg [95% CI, 0.8-1.0]; post-DDCP: 0.8 U/kg [95% CI, 0.7-0.9]; P = 0.22),</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HbA1c</td>
<td>No sig. diff. in HbA1c level at 12 months (pre-DDCP: 8.4% [95% CI, 8.0%-8.9%]; post-DDCP: 8.2% [95% CI, 7.9%-8.5%]; P = 0.37)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adverse events</td>
<td>No sig. diff. in adverse events over the first year after diagnosis. Both</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
| Forsander 2000 | 7 | 36 newly diagnosed children with type 1 diabetes  
Ages 3-15  
April 1986 – January 1989  
Sweden  
An increased risk for poor glycemic control was recorded in children living in one-parent families (p = 0.03) or in families where the father had a low level of education (p = 0.04). Younger age (p = 0.05), a single-parent family (p = 0.05) and poor glycemic control (p = 0.02) were associated with more days of rehospitalization. | Early discharge to hospital family apartment (n = 19) vs. Conventional hospital care (n = 19)  
The control group was treated initially in a hospital ward, while the study group received problem-based learning and family-therapeutic and social support in an outpatient training apartment. | Glycaemic control HbA1c  
Hospital readmission  
Glycaemic control:  
At 2 years after diagnosis, study group mean HbA1c 6.2 [0.9] versus 6.0 [0.9] in control group (p=0.46); no significant difference  
At 5 years, study group mean 7.3 [1.3] versus 7.1 [1.3] in control group (p=0.58); no significant difference  
Hospital readmission days:  
Study group median 1.0 days; control group 2.0 (p=0.83); no significant difference | Randomisation:  
Method of randomisation not reported.  
Losses to follow-up:  
2 children lost to follow-up because they moved to another region  
Unknown number of days each group spent in hospital. | RCT | II |
|---|---|---|---|---|---|---|---|---|
| Kirk 2003 | 8 | 36 newly diagnosed children with type 1 diabetes  
Ages 0-19  
1994-April 2002  
UK  
Retrospective Survey of initial management over 8 years following specialist nurse appointment in 1994 | Number able to be fully home managed from diagnosis  
Mean number of days newly diagnosed patients were admitted  
From April 1995 onwards mean of 2.0 days, change from 1994 when average of 6.3 days | Fewer admissions at diagnosis and fewer episodes of readmission in outpatient treated group post 1988  
36 patients were readmitted for diabetes-related problems. All of these patients were treated as inpatients at diagnosis. | A very small study in City Hospital Birmingham UK. Authors make comment that their figures are not as good as those from the Birmingham Children’s Hospital and relate this to social disadvantage (60% of Asian descent).  
Non comparative cohort study | Non comparative cohort study | IV |
| Lee 1992 | 9 | New diagnosis T1D <18 yrs, presenting to Texas children’s hospital, approximately 30-50 cases per year  
Pre 1988 group were all hospitalized at diagnosis. Post 1988 an outpatient focused approach used when possible. | Admission rate  
Cost  
This institution reported $100,000 saving per year | Fewer admissions at diagnosis and fewer episodes of readmission in outpatient treated group post 1988  
36 patients were readmitted for diabetes-related problems. All of these patients were treated as inpatients at diagnosis. | American healthcare system therefore cost data may not be relevant to Australian health care system.  
Retrospective case-series notes review | Retrospective case-series notes review | III-3 |
### 3.2 Differences in glycaemic control between urban and rural children and adolescents with type 1 diabetes in the Australian health care system

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref No</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Comments</th>
<th>Design</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handelman 2001</td>
<td>31</td>
<td>Audit of 1,190 children with T1D aged &lt;15 years.</td>
<td>Compared urban with rural children.</td>
<td>HbA1c</td>
<td>Median HbA1c was 8.2% (interquartile range 7.6-9.1%)</td>
<td>Confirmed homogeneity of metabolic control in NSW and ACT regardless of location, socioeconomic status or system of care. Social disadvantage was assessed using a graded postcode-based social disadvantage risk score. Australian study.</td>
<td>Multicentre, population-based, cross-sectional study</td>
<td>IV</td>
</tr>
<tr>
<td>Cameron 2002</td>
<td>32</td>
<td>47 children with TID &lt;18 years of age from three regional Victorian communities (Horsham, Warrnambool, Sale) were</td>
<td>Compared urban with rural children.</td>
<td>HbA1c</td>
<td>Median yearly HbA1C for patients were not obviously different between the regional and</td>
<td>Homogeneity of metabolic control in Victoria, Australia</td>
<td>Comparative</td>
<td>IV</td>
</tr>
</tbody>
</table>
compared with 120 age-, sex- and duration of diabetes-matched children attending the Royal Children's Hospital (RCH) diabetes clinic in Melbourne.

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref No</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Comments</th>
<th>Design</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hampson 2001</td>
<td>28</td>
<td>Systematic review of 62 studies from Health Technology Assessment Program UK.</td>
<td>Question asked “Do educational and psychosocial interventions for adolescents with type 1 diabetes have beneficial effects on biological and psychosocial outcomes?”</td>
<td>Psychosocial&lt;br&gt;Self or parent reports of changes in psychological or interpersonal constructs (e.g. self-efficacy, diabetes-specific stress)</td>
<td>Small to medium effect on HbA1c and psychosocial outcome of educational and psychosocial intervention.&lt;br&gt;Mean of 12 pooled effect sizes for psychosocial outcomes was 0.37 (95% CI 0.19-0.55)</td>
<td>Rigorous search strategy with appropriate inclusion criteria.&lt;br&gt;62 studies in total.&lt;br&gt;25 RCTs reviewed (16 with sufficient detail to enable effect sizes to be calculated).&lt;br&gt;37 other study designs eg non RCT’s without control groups, pre and post intervention studies&lt;br&gt;The meta-analysis of the RCT’s should be treated with caution due to the variation in studies and intervention</td>
<td>Systematic review</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Skills training (35% studies)  &lt;br&gt;Dietary interventions (19%)  &lt;br&gt;Emotional/psychological interventions (18%)</td>
<td>Metabolic measures&lt;br&gt;Compared behavioural intervention (education or skills training) with control group.</td>
<td>Mean of 12 pooled effect sizes was 0.33 (95% CI 0.04 – 0.70) for glycated haemoglobin with outliers; significant heterogeneity (0.08 without 2 outliers)</td>
<td>These studies demonstrate the variety of intervention and outcomes that have been studied. All the pre-, post design studies reported some benefit - however because of the low level of study design and small numbers these benefits should be treated as provisional until more rigorous results are available</td>
<td></td>
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</tr>
</tbody>
</table>
3.4 Technical Reports and Consensus Statements used to formulate the recommendations and principles of clinical practice.

<table>
<thead>
<tr>
<th>Ref No</th>
<th>Technical Reports/Consensus Statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>International Society for Pediatric and Adolescent Diabetes: ISPAD Consensus Guidelines for the Management of Type 1 Diabetes Mellitus in Children and Adolescents. Zeist, Netherlands, Medforum, 2000</td>
</tr>
<tr>
<td>14</td>
<td>Australasian Paediatric Endocrine Group: APEG Handbook on Childhood and Adolescent Diabetes. Sydney, Australasian Paediatric Endocrine Group, 1996</td>
</tr>
<tr>
<td>17</td>
<td>American Diabetes Association: Standards of Medical Care for Patients With Diabetes Mellitus. Diabetes Care 26:33S, 2003</td>
</tr>
</tbody>
</table>

Chapter 4: Insulin Preparations and Storage

4.1 Benefits of animal insulin over human insulin use in children and adolescents with type 1 diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref No</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Comments</th>
<th>Design</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Richter 2002 (Cochrane systematic review)</td>
<td>7</td>
<td>Patients with diabetes mellitus all age groups</td>
<td>Animal insulin versus human insulin.</td>
<td>Glycaemic Control: HbA1c, Fasting BGL, Insulin dose</td>
<td>Parallel designed studies reported that human insulin was associated with a nonsignificant mean (pooled weighted mean difference) lowering of HbA1c</td>
<td>Rigorous search strategy. Inclusion criteria included diabetic patients of all ages. Data collection and analysis performed by 2 independent reviewers. Significant heterogeneity detected. Despite heterogeneous study designs participants and locations neither parallel or crossover trials suggested an important difference between insulin species as measured by glycated haemoglobin, fasting plasma glucose and insulin dose. No significant difference in metabolic control or hypoglycaemic episodes was found. Quality of life, mortality and long-term complications not assessed systematically in the RCT. Qualitative assessments not reported</td>
<td>Systematic Review (Cochrane)</td>
<td>I</td>
</tr>
</tbody>
</table>

4.2 Treatment of children with type 1 diabetes with insulin glargine

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref No</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Comments</th>
<th>Design</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>NICE Health Technology Appraisal No 53 2002</td>
<td>16</td>
<td>4 published RCT’s in type 1 diabetes (and 2 in type 2 diabetes) 4 fully published open label randomised control trials in patients with type 1 diabetes. Seven published abstracts and One unpublished abstract made available by manufacturer, three observational studies</td>
<td>Once daily insulin glargine compared with once or twice daily NPH</td>
<td>FPG</td>
<td>Significantly decreased FPG in 3 out of 4 studies. Fourth study showed no difference</td>
<td>Guidance: Recommend that insulin glargine should be considered as a treatment option in people with type 1 diabetes</td>
<td>Systematic Review</td>
<td>1</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>HbA₁c</td>
<td>3 out of 4 studies found no difference in HbA₁c. One study found stat sig improvement in HbA₁c with glargine (trial duration over only 4 weeks therefore cannot be attributed to only glargine)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Nocturnal hypoglycaemia</td>
<td>One study found less nocturnal hypo in glargine c/w once daily NPH. But similar when glargine c/w twice daily NPH. One study showed fewer nocturnal hypoglycaemia in glargine group versus NPH group (36% vs 56%, p&lt;0.05). One study showed no diff.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Severe hypoglycaemia</td>
<td>One study showed severe hypo. Fourth study did not distinguish between nocturnal and other hypos. 3 studies reported severe hypo. One reported sig less with glargine. 2 studies no sig</td>
<td></td>
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</tbody>
</table>
### 4.3 Metformin as an adjunct therapy to insulin in the treatment of children and adolescents with type 1 diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref No</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Comments</th>
<th>Design</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamilton</td>
<td>26</td>
<td>Type 1 diabetics</td>
<td>Metformin versus placebo for 3 months</td>
<td>HbA1c</td>
<td>Mean change in metformin group: -0.3% [0.7]; +0.3 [0.7] in placebo group (p=0.03); significant decrease</td>
<td>Randomisation: computer generated; method of allocation not reported</td>
<td>RCT</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td> </td>
<td>27 adolescents with insulin requirement &gt;1 unit/kg/day and HbA1c &gt;8%</td>
<td> </td>
<td>Fasting BGL (mmol/l)</td>
<td> </td>
<td>Metformin group had mean reduction -0.9 [3.8] versus placebo -0.5 [3.2] (p=0.03); significant decrease</td>
<td> </td>
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<tr>
<td> </td>
<td> </td>
<td>14 in metformin group, 13 in placebo group</td>
<td> </td>
<td>Insulin dose (units/kg/day)</td>
<td> </td>
<td>Metformin group mena change -0.14 [0.1] versus placebo +0.02 [0.2] (p=0.01); significant decrease</td>
<td> </td>
<td> </td>
</tr>
<tr>
<td> </td>
<td> </td>
<td>Inclusion criteria set to minimise risk of recruiting type 2 diabetes subjects</td>
<td> </td>
<td>BMI</td>
<td> </td>
<td>Non sig. trend to lower BMI in metformin group (p=0.35)</td>
<td> </td>
<td> </td>
</tr>
<tr>
<td> </td>
<td> </td>
<td>18 females, eight males</td>
<td> </td>
<td>Hypoglycaemia</td>
<td> </td>
<td>Severe hypoglycaemic episode in 2 metformin subjects due to missing meal. Overall mild hypoglycaemia was increased in metformin group (p=0.03)</td>
<td> </td>
<td> </td>
</tr>
<tr>
<td>Sarnblad</td>
<td>27</td>
<td>30 adolescents with T1D (16 in metformin group and 14 in placebo group)</td>
<td>oral metformin or placebo for 3 months</td>
<td>HbA1c</td>
<td>Mean value decreased significantly in the group treated with metformin, from 9.6</td>
<td>Significance of final HbA1c levels not stated, but a recalculation shows the mean difference to be statistically nonsignificant (mean difference 0.50, 95% CI -1.50 to 0.50)</td>
<td>RCT</td>
<td>II</td>
</tr>
<tr>
<td> </td>
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</tbody>
</table>

Appendix 2: Evidence Tables
Australian Clinical Practice Guidelines: Type 1 Diabetes in Children and Adolescents
mean age = 17.0 [1.6] years
mean glycated haemoglobin (HbA1c) 9.3 [1.2] %
daily insulin dosage 1.2 [0.3] U/kg

Initial metformin dose 500mg daily for 1 week, followed by 500mg twice daily for 3 weeks, then 1000mg twice daily for rest of study period

Peripheral insulin sensitivity (euglycaemic hyperinsulinaemic clamp) at baseline and at end of study

Peripheral glucose uptake divided by mean plasma insulin concentration was increased in metformin (p<0.05) but not in placebo group. Initial insulin sensitivity was inversely correlated to changes in HbA1c (r=-0.62; p<0.05) and positively correlated to changes in insulin sensitivity (r=0.77; p<0.01)

Randomisation: Method not stated
Blinding: All patients and investigators were blinded
Losses to follow-up: 4/30 – 2 patients excluded at randomisation due to low HbA1c; 1 patient excluded due to low motivation (many missed doses); 1 patient left study due to nausea
In 1 patient (metformin group), sensitivity not measured due to technical problems
Side effects: 1 patient in metformin group had nausea and mild abdominal pain during study, 1 had mild abdominal discomfort at final examination; 5 in placebo group had gastrointestinal symptoms near start of study, 1 had stomach pain throughout study

Gomez 2002 28 Type 1 diabetics.
Adolescents/young adults (19.3 +/- 3.4yrs) n=10
Metformin 250mg BD (dose increased to max of 2500mg/day depending on side effects reported.) Insulin dose reduced if required.

HbA1c at baseline
3months
6months
Severe hypoglycaemic episodes
HbA1c decreased in 7/10 patients (not statistically significant).
2/10 patients had one severe hypoglycaemic episode

Very small sample size.
Not randomised, no controls (results compared to own pre-treatment HbA1c)
No comparative pre-treatment hypo information given (although authors say this translates to approx 40 per 100 patient years)
Case series (pre -test and post-test) IV

4.4 Technical Reports and Consensus Statements used to formulate the recommendations and principles of clinical practice.

<table>
<thead>
<tr>
<th>Ref No</th>
<th>Technical Reports/Consensus Statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>29</td>
<td>Australasian Paediatric Endocrine Group: APEG Handbook on Childhood and Adolescent Diabetes. Sydney, Australasian Paediatric Endocrine Group, 1996</td>
</tr>
<tr>
<td>30</td>
<td>National Institute for Clinical Excellence. Type 1 Diabetes (Childhood): Diagnosis and Management of Type 1 Diabetes in Children and Young People (DRAFT). 2004.</td>
</tr>
<tr>
<td>31</td>
<td>International Society for Pediatric and Adolescent Diabetes: ISPAD Consensus Guidelines for the Management of Type 1 Diabetes Mellitus in Children and Adolescents. Zeist, Netherlands, Medforum, 2000</td>
</tr>
</tbody>
</table>
## Chapter 5: Insulin Regimens and delivery

### 5.1 Relationship of number of daily insulin injections with glycaemic control.

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref No</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Comments</th>
<th>Design</th>
<th>Level</th>
</tr>
</thead>
</table>
| Craig 2002   | 2      | 1190 children and adolescents aged 1.2-15.8 years with type 1 diabetes, identified from three hospital-based paediatric diabetes units, four private city-based paediatric practices and 18 regional outreach clinics in NSW and the ACT from 1 September to 31 December, 1999 | Cross sectional audit | HbA1c level and incidence of severe hypoglycaemia | Significant predictors of HbA1c level in multiple regression model were: duration and insulin dose/kg  
At least one episode of severe hypoglycaemia in the previous three months was reported in 6.7%, and the rate of severe hypoglycaemia was 36/100 patient-years.  
Significant predictors of hypoglycaemia in a Poisson regression model were younger age (P = 0.03), male sex (P = 0.04), longer diabetes duration (P = 0.02), and > 3 daily insulin injections (P = 0.02), but not HbA1c level. | Australian data,  
In multiple regression model number of injection per day was not a predictor of HbA1c, but multiple injections (>3 per day) was a predictor of hypoglycaemia. | Multicentre, population-based, cross-sectional study | IV               |
| Mortensen 1997 | 3      | 22 paediatric departments from 18 countries in Europe, Japan, and North America.  
Blood samples and information were collected from March through August 1995 on 2,873 children who were born in 1977 or later and seen in the outpatient clinics. | Survey | HbA1c levels were determined once and analysed centrally (normal range, 4.4-6.3%; mean, 5.4%).  
Year of birth, sex, duration of diabetes, height, body weight, insulin regimen, and number of episodes of severe hypoglycaemia during the past 3 months were recorded. | Average HbA1c was 8.6 +/- 1.7%, but varied significantly (P < 0.0001) between centres.  
Hypoglycaemia (unconsciousness and/or seizures) was related to younger age (0-8 years) and lower HbA1c level.  
The incidence of hypo, based on the 3-month period, was 22 per 100 patient-years.  
Sixty percent of the children (n = 1,707) had two injections daily, while 37% (n = 1,071) were on three or more.  
HbA1c increased during maturation for both sexes.  
No difference in glycaemic control was found among adolescents treated with two, three, and four or more daily injections.  
Adolescents on four or more injections received significantly (P < 0.001) more insulin.  
Girls on four or more injections had significantly (P < 0.01) higher BMI than girls | cross-sectional clinic data and therefore non-population-based survey | IV               |
<p>| DCCT 1993 | 17 | 1441 patients with T1D aged 13-39 years. 726 with no retinopathy at baseline (primary intervention group) and 715 with mild retinopathy (secondary intervention group) | Intensive insulin therapy (by multiple daily injections or insulin pump) with frequent BG monitoring (n=704; 348 primary and 366 secondary prevention)  OR  Conventional therapy with 1 or 2 insulin injections daily and once daily monitoring (n=704; 352 primary and 352 secondary prevention) | Development of diabetes complications on twice-daily insulin.  Retinopathy: intensive therapy reduced the risk of retinopathy by 76% (95% CI 62-85) in patients with no retinopathy at baseline (p&lt;0.002), and by 54% (95% CI 39-66) in those with mild retinopathy at baseline (p=0.001); combined 63% (95% CI 52-71), p&lt;0.002.  Neuropathy: At 5 years, intensive therapy reduced incidence of clinical neuropathy by 69%; 95% CI 24-87 (3% in intensively treated group vs 10% in conventionally treated group) p=0.006 in patients with no retinopathy at baseline; and by 57% (95% CI 29-73); p=0.002 in those with mild retinopathy at baseline; combined 60% (95% CI 38-74), p&lt;0.002  Nephropathy: Intensive therapy reduced risk of microalbuminuria by 39% (95% CI 21-52) and albuminuria by 54% (95% CI 19-74); Intensive therapy reduced the mean adjusted risk of microalbuminuria by 34% (p=0.04) in patients with no retinopathy at baseline and by 43% in those with mild retinopathy at baseline (p=0.001)  Adverse events: Incidence of hypoglycaemia increase 2-3 fold on intensive therapy (19 versus 62 hypoglycaemic episodes per 100 patient years, p&lt;0.001).  Landmark study, rigorous multicentre study supervised by NIH, USA, See other DCCT references Follow up period of 6.5 years (trial terminated by independent monitoring committee)  Blinding: Standard therapy group blinded to HbA1c results; intensive therapy group could not be blinded to HbA1c because they were using it as a management tool  Research group blinded to effects of the two treatment regimens  Losses to follow-up: 99% of patients completed study; &gt;95% of all scheduled examinations completed; 11 patients died; 32 patients assigned to inactive status for some time during trial due to unavailability or investigator’s decision that continuation of treatment would be | RCT II |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Study Details</th>
<th>Diabetes Complications</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>White 2001 (EDIC follow up of DCCT adolescent cohort)</td>
<td>18 of 195 adolescents in the DCCT adolescent cohort participated in EDIC (Epidemiology of Diabetes Interventions and Complications)</td>
<td>Observational four year follow up from close of DCCT (DCCT = Intensive insulin therapy and multiple daily injections with frequent BG monitoring OR Conventional therapy with 1 or 2 insulin injections daily and once daily monitoring)</td>
<td>HbA1c, During 7.4 years of DCCT mean HbA1c was lower with intensive therapy than conventional therapy (8.06% vs 9.76%; p &lt; .0001) The subsequent first 4 years of EDIC mean HbA1c was similar for former intensive and former conventional groups (8.38% vs 8.45%). Concluded that even though the diff. between HbA1c lessened during EDIC, the benefit of intensive therapy still persisted.</td>
<td>Rigorous study. Supervised by NIH (see other entries for DCCT). Blinding: Retinopathy assessors were blinded to the DCCT assignment of participants RCT II</td>
</tr>
<tr>
<td>Bougnères 1993</td>
<td>20 186 patients aged 10-18 yr with IDDM, who were previously treated with two daily insulin injections, were included without any selection into a randomized trial (1 yr).</td>
<td>They were either switched to three injections (regular prebreakfast, regular prelunch, and [regular+ultralente] predinner) (n=91) OR remained on two injections ([regular+intermediary] prebreakfast and predinner) subcutaneous</td>
<td>HbA1c, GHb, decreased from 9.8 +/- 0.1 to 9.3 +/- 0.2% (P &lt; 0.05) in the three-injection group, whereas it increased from 9.5 +/- 0.3 to 9.8 +/- 0.3% (P &lt; 0.05) in the two-injection group, resulting in a modest (0.75%) but significant difference (P &lt; 0.05) between GHb change in the two groups. The difference reached 1.4% (P &lt; 0.0002) in patients with GHb &gt; 11.2% at entry.</td>
<td>Multicentre INSERM study centres in France. Randomisation: table of random numbers Losses to follow-up: 19 primary refusals RCT II</td>
</tr>
</tbody>
</table>
injections (n=95). Frequency of severe hypoglycaemia and DKA

There were 205 enrolled, 19 primary refusals following randomisation and these patients were excluded from the analysis. Of the remaining 186 patients there were no differences in baseline characteristics. The frequency of hypoglycaemia and DKA was similar in the two groups.

5.2 The length of needle for the injection for insulin therapy in the treatment of children with type 1 diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref No</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Comments</th>
<th>Design</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tubiana-Rufi</td>
<td>1999</td>
<td>50 type 1 diabetic children (3-18 yrs)</td>
<td>2 injections performed on each child on 2 groups of children.</td>
<td>Frequency of intramuscular injections by ultrasonography</td>
<td>With 12.7 mm needles 86% of injections were intramuscular (88% in arm, 84% in thigh)</td>
<td>Open label crossover study Order of injections with different needle lengths was randomised</td>
<td>RCT</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean age 11.5 [3.5]</td>
<td>1st group of 25 children (randomised then crossed over to opposite)</td>
<td></td>
<td>38% of injections with 8mm needle were in muscle (48% in the arm and 28% in the thigh region).</td>
<td>25 children received injection in the thigh, 25 in the arm; method of selecting injection site not stated</td>
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<td></td>
<td></td>
<td>BMI between 3rd &amp; 60th percentiles for age and sex.</td>
<td>2nd group of 25 children (randomised then crossed over to opposite)</td>
<td></td>
<td>Significant reduction with 8mm needle p &lt; 0.01 arm p &lt; 0.001 thigh</td>
<td>All measurements (using ultrasound) were performed by the same operator</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>C: 12.7 mm in arm D: 8 mm in arm</td>
<td></td>
<td>Conclusion: 8mm needles significantly reduce risk of IM injections in slim or normal weight diabetic children and</td>
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</table>
### 5.3 Children and adolescents with type 1 diabetes and management with insulin pump therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref No</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Comments</th>
<th>Design</th>
<th>Level</th>
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</thead>
<tbody>
<tr>
<td>Pickup 2002</td>
<td>43</td>
<td>12 RCTs</td>
<td>Overall 301 patients received insulin pump, 299 received insulin injections. Timeframe 2.5 to 24 months.</td>
<td>Continuous s.c. insulin infusion or Optimised s.c. insulin injections</td>
<td>Mean BGL: Standardised mean difference in BGL was 0.56 (95% CI 0.35 - 0.77) lower in pump patients.</td>
<td>Search strategy included Medline, Embase and Cochrane database. Other data from manufacturer’s and patient support groups. Appropriate inclusion criteria for selected articles. Some statistical heterogeneity between studies was evident. Provided an effect size corrected for possible publication bias Data examined by 2 reviewers. Side effects not reported.</td>
<td>Systematic review of RCTs</td>
<td>1</td>
</tr>
<tr>
<td>Weissberg-Benchell 2003</td>
<td>44</td>
<td>52 studies (12 studies paediatric, 33 adult, 7 mixed adult/paediatric) 1547 patients total Age range 2.3-49.8 years, mean 26 +/- 10.8 years</td>
<td>Continuous s.c. insulin infusion CSII or Optimised s.c. insulin injections</td>
<td>HbA1c: Standardised mean difference was 0.44 (95% CI 0.2-0.63) lower in pump patients. Total daily insulin dose: Standardised mean difference was 0.58 (95% CI 0.34-0.83) lower in pump patients. This represented reduced total daily insulin dose by 14% in pump patients.</td>
<td>Articles obtained by searching Medline, PubMed and reference lists of review and other articles. English studies only. Appropriate inclusion criteria used however details of how inclusion criteria were applied are not stated. No distinction made between studies of different designs and quality. All parallel studies pooled without taking account of individual study design. Publication bias assessed by comparing results from unpublished data from abstracts presented at major meetings. Paediatric and adult studies analysed together.</td>
<td>Systematic review of 52 studies (mixed study designs including RCTs)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>NHS NICE 2003</td>
<td>49</td>
<td>Systematic review of all insulin pump studies included paediatric section</td>
<td></td>
<td></td>
<td></td>
<td>Appropriate search strategy and inclusion criteria used. No published RCTs in the paediatric</td>
<td>Systematic Review/Technology Appraisal</td>
<td>T</td>
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</table>
Appendix 2: Evidence Tables

Australian Clinical Practice Guidelines: Type 1 Diabetes in Children and Adolescents

which identified 8 paediatric studies (case series) included adolescent section which included 2 RCT’s

CSII compared with MDI Glycated Haemoglobin (GHb)

One study found no difference in glycated Hb at 6 months follow-up there was no significant difference between CSII and MDI (8.5 vs 8.7%, p=NS). A second study found clear benefit on glycated haemoglobin- after 4 months follow-up GHb was significantly lower in CSII than MDI (8.8 vs 9.6%, p<0.05).

population. All paediatric studies identified were case series.

Only 2 RCTs in adolescents.

No increase in serious hypoglycaemia;

Number of events too small for statistical analysis (1 in each group).

No other significant adverse events recorded in either study.

5.4 Technical reports and Consensus Statements used to formulate the recommendations and principles of clinical practice.

<table>
<thead>
<tr>
<th>Ref No</th>
<th>Technical Reports/Consensus Statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Australasian Paediatric Endocrine Group: APEG Handbook on Childhood and Adolescent Diabetes. Sydney, Australasian Paediatric Endocrine Group, 1996</td>
</tr>
<tr>
<td>61</td>
<td>International Society for Pediatric and Adolescent Diabetes: ISPAD Consensus Guidelines for the Management of Type 1 Diabetes Mellitus in Children and Adolescents. Zeist, Netherlands, Medforum, 2000</td>
</tr>
</tbody>
</table>

Chapter 6: Glycaemic Control

6.1 Benefits of near patient testing of HbA1c at outpatient visits.

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref No</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Comments</th>
<th>Design</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grieve</td>
<td>1999</td>
<td>Health technology Assessment., UK</td>
<td>allocation to either near patient testing (NPT) n=302 (ie HbA1c results available at the time of consultation) or not n=297</td>
<td>Number of management changes made during consultation</td>
<td>In those with poor control: more likely to have management changes made if NPT used; odds ratio 1.75 (95% CI 1.12-2.72)</td>
<td>Randomisation: Assignment of patients to groups according to whether number of ticket given on arrival was odd or even. Blinding: Administrative staff who handed out tickets to allocate patients to groups were unaware of</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>599 patients with T1D attending diabetes clinics at Guy’s and St Thomas Hospitals UK</td>
<td></td>
<td></td>
<td>In those with good control: no diff NPT leads to more management changes in this with poor glycaemic control</td>
<td></td>
<td>Quasi-RCT</td>
<td>III-1</td>
</tr>
</tbody>
</table>
6.2 Benefits of improved glycaemic control on development of microvascular and macrovascular complications.

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref No</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Comments</th>
<th>Design</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCCT 1993</td>
<td>1</td>
<td>1441 patients with T1D aged 13-39 years, 726 with no retinopathy at baseline (primary intervention group) and 715 with mild retinopathy (secondary intervention group)</td>
<td>Intensive insulin therapy (by multiple daily injections or insulin pump) with frequent BG monitoring (n=704; 348 primary and 366 secondary prevention) or Conventional therapy with 1 or 2 insulin injections daily and once daily monitoring (n=704; 352 primary and 352 secondary prevention)</td>
<td>Development of diabetes complications</td>
<td>Retinopathy: intensive therapy reduced the risk of retinopathy by 76% (95% CI 62-85) in patients with no retinopathy at baseline (p&lt;0.002), and by 54% (95% CI 39-66) in those with mild retinopathy at baseline (p=0.001); combined 63% (95% CI 52-71), p&lt;0.002. Neuropathy: At 5 years, intensive therapy reduced incidence of clinical neuropathy by 69% (95% CI 24-87), 3% in intensively treated group vs 10% in conventionally treated group p=0.006 in patients with no retinopathy at baseline; and by 57% (95% CI 29-73), p&lt;0.002 in those with mild retinopathy at baseline; combined 60% (95% CI 38-74), p&lt;0.002. Nephropathy: Intensive therapy reduced risk of microalbuminuria by 39% (95% CI 21-52) and albuminuria by 54% (95% CI 19-74); Intensive therapy reduced the mean adjusted risk of microalbuminuria by 34% (p=0.04) in in patients with no retinopathy at baseline and by 43% in those with mild</td>
<td>Landmark study. Rigorous multicentre study supervised by NIH, USA See other DCCT references Follow up period of 6.5 years (trial terminated by independent monitoring committee) Blinding: Standard therapy group blinded to HbA1c results; intensive therapy group could not be blinded to HbA1c because they were using it as a management tool</td>
<td>RCT</td>
<td>II</td>
</tr>
</tbody>
</table>

Doctors and patients were not aware of group allocation until the time of intervention, by which it was impossible to reverse the allocation. Equipment failure: NPT – 1 test not processed Conventional testing – 5 tests not processed.
<p>| DCCT 1994 | 2 | Adolescent subgroup of DCCT trial. Age 13-17 years | Intensive insulin therapy (n=95) (by multiple daily injections or insulin pump) with frequent BG monitoring OR Conventional therapy with 1 or 2 insulin injections daily and once daily monitoring (n=114) | Development of diabetes complications Retinopathy: Intensive therapy decreased the risk of retinopathy by 53% (CI 1-78%, p=0.048) (in those with no retinopathy) and 70% (CI 25-88%, p=0.010) (in those with mild retinopathy) | Landmark study. See other DCCT references <strong>Blinding:</strong> Standard therapy group blinded to HbA1c results; intensive therapy group could not be blinded to HbA1c as they were using it as RCT II |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Duration</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Study Design</th>
<th>Evidence Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCCT 1995</td>
<td>3 years</td>
<td>1441 patients with T1D, 726 with no retinopathy at entry</td>
<td>Intensive insulin therapy (by multiple daily injections or insulin pump) with frequent BG monitoring</td>
<td>Development and progression of retinopathy</td>
<td>Mean HbA1c during DCCT was dominant predictor of retinopathy progression, and the risk gradients were similar in the two groups; a 10% lower HbA1c (e.g., 8 vs. 7.4 years) was associated with a 9% lower rate of retinopathy; p = 0.042 in those with mild retinopathy</td>
<td>RCT II</td>
</tr>
</tbody>
</table>

Research group blinded to the effects of the two treatment regimens; Investigators and patients unaware of outcome data unless predetermined 'alert' criteria (e.g., development of retinopathy) were reached; Retinopathy assessed by operators who were unaware of treatment group assignment. Losses to follow-up: No patients voluntarily withdrew; 2 patients died; 2 patients assigned to inactive status for some time. >95% of scheduled examinations were completed; overall time spent in assigned treatment was 95%; Independent data monitoring committee determined that study results warranted terminating trial after mean follow-up of 6.5 years (overall).
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Follow-up period</th>
<th>Patients with HbA1c ≤6.5% excluded from study</th>
<th>Patients with HbA1c level &lt;6.5%</th>
<th>Retinopathy progressed in</th>
<th>Baseline and 7.15 with mild retinopathy</th>
<th>Baseline and 7.15 with retinopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCCT 1996</td>
<td>6.5 years</td>
<td>726 with no retinopathy</td>
<td>1441 patients</td>
<td>7.2% is assoc. with a 43% lower risk in conventional gp.</td>
<td>OR Convention therapy with 1 or 2 insulin injections daily and once daily monitoring.</td>
<td>Primary prevention cohort (intensive insulin treatment n=348 vs standard conventional treatment n=352) Secondary intervention cohort (intensive insulin treatment n=366 versus standard conventional treatment n=352)</td>
</tr>
<tr>
<td>Nathan 2003</td>
<td>4 years</td>
<td>1441 patients who participated in the DCCT</td>
<td>1229 patients</td>
<td>7.2% is assoc. with a 43% lower risk in conventional gp.</td>
<td>OR Conventional therapy with 1 or 2 insulin injections daily and once daily monitoring.</td>
<td>Primary prevention cohort (intensive insulin treatment n=348 vs standard conventional treatment n=352) Secondary intervention cohort (intensive insulin treatment n=366 versus standard conventional treatment n=352)</td>
</tr>
</tbody>
</table>
### Interventions and Complications

**N = 611**

- **Conventional and n = 618 intensive therapy.**

### Observational four year follow up from close of DCCT (DCCT = Intensive insulin therapy and multiple daily injections with frequent BG monitoring OR Conventional therapy with 1 or 2 insulin injections daily and once daily monitoring)

#### Diabetes complications

- **HbA1c**
  - During 7.4 years of DCCT mean HbA1c was lower with intensive therapy than conventional therapy (8.06% vs 9.76%; p < 0.0001)
  - The subsequent first 4 years of EDIC mean HbA1c was similar for former intensive and former conventional groups (8.38% vs 8.45%).
  - Concluded that even though the difference between HbA1c lessened during EDIC, the benefit of intensive therapy still persisted.

#### Retinopathy

- The prevalence of worsening retinopathy and of progression to proliferative or severe nonproliferative retinopathy were reduced by 74% (p < 0.001) and 78% (p < 0.007), respectively, in the former intensive therapy group compared with the former conventional group.

### Craig 2002

- **9**

#### Cross sectional audit

**HbA1c level and incidence of severe hypoglycaemia**

- Significant predictors of HbA1c level in multiple regression model were:
  - Duration and insulin dose/kg
  - At least one episode of severe hypoglycaemia in the previous three months was reported in 6.7%, and the rate of severe hypoglycaemia was 56/100 patient-years.
  - Significant predictors of hypoglycaemia in a Poisson regression model were younger age (P = 0.03), male sex (P = 0.04), longer diabetes duration (P = 0.02), and > 3 daily insulin injections (P = 0.02), but not HbA1c level.
  - Median HbA1c 8.2% (IQR range 7.6-9.1%) in both urban and rural group.

- In multiple regression model number of injection per day was not a predictor of HbA1c, but multiple injections (>3 per day) was a predictor of hypoglycaemia.

#### Fewer than 25% achieve the recommended HbA1c <7.5%

### White 2001 (EDIC follow up of DCCT adolescent cohort)

- **6**

#### Of 195 adolescents in the DCCT adolescent cohort, 175 (91%) participated in EDIC (Epidemiology of Diabetes Interventions and Complications)

- **Diabetes complications**
  - **HbA1c**
    - Retinopathy:
      - The prevalence of worsening retinopathy and of progression to proliferative or severe nonproliferative retinopathy were reduced by 74% (p < 0.001) and 78% (p < 0.007), respectively, in the former intensive therapy group compared with the former conventional group.

### RCT II

- **Craig 2002**

#### Multicentre, population-based, cross-sectional study

- **IV**

#### Rigorous study. Supervised by NIH (see other entries for DCCT).

#### Blinding:

- Retinopathy assessors were blinded to the DCCT assignment of participants.
| Handelman 2001 | 10 | Audit of 1,190 children with T1D. Case attainment based on Diabetes Register was 67% of children in NSW and ACT. | Compared urban with rural children. | HbA1c | Median HbA1c 8.2% (IQR range 7.6-9.1%) in both urban and rural group. | Confirmed homogeneity of metabolic control in NSW and ACT regardless of location, socioeconomic status or system of care. Fewer than 25% achieve the recommended HbA1c <7.5% | Multicentre, population-based, cross-sectional study | IV |

6.3 Technical Reports and Consensus Statements used to formulate the recommendations and principles of clinical practice.

<table>
<thead>
<tr>
<th>Ref No</th>
<th>Technical Reports/Consensus Statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>National Institute for Clinical Excellence. Type 1 Diabetes (Childhood): Diagnosis and Management of Type 1 Diabetes in Children and Young People (DRAFT). 2004.</td>
</tr>
<tr>
<td>39</td>
<td>International Society for Pediatric and Adolescent Diabetes: ISPAD Consensus Guidelines for the Management of Type 1 Diabetes Mellitus in Children and Adolescents. Zeist, Netherlands, Medforum, 2000</td>
</tr>
</tbody>
</table>

Chapter 7: Nutrition

7.1 Low glycaemic index diets in the management of type 1 diabetes in children and adolescents

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref No</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Comments</th>
<th>Design</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilbertson 2001 &amp; Gilbertson 2003</td>
<td>6, 16</td>
<td>Children and adolescents ages 8-13 yrs with T1D (N=104)</td>
<td>low GI diet (GI 77) versus high GI diet (GI 79)</td>
<td>At 3, 6, 12 months HbA1c Hypoglycaemia Hyperglycaemia Weight, height, dietary intake, quality of life.</td>
<td>No difference in HbA1c at 3 and 6 months. After 12 months flexible low GI diet pts had significantly better HbA1c (8.05 vs 8.62, p=0.05). This difference between groups was significant, even after adjusting for baseline values (P=0.05). There were fewer episodes of excessive hyperglycaemia defined as &gt;15/month (35 vs 66%, P=0.006) and better QOL for children and parents in flexible-low GI diet. There were no differences in number of hypoglycaemic episodes. Mean GI of diets was not different in the 2 groups despite differences in...</td>
<td>Randomisation: Computer-generated random numbers, method of allocation concealment not stated Blinding: Assessor of dietary adherence not blinded to participant’s diet allocation, but all other data analysis performed by another researcher blinded to diet allocation Losses to follow-up: 15 participants dropped out (14%), 11 from measured CHO diet and 4 from flexible-low GI diet. Of the 89</td>
<td>RCT</td>
<td>II</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Participants</td>
<td>Outcome Measures</td>
<td>Findings</td>
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<tr>
<td>Brand Miller 2003</td>
<td>Meta-analysis of RCT’s to determine whether low-GI diets, compared with conventional or high-GI diets, improved overall glycaemic control in individuals with diabetes, as assessed by reduced HbA1c or fructosamine levels</td>
<td>14 studies, 356 subjects (203 with type 1 diabetes, 153 with type 2 diabetes)</td>
<td>low-GI diets, compared with conventional or high-GI diets diets (average GI difference 22 (range 2-37))</td>
<td>Glycaemic control (HbA1c, and fructosamine level)</td>
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<tr>
<td>In the 8 studies in which HbA1c was determined the low GI diet has a small but clinically useful effect on medium-term glycaemic control in patients with diabetes. (decrease of HbA1c of 0.43%, CI 0.72-0.13)). If final HbA1c values were adjusted for baseline values the mean difference was reduced to -0.34 units (CI -0.64 to -0.05 assuming independence.</td>
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<tr>
<td>Inclusion criteria included: English studies, 1981-2001, properly randomised, cross-over or parallel, type 1 or 2 DM, identified in Medline using “glycemic index” in title. Only 1 study gave SD’s for individual low-GI or high-GI differences and these data were assumed for the statistical analysis of remaining studies. Conclusion was low-GI foods in place of conventional or high-GI foods has a small but clinically useful effect on medium-term glycaemic control. Studies not specific for children or T1D. Only 2 included children with T1D One study included 104 children with type 1 diabetes. Many studies involved less than 25</td>
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<td></td>
</tr>
<tr>
<td>Meta-analysis of RCT’s</td>
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</tbody>
</table>
### 7.2 Adjusting insulin dose for carbohydrate quantity in the management of type 1 diabetes in children and adolescents

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref No</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Comments</th>
<th>Design</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delahanty</td>
<td>1993</td>
<td>DCCT population – adults and adolescents</td>
<td>84 item questionnaire to determine whether specific diet-related behaviours practised by TID patients in intensive treatment group of the DCCT were associated with lower HbA1c values. Self reported retrospective dietary behaviour</td>
<td>HbA1c</td>
<td>Adherence to prescribed meal plan and adjusting food and/or insulin in response to hyperglycaemia were associated with lower HbA1c levels. Those who adhered to prescribed meal plan &gt;90% of time had average HbA1c 0.9% lower than subjects adhering to prescribed meal plan. Over-treating hypoglycaemia and consuming extra snacks</td>
<td>623 of 687 (90%) potential participants completed the questionnaire. Survey instrument pretested with 101 intensively treated participants in the feasibility stage</td>
<td>RCT</td>
<td>IV</td>
</tr>
</tbody>
</table>

| Collier 1988 | 18     | 7 children with type 1 diabetes; 6 males, 1 female | Average age 12 ± 2 years                                                   | Glycaemic index and Cholesterol | Mean GI for low GI diet 68.7 [sem 2.5] versus 81.5 [sem 1.1] for high GI diet, p < 0.005 Reduced after low GI diet but not after high GI diet (final figures and statistical significance not given for the comparison of high and low GI diets) | Randomisation: Crossover – order of diets randomised. Method of randomisation not stated. Blinding: Not feasible for participants. Losses to follow-up: None reported. Adherence: Participants received dietary advice on an individual basis to maximise adherence. | RCT (Crossover) | II    |
beyond the meal plan were associated with higher HbA1c levels. Adjusting insulin dose for meal size and content and consistent consumption of an evening snack were associated with lower HbA1c (p<0.03 for differences between responding <50%, =50% or >50% of the time).

DAFNE study group 2002

- 169 adults with T1D in secondary care clinics in 3 English health districts. Subjects had moderately to poor diabetes control (HbA1c 7.5-12%) and duration of diabetes > 2 years.
- Mean age 40 (SD9)
- Mean diabetes duration 16.6 yr (SD 9.6)
- 6 month and 1 year follow up
- Training in (DAFNE) dose adjustment for carbohydrate intake.
  - Randomised to receive training immediately (n=69) or later (n=72)
  - DAFNE is adult education in flexible, intensive insulin management.
  - Severe hypos
  - Impact of diabetes on quality of life (ADDQoL)
- HbA1c
- Sig. better in immediately trained DAFNE patients than those trained after 6 months (mean HbA1c 8.4% vs 9.4%, t=6.1, P<0.0001).
- Impact of diabetes on dietary freedom improved in immediate trained group (t=5.4, P=0.0001)
- Unchanged – severe hypoglycaemia in 12/67 vs 11/72 (p=0.68)
- ADDQoL significantly improved in immediate trained subjects after 1 year (t=2.9, P=0.01)
- Randomisation:
  - computer generated random number list.
  - Allocation by use of sealed opaque envelopes in consecutive order.
- Relevance to children is debatable.
- Possible bias in that groups consisted of volunteers.
- Losses to follow-up:
  - 1016 letters sent, 423 replied, 299 expressed interest in study, 169 randomised, 27 did not participate after randomisation so intention to treat analysis was not possible.
- RCT II

7.3 The effect of moderate use of sugars on glycaemic control in children and adolescents with type 1 diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref No</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Comments</th>
<th>Design</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loghmani 1991</td>
<td>21</td>
<td>10 patients with insulin dependent diabetes Age 7-12 USA</td>
<td>Sucrose-free diet (2% calories from sucrose) vs. Sucrose-containing isocaloric diet (10% calories from sucrose)</td>
<td>Change in blood glucose (18 measurements per day)</td>
<td>No significant differences: Area under the glucose response curve 3672 +/- 240 mg/dl per hr (Sucrose-free) vs. 3575 +/- 285 mg/dl per hr (Sucrose-containing) p=0.74</td>
<td>Crossover design: participants received both diets, each for 2 days consecutively, in random order</td>
<td>RCT</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Urinary glucose</td>
<td>No difference in urinary glucose 35.6 +/- 7.5 (Sucrose-free) vs. 34.5 +/- 7.5 gm/day (Sucrose containing) p=0.84</td>
<td>Randomisation: Method not stated</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Blinding: Not stated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>N</td>
<td>Patients</td>
<td>Type 1 Diabetes</td>
<td>Age</td>
<td>Country</td>
<td>Diet 1</td>
<td>Diet 2</td>
<td>Method</td>
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<tr>
<td>Rickard 1998</td>
<td>22</td>
<td>9 patients</td>
<td>11-16</td>
<td>USA</td>
<td>Sucrose (2%) free diet vs. Sucrose (17%) containing diet</td>
<td>All subjects rendered euglycaemic with insulin clamp overnight prior to study, then placed on 0.35 mU/kg/min insulin infusion during 4 hour intense study period to see effect of sucrose in diet.</td>
<td>Significant difference: Area under the glucose response curve 37 +/- 3.5 (SEM) mmol/L (sucrose-free) vs. 42 +/- 4.7 mmol/L (sucrose containing) P=0.01. Peak glucose response was approx 1 hour earlier (p&lt;0.01) and was lower (p&lt;0.01) with sugar-containing diet than with sugar-free diet. Higher glycaemic response to low sucrose diet attributed to increased starch content.</td>
<td>Crossover design: participants received both diets, each for 2 days consecutively, in random order. Randomisation: Pseudo-randomised - patients allocated to treatment groups based on their ability to attend hospital on one of two days for dietary assessment. Blinding: Not stated. Losses to follow-up: Data from 4 children excluded from analysis (3).</td>
</tr>
<tr>
<td>Schwinghan dl 1994</td>
<td>23</td>
<td>24 type 1 patients</td>
<td>8-26</td>
<td>Austria</td>
<td>Sucrose free diet (n=11) vs. Sucrose (5%) containing diet (n=13)</td>
<td>No significant difference: 9.0% (sucrose diet) vs. 9.1% (sucrose free diet).</td>
<td>Randomisation: Pseudo-randomised - patients allocated to treatment groups based on their ability to attend hospital on one of two days for dietary assessment. Blinding: Not stated.</td>
<td>Quasi-RCT III-1</td>
</tr>
</tbody>
</table>
## 7.4 Technical Reports and Consensus Statements used to formulate the recommendations and principles of clinical practice.

<table>
<thead>
<tr>
<th>Ref No</th>
<th>Technical Reports/Consensus Statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>Australasian Paediatric Endocrine Group: APEG Handbook on Childhood and Adolescent Diabetes. Sydney, Australasian Paediatric Endocrine Group, 1996</td>
</tr>
</tbody>
</table>

### Wang 1991

- **Participants:** 8 IDD patients (Age 7-16, USA)
- **Intervention:** Oatmeal alone (OM) vs. Oatmeal + sucrose (OMS) vs. Oatmeal + protein (OMP) vs. Oatmeal + protein + sucrose (OMPS)
- **Randomisation:** Latin square, where patients were randomised to four different breakfasts on four different days
- **Blinding:** Not reported
- **Outcomes:** Change in blood glucose
- **Findings:** No significant differences in peak glucose values, change of rise, glucose area under the curve (p>0.05). Combined peak times of breakfasts without added protein and fat (mean 37.5 [SEM8] min (SEM) vs 54.4 [8] min, p<0.05 for breakfasts with added protein and fat. Study suggests a small amount (up to 14%) of simple sugar replacing a portion of complex carbohydrate may not cause an exaggerated glycaemic response.

### Wise 1989

- **Participants:** 16 type 1 diabetes patients (Age 16-39, USA)
- **Intervention:** Sucrose (7%) added to snacks (n=8) vs. Sucrose free (1%) (n=8)
- **Randomisation:** Method not stated, however snacks were colour-coded by a third party
- **Blinding:** Membership of each group unknown to patients, dieticians and physicians
- **Outcomes:** Mean blood glucose
- **Findings:** No significant difference: 8.8 nM (sucrose group) vs. 7.4 nM (sucrose-free) on day 5
### Chapter 8: Physical Activity

#### 8.1 Long-term effects of physical activity in children and adolescents with type 1 diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref No</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Comments</th>
<th>Design</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roberts 2002</td>
<td>6</td>
<td>Adolescents with T1D were assigned to groups with either lower or higher than 9% glycosylated haemoglobin (HbA1c), and submitted to 12 weeks of supervised training followed by 12 weeks of unsupervised training (n = 12 per group) (age 14.0 +/- 1.2 years) Duration of diabetes 5.0 +/- 3.1 years.</td>
<td>12 weeks of supervised training followed by 12 weeks of unsupervised training (n = 12 per group).</td>
<td>Aerobic capacity was estimated by Aerobic Power Index submaximal test using an ergomedic 818 exercise bike.</td>
<td>Supervised training caused a 17% rise in the patients’ aerobic capacity which during the ensuing period of unsupervised training decreased to pre-training levels (p &lt; 0.05), thus suggesting a poor compliance with unsupervised training.</td>
<td>Patients were selected from clinic patients. Short-term training programme (12 weeks) only</td>
<td>Pre test and post test</td>
<td>IV</td>
</tr>
<tr>
<td>Mosher 1998</td>
<td>7</td>
<td>10 male adolescents with T1D (aged 17.2 +/- 1.2 years) and 10 adolescent nondiabetic (ND) subjects (19.4 +/- 1.3 years).</td>
<td>Mixed endurance and calisthenic/strength activities performed at a rapid pace three times weekly for 12 weeks.</td>
<td>Hypoglycaemia Cardiorespiratory endurance Lean body mass Strength Fasting blood plasma glucose and HbA1c</td>
<td>Only one subject with IDDM experienced hypoglycaemia after a single exercise session. Both subject groups improved their cardiorespiratory endurance (p &lt; .05). Lean body mass of T1D subjects increased by 3.5% (p &lt; .05). Subjects with and without T1D lowered their percent body fat (p &lt; .05 and .001, respectively). Strength improvement of IDDM subjects ranged from 13.7% (p &lt; .001) to 44.4% (p &lt; .01), depending upon the manoeuvre. Fasting blood plasma glucose for all subjects was unchanged by training, but glycosylated haemoglobin A1c of T1D subjects was reduced by 0.96 percentage point (p &lt; .05). Reductions of HbA1c benefited subjects with poor preconditioning glycaemic control.</td>
<td>No selection protocol indicated. Data analysed using a 2x2 analysis of variance (ANOVA) for repeated measures. Did not follow up after study period to see if benefit was maintained</td>
<td>Pretest, posttest intervention on trial with control group</td>
<td>IV</td>
</tr>
</tbody>
</table>
### Lipids

Low-density lipoprotein cholesterol was decreased in subjects with IDDM ($p < .05$), but not total cholesterol or triglycerides.

| Campaigne 1984 | 8 | Children aged 5-11 yr with T1D | Experimental group of children ($N = 9$) took part in a 30-min vigorous exercise program three times a week for 12 wk; the control group ($N = 10$) did not | HbA1 and FBG | The experimental group significantly ($p < 0.05$) decreased their HbA1 and FBG while the control group showed no change. | Peak aerobic capacity | The experimental group significantly ($p < 0.05$) increased their peak aerobic capacity when compared with baseline values (47.14 +/- 1.94 versus 50.69 +/- 1.30). | Randomisation: Method of randomisation not stated | Blinding: Not stated | Losses to follow-up: Not stated, but patients were required to attend at least 75% of exercise classes to be included in the final analyses | RCT | II |

### 8.2 Technical Reports and Consensus Statements used to formulate the recommendations and principles of clinical practice.

<table>
<thead>
<tr>
<th>Ref No</th>
<th>Technical Reports/Consensus Statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>National Institute for Clinical Excellence. Type 1 Diabetes (Childhood): Diagnosis and Management of Type 1 Diabetes in Children and Young People (DRAFT). 2004.</td>
</tr>
<tr>
<td>4</td>
<td>Australasian Paediatric Endocrine Group: APEG Handbook on Childhood and Adolescent Diabetes. Sydney, Australasian Paediatric Endocrine Group, 1996</td>
</tr>
</tbody>
</table>

### Chapter 9: Diabetic Ketoacidosis

#### 9.1 Aetiology, epidemiology, risk factors, cerebral oedema and management of diabetic ketoacidosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref No</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Comments</th>
<th>Design</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Komulainen 1996</td>
<td>2</td>
<td>745 Finnish children at diagnosis of T1DM</td>
<td>Frequency of DKA</td>
<td>Higher rate of DKA in those aged &lt; 2 years or &gt; 10 years (&lt; 2 years: 53.3%; 2-10 years: 16.9%; &gt; 10 years: 33.3%). Children from families with poor parental educational level had DKA more often than those from families with high parental education (24.4% v 16.9%, $p&lt;0.05$). DKA less common in those with residual insulin secretion (serum C peptide &gt; 0.10 nmol/L), $p&lt;0.05$</td>
<td>Cross sectional</td>
<td>IV</td>
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<tr>
<td>Study</td>
<td>Study Design</td>
<td>Year</td>
<td>Participants</td>
<td>Intervention</td>
<td>Outcomes</td>
<td>Methodology</td>
<td>Case-Control</td>
<td>Notes</td>
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<tr>
<td>Barrett 1982</td>
<td>Case-control</td>
<td>1982</td>
<td>15 diabetic subjects with DKA; 6 non diabetic controls</td>
<td>IV “low-dose” insulin (6-10 U/hour)</td>
<td>Mean glucose clearance during insulin treatment in those with DKA was significantly slower than in the controls (half time of fall in plasma glucose 6.1 ± 0.6 vs 3.31 ± 0.03 hours, P &lt; 0.001)</td>
<td>Not randomised; non-diabetic control group used for comparison</td>
<td>III-2</td>
<td></td>
</tr>
<tr>
<td>Yki-Jarvinen 1984</td>
<td>Case-control</td>
<td>1984</td>
<td>14 newly diagnosed T1DM patients after disappearance of ketosis and after 3 months of insulin therapy; 14 non diabetic controls</td>
<td>Insulin sensitivity (IS) and hepatic glucose production measured using euglycaemic insulin clamp</td>
<td>IS, as measured by rate of glucose metabolism, was 35% lower in newly diagnosed T1DM patients compared with controls (P &lt; 0.005); after 3 months of insulin therapy in subjects with diabetes, IS was comparable in both groups.</td>
<td>Case-control</td>
<td>III-2</td>
<td></td>
</tr>
<tr>
<td>Christensen 1974</td>
<td>Case-control</td>
<td>1974</td>
<td>14 patients with diabetes (10 with DKA); 23 non-diabetic controls</td>
<td>Plasma norepinephrine and epinephrine levels</td>
<td>Plasma norepinephrine levels were elevated in all DKA patients and correlated with degree of metabolic decompensation (as measured by plasma carbon dioxide, P &lt; 0.02), compared with controls; epinephrine was elevated in half of those with DKA</td>
<td>Non-diabetic control group used for comparison</td>
<td>Case-control</td>
<td>III-2</td>
</tr>
<tr>
<td>Barnes 1978</td>
<td>Case-control</td>
<td>1978</td>
<td>5 pituitary-ablated T1DM patients and 5 T1DM patients with normal pituitary function</td>
<td>Withdrawal of insulin for 12-hours in both groups; cortisol replacement in pituitary-ablated patients</td>
<td>Measurement of glucose, ketone bodies, growth hormone, cortisol at baseline and 12 hours</td>
<td>Small number of cases but groups comparable in age, weight and diabetes duration. Insulin requirement significantly lower in pituitary ablated subjects (p &lt; 0.05)</td>
<td>Case-control</td>
<td>III-2</td>
</tr>
<tr>
<td>Bolli 1979</td>
<td>Cohort study</td>
<td>1979</td>
<td>13 T1DM patients with DKA (Group A - severe ketoacidosis, n = 5, Group B (moderate ketoacidosis, n = 8))</td>
<td>Measurement of plasma and urinary catecholamines, before and during treatment</td>
<td>In group A plasma catecholamines were significantly higher than in group B, both before and in the course of therapy (p &lt; 0.05).</td>
<td>Study demonstrated a causal association between sympathetic activity and degree of ketoacidosis</td>
<td>Cohort study</td>
<td>III-2</td>
</tr>
<tr>
<td>MacGillivray 1982</td>
<td>Case-control</td>
<td>1982</td>
<td>38 healthy T1DM patients, 25 patients with acute ketoacidosis, 20 non diabetic controls</td>
<td>Measurement of diurnal concentrations of glucose, regulatory hormones, and electrolytes were measured serially over 25 hours</td>
<td>Patients with DKA had elevated adrenaline and cortisol levels, 50% had elevated glucagon and growth hormone levels</td>
<td>Study demonstrated a causal association between elevated counter-regulatory hormones and ketoacidosis</td>
<td>Case-control</td>
<td>III-2</td>
</tr>
<tr>
<td>Study</td>
<td>Participants</td>
<td>Design</td>
<td>Outcomes</td>
<td>Notes</td>
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<tr>
<td>Daneman 1990</td>
<td>Children aged &lt;16 years at diagnosis of type 1 diabetes from Oulu (Finland, n = 43) and Toronto (n = 87) during 1984-5</td>
<td>Comparative Cohort study</td>
<td>Frequency of DKA, risk factors for DKA</td>
<td>Amongst the Finnish group, those from multiplex families had a higher C-peptide concentration and lower frequency of ketoacidosis than those from simplex families (p &lt; 0.05)</td>
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<tr>
<td>Mallare 2003</td>
<td>139 new onset type 1 diabetes patients; age 0.5 to 18 years; from 1995 to 1998</td>
<td>Retrospective Cohort study (Case series)</td>
<td>Prevalence of DKA, risk factors for DKA</td>
<td>38% presented in DKA. Associations: no private health insurance (odds ratio 3.17 (95% CI 1.2-8.3) p=0.03); missed diagnosis (68% in DKA vs 32% where diagnosis not missed, odds ratio 4.6 (95% CI 1.9-11.7), p=0.001)</td>
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<tr>
<td>Kent 1994</td>
<td>26 young females with T1DM with a history of recurrent DKA and poorly controlled diabetes; matched control group of patients with stable diabetes</td>
<td>Case control study / interrupted time series</td>
<td>Mortality, cause of death</td>
<td>5/26 (19%) died during a mean follow up period of 10.5 years. Causes of death not certain, but DKA “probably” caused death in 2 cases; rates of DKA fell during follow up into adulthood</td>
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<tr>
<td>Pinhas-Hamiel 1997</td>
<td>Adolescents with T2DM diagnosed 1982-1995, USA</td>
<td>Retrospective Case Series</td>
<td>Clinical features at presentation</td>
<td>Only 42/60 had ICA performed; cases of T1DM may have been misclassified as T2DM</td>
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<tr>
<td>Scott 1997</td>
<td>Adolescents with T2M (n=50) compared with matched group with T1DM</td>
<td>Case control study</td>
<td>Clinical features at presentation</td>
<td>DKA was present in &gt;25% of patients with T2DM</td>
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<tr>
<td>Flood 2001</td>
<td>247 admissions with DKA, age ≤ 21 years</td>
<td>Retrospective cohort study</td>
<td>Rate and predictors of DKA</td>
<td>Presumed viral infection present in 17.8% of cases of DKA, bacterial infection in 12.9% (these were more common in children aged &lt; 3 years, p=0.03)</td>
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<tr>
<td>Morris 1997</td>
<td>DARTS/</td>
<td>Case series</td>
<td>The prescribed insulin dose and Associations between</td>
<td>Direct evidence of poor case series</td>
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<tr>
<td>Study</td>
<td>Year</td>
<td>Population</td>
<td>Intervention</td>
<td>Outcome</td>
<td>Study Design</td>
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<tr>
<td>Golden 1985</td>
<td>21</td>
<td>44 children with a history of recurrent DKA</td>
<td>Medical, educational, and psychosocial interventions</td>
<td>Incidence of recurrent DKA</td>
<td>Time series study</td>
<td></td>
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<tr>
<td>Musey 1995</td>
<td>22</td>
<td>African American patients with newly diagnosed or established diabetes: 56 adults, age 37.4 ± 1.7 years, 36 episodes of DKA over 3 months</td>
<td>Aetiology of DKA</td>
<td>Of those with known diabetes, 75% of DKA episodes, 67% were due to cessation of insulin. 50% stopped insulin due to lack of money to buy insulin or transportation to the hospital; 21% stopped insulin due to lack of appetite; 14% stopped insulin because of behavioural or psychological reasons; 14% because they did not know how to manage diabetes on sick days</td>
<td>Cohort study (consecutive series)</td>
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<tr>
<td>Cohn 1997</td>
<td>23</td>
<td>Admissions to</td>
<td>Prevalence of DKA, More females than males were</td>
<td>Gender differences not likely to</td>
<td>Cohort study</td>
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<tr>
<td>Study</td>
<td>Year</td>
<td>Participants</td>
<td>Methods</td>
<td>Findings</td>
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<tr>
<td>Al Adsani et al. 2000</td>
<td>24</td>
<td>59 patients with T1DM (30 males, 29 females), aged 18 to 30 years, 3 year study period, Kuwait</td>
<td>Prevalence and aetiology of DKA</td>
<td>Admissions to hospital were for DKA; 23 females vs 12 males, NS (p &gt; 0.05). Insulin omission was the most common cause of DKA (11/35); infection in 2/35</td>
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<tr>
<td>Rewers 2002</td>
<td>25</td>
<td>1243 children with T1DM aged &lt; 19 years from Denver, Colorado were followed from Jan 1, 1996 to Dec 31, 2000</td>
<td>Incidence and aetiology of DKA</td>
<td>Incidence of DKA was 8/100 person-years and increased with age in girls (P&lt;.001 for trend). In multivariate analyses, stratified by age (&lt;13 vs &gt; or =13 years), the risk of DKA in younger children increased with higher HbA1c (RR, 1.68 per 1% increase; 95% CI 1.45-1.94) and higher insulin dose (RR, 1.40 per 0.2 U/kg per day; 95% CI 1.20-1.64). In older children, the risk of DKA increased with higher HbA1c (RR, 1.43; 95% CI 1.30-1.58), higher insulin dose (RR, 1.13; 95% CI 1.02-1.25), underinsurance (RR, 2.18; 95% CI 1.65-2.95), and presence of psychiatric disorders (for boys, RR, 1.59; 95% CI 0.96-2.65; for girls, RR, 3.22; 95% CI 2.25-4.61).</td>
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<tr>
<td>Liss 1998</td>
<td>26</td>
<td>25 children (aged 9-17 years) with T1DM (no history of DKA hospitalization) and parents</td>
<td>Psychiatric disorders (DISC)</td>
<td>More diagnoses reported by DKA children than controls (mean 1.9, SD 1.9 vs 0.2, SD 0.4; p&lt;0.001). Majority cases: anxiety, affective and disruptive behaviour disorders. 88% of cases met criteria for at least 1 psych disorder v 28% controls (p&lt;0.001). Self-esteem &amp; social competence lower among cases</td>
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</table>

Cases and controls matched on age, sex, ethnicity. DKA subjects were in poor control at study entry and diagnosis as reported by mean number of hospitalisations and A&E visits compared with controls (both p<0.001).
<table>
<thead>
<tr>
<th>Study Description</th>
<th>Year</th>
<th>Country</th>
<th>Study Design</th>
<th>Participants</th>
<th>Outcomes</th>
<th>Incidence of DKA, risk factors for DKA</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Families of cases scored lower on problem-solving and diabetes-specific ‘warmth’ caring</td>
<td>1984</td>
<td>Frederiksborg County, Denmark 1960-1979 compared with 1943-1963; adolescents and young adults</td>
<td>Incidence of DKA</td>
<td>Incidence of DKA at the county hospital increased from 60 per 100,000 (1943-1963) to 120 per 100,000 (1960-1979). Mortality decreased in second time period. Recurrent DKA was associated with lower socioeconomic status.</td>
<td>Statistical significance not reported</td>
<td>Cohort study IV</td>
<td></td>
</tr>
<tr>
<td>Mecklenburg 1986</td>
<td>28</td>
<td>Frederiksborg County, Denmark 1960-1979 compared with 1943-1963; adolescents and young adults</td>
<td>Frequencies of infusion system failure and DKA rate</td>
<td>7 episodes of DKA</td>
<td>May not be representative today due to improved pump technology and education</td>
<td>Prospective Cohort study IV</td>
<td></td>
</tr>
<tr>
<td>The Diabetes Control and Complication s Trial Research Group 1995</td>
<td>29</td>
<td>217 patients on CSII followed for one year</td>
<td>Conventional vs intensive diabetes treatment</td>
<td>Adverse events: mortality, morbidity, DKA, hypoglycaemia</td>
<td>No difference in rate of DKA between two groups Amongst intensively treated patients, the DKA rate was higher in those treated with CSII than with multiple daily injections (3.09/100 patient years vs 1.39 per 100 patient years, P=0.003)</td>
<td>See other DCCT references</td>
<td></td>
</tr>
<tr>
<td>Bode BW 1996</td>
<td>30</td>
<td>225 patients using CSII, compared with use of multiple daily injections in same patients</td>
<td>Incidence of DKA and severe hypoglycaemia</td>
<td>No difference in rate of DKA between two groups (pns)</td>
<td></td>
<td>Cohort study (interrupted time series) III-2</td>
<td></td>
</tr>
<tr>
<td>Boland 1999</td>
<td>31</td>
<td>1,260 children aged &lt; 15 years at the time of diagnosis of T1DM from 24 centres in Europe</td>
<td>Treatment with CSII (n=25) vs multiple daily injections (n=50)</td>
<td>Incidence of DKA and hypoglycaemia, psychosocial outcomes</td>
<td>No statistically different in rate of DKA between two groups (1/100 patient years in CSII and 2/100 patient years in MDI group, NS)</td>
<td>Not randomised (patients selected CSII or MDI) Cohort study III-2</td>
<td></td>
</tr>
<tr>
<td>Levy-Marchal 2001</td>
<td>32</td>
<td>1,260 children aged &lt; 15 years at the time of diagnosis of T1DM from 24 centres in Europe</td>
<td>Incidence and predictors of DKA</td>
<td>Odds ratio for DKA in the under 5 age-group was 1.02 (95%CI:0.69-1.50) relative to the older children; DKA recorded in 11 centres: significant variation between centres in the frequency of DKA (range 26 to 67%); An inverse correlation between the frequency of DKA and the background incidence of T1DM was found in these centres</td>
<td></td>
<td>Cohort study IV</td>
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<tr>
<td>Study</td>
<td>N</td>
<td>Description</td>
<td>Outcomes</td>
<td>Study Type and Design</td>
<td>Evidence Level</td>
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<tr>
<td>Punnose 2002</td>
<td>33</td>
<td>Children with newly diagnosed T1DM (n=35) from 1990-98, mean age 9.2 +/- 4.1 years, United Arab Emirates</td>
<td>Incidence of DKA: 28/35 (80%) patients presented with DKA and 28% developed recurrent DKA in follow up</td>
<td>Cohort Study/interrupted time series</td>
<td>III-3</td>
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<tr>
<td>Laing 1999</td>
<td>34</td>
<td>23,752 patients with T1DM aged &lt; 30 years, diagnosed from 1972-93 and followed to 1997, UK</td>
<td>Mortality: Mortality rate from acute complications of diabetes were higher than any other cause-specific rates in those aged &lt; 20 years (SMR 273, 95% CI 196 – 381 in males; SMR 281 95% CI 201 – 303 in females); overall 54% of male and 76% of female deaths were certified to DKA</td>
<td>Age-specific mortality rates not reported for DKA</td>
<td>Population based cohort study</td>
<td>III-3</td>
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<tr>
<td>Edge 2001</td>
<td>35</td>
<td>Cases of CE in the UK, reported through the British Paediatric Surveillance Unit between October 1995 and September 1998. Episodes of DKA reported by 225 paediatricians identified as caring for children with diabetes, between March 1996 and February 1998.</td>
<td>Cases of CE and DKA: The risk of developing CE was 6.8 per 1000 episodes of DKA in all patients with diabetes (34 cases of CE and 2940 cases of DKA). The risk was higher in newly diagnosed patients (11.9 per 1000 episodes) as opposed to patients with established diabetes (3.8 per 1000), p = 0.039. Out of the 34 cases of CE 8 resulted in death (24%).</td>
<td>Cross sectional (audit)</td>
<td>Large study using BPSU (British Paediatric Surveillance System); number of cases may be under-reported</td>
<td>IV</td>
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<tr>
<td>Glaser 2001</td>
<td>36</td>
<td>61 children with DKA and CE, compared to children with DKA and no CE, 181 randomly selected and 174 children matched to the CE children</td>
<td>Logistic analysis for the factors associated with CE. Mortality from DKA and CE: Occurrence of CE: 61/6977 (0.9%) hospitalisation for DKA. CE significantly associated with (compared to randomly selected group): Lower initial partial pressure of arterial carbon dioxide: RR for each decrease of 7.8 mmHg, 3.4 (95%CI 1.9-6.3) (p &lt; 0.001) Higher initial serum nitrogen concentration: RR for each increase of 9 mg per decilitre, 1.7 (95%CI 1.2-2.5, p = 0.003) (these were also both</td>
<td>Comparative study with historical controls</td>
<td>IV</td>
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</tbody>
</table>
| Reference | Year | Cases | Study Design | Study Details | Significance
|-----------|------|-------|--------------|---------------|----------------|
| Rosenbloom 1990 | 37 | 69 cases of DKA and CE | Risk factors for CE | CE appeared to be associated with younger age and new onset T1DM | Statistical significance not reported for most comparisons
| Edge 1999 | 38 | Deaths caused by diabetes in patients under the age of 20 between 1990 and 1996 in the UK from Office of National Statistics (England and Wales) | Death | 116 deaths notified and 83 were caused by diabetes. The standardised mortality ratio was 2.3 (95%CI 1.9 to 2.9), highest for the age group 1-4 at 9.2 (95%CI 5.4 to 14.7). DKA or hyperglycaemia was implicated in 83% (69/83) deaths in patients under the age of 20 between 1990 and 1996 in the UK. CE causes 69% (25/36) of deaths in children with diabetes under the age of 12. | Cross sectional
| Bello 1990 | 39 | Retrospective case note review of 1006 episodes of DKA. The group included 11 cases of cerebral oedema. | Data for the 11 cases of cerebral oedema were compared with 20 randomly chosen cases of DKA without cerebral oedema | Overall frequency of cerebral oedema was 0.7% of all DKA cases. Incidence in new onset T1D was 3.3%, compared with known diabetes (0.23%, p<0.05). CE associated with: Younger age (6.6 years vs 13.8 years, p<0.05) Longer duration of symptoms (49 hours vs 16 hours, p<0.001) New T1D (0 patients vs 1 patient, p<0.01) | Case series
<p>| Duck 1988 | 40 | 32 cases of DKA and brain | Predictors of brain herniation | Overall rate of third administration was inversely | Historical controls used for compared | Case series | III-3 |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Participants</th>
<th>Methods</th>
<th>Results</th>
<th>Study Design</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harris 1990</td>
<td>41</td>
<td>Group 1: 119 patients aged 13 months to 30 years, 219 episodes of DKA (retrospective review) Group 2: 40 patients aged 1.5 to 20 years studied prospectively USA</td>
<td>Complication rate, change in serum sodium as serum glucose declined</td>
<td>Group 1: complications were more likely to occur among patients with a failure of the concentration of sodium to rise as glucose declined (P&lt;0.01) Group 2: Serum sodium concentration rose in 55/58 (95%) of episodes as glucose declined. No patient had a major complication</td>
<td>Cohort study</td>
<td>III-3</td>
</tr>
<tr>
<td>Hale 1997</td>
<td>42</td>
<td>4 children with T1DM aged &lt; 5 years with DKA leading to CE compared to 10 aged matched controls with DKS but no CE USA</td>
<td>Children with CE vs. children with no CE: Weight, serum glucose, minimum serum sodium, minimum serum osmolarity, age, body surface area, initial serum sodium, initial serum bicarbonate</td>
<td>Weight: 13.0 ± 3.7 vs. 9.1 ± 2.2kg (p&lt;0.05) Serum glucose: 26.3 ± 3.3 vs. 43.1 ± 19.7 mmol/L (p&lt;0.05) Minimum serum sodium: 128.8 ± 4.4 vs.142.2 ± 8.9 (p &lt; 0.02) Minimum serum osmolarity: 265.5 ± 10 vs. 296.7 ± 15.3 (p &lt; 0.01) No difference in initial age, body surface area, serum sodium, serum bicarbonate values</td>
<td>Case control</td>
<td>IV</td>
</tr>
<tr>
<td>Durr 1992</td>
<td>43</td>
<td>7 patients with uncontrolled T1DM</td>
<td>Correlates of CE (glucose, sodium, bicarbonate, vasopressin, haematocrit)</td>
<td>6/7 had evidence of CE on brain CT scan. Initial CE correlated with BGL and inversely with bicarbonate, but not with other variables The change in calculated effective plasma osmolality predicted the progression of CE during therapy (using regression analysis)</td>
<td>Case series</td>
<td>IV</td>
</tr>
<tr>
<td>Bureau 1980</td>
<td>44</td>
<td>8 dogs with Bicarbonate infusion</td>
<td>Delivery of oxygen to Bicarbonate therapy in DKA</td>
<td>Not a human study however</td>
<td>Case control</td>
<td>III-2</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Age</td>
<td>Setting</td>
<td>Intervention</td>
<td>Outcome</td>
<td>Study Design</td>
</tr>
<tr>
<td>-------</td>
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</tr>
<tr>
<td>Mahoney 1999</td>
<td>45</td>
<td>153 children admitted for one or more episodes of DKA over 12 years</td>
<td>Age &lt; 19 years</td>
<td>USA</td>
<td>Frequency and predictors of brain herniation</td>
<td>9 cases of brain herniation; Severity of acidosis, hypercapnoea and rate of initial fluid administration were risk factors. None of the children with pH &gt; 7.1 and PCO2 &gt; 20 mm Hg had brain herniation. In 119 patients with pH &lt; 7.1 or &lt; 20 mm Hg, 0/32 receiving less than 25 mL/kg, 1/42 receiving 25-50 mL/kg, and 8/40 receiving more than 50 mL/kg of IV fluid during the first 4 hours of therapy sustained brain herniation (p&lt;0.001 for &lt; 50mL/kg vs &gt; 50mL/kg). Decline in serum glucose concentration between admission and onset of brain herniation was not a significant predictor of CE (NS).</td>
</tr>
<tr>
<td>Mel 1995</td>
<td>46</td>
<td>Children with DKA and CE, age range 1 to 15 years, 1972 to 1992</td>
<td>Victoria, Australia</td>
<td>Rapid correction of dehydration (over 6 hours) with fluid isotonic for sodium vs. dehydration over 24h using half normal saline.</td>
<td>CE</td>
<td>CE incidence: 0.19% (6/3134) vs. 0.18% (6/3373)</td>
</tr>
<tr>
<td>Monroe 1997</td>
<td>47</td>
<td>Children admitted with DKA during an 18-month period (n = 79)</td>
<td>USA</td>
<td>Hospital and ICU length of stay, need for ICU admission</td>
<td>Pediatric risk of mortality (PRISM) scores were significantly correlated with length of stay</td>
<td>Retrospective case series</td>
</tr>
<tr>
<td>Bonadio 1988</td>
<td>48</td>
<td>63 pediatric emergency department visits for DKA</td>
<td>USA</td>
<td>Predictors of need for admission for management of DKA (compared with outpatient management)</td>
<td>27 patients had serum pH &lt; 7.20 or bicarbonate &lt; 10 mmol/L at admission, 25 (92%) had persistence of metabolic acidosis after three hours of outpatient therapy and were hospitalized. 36 patients had serum pH ≥ 7.20 or bicarbonate concentration ≥ 10 mmol/L (at admission, 34 (94%) had</td>
<td>Case series</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Sample Size / Description</td>
<td>Intervention</td>
<td>Outcomes</td>
<td>Study Design</td>
<td></td>
</tr>
<tr>
<td>-------</td>
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<td>--------------</td>
<td></td>
</tr>
<tr>
<td>Mackenzie 1989</td>
<td>102 children with acute gastroenteritis</td>
<td>Resolution of metabolic acidosis within three hours of initiating outpatient therapy and were discharged home. The relapse rate in each group was similar.</td>
<td>Accuracy of clinical assessment of dehydration, as judged by subsequent weight recovery in hospital</td>
<td>Degree of dehydration was overestimated by a mean of 3.2%, leading to unnecessary hospital admissions and overtreatment with intravenous fluid.</td>
<td>Interrupted time series</td>
<td></td>
</tr>
<tr>
<td>Adrogue 1982</td>
<td>53 Adults with DKA without extreme volume deficit</td>
<td>Group 1: (n=12) normal saline infused at ~14 mL/kg per hour in the initial 4 hours ~7 mL/kg per hour) during subsequent 4 hours. Group 2 (n=11), normal saline was infused at half the rates of Group 1</td>
<td>Plasma bicarbonate increment at 2, 4, 8, 16, and 24 hours after admission</td>
<td>Statistically significantly greater increment in bicarbonate level from admission at 4 hours in Group 1 vs Group 2 (3.7 vs 0.7 mmol/L) and at 24 hours Group 1 vs Group 2 (13.2 vs 8.4 mmol/L). Results suggest that slower fluid deficit correction with an isotonic solution results in earlier reversal of acidosis.</td>
<td>Controlled trial</td>
<td></td>
</tr>
<tr>
<td>Winter 1979</td>
<td>Case report 9 year old boy</td>
<td>Potassium replacement during treatment of DKA using potassium phosphate salt. Despite resolution of DKA he developed hypocalcaemia, hypomagnesaemia and hyperphosphataemia.</td>
<td>The phosphate load in potassium phosphate may cause low calcium and magnesium</td>
<td>Case report</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zipf 1979</td>
<td>9 children aged 9-17</td>
<td>Potassium phosphate infusion (20-40 meq per litre of fluid)</td>
<td>Adverse events</td>
<td></td>
<td>Case series</td>
<td></td>
</tr>
<tr>
<td>Gibby 1978</td>
<td>21 adults with DKA</td>
<td>11 treated with IV phosphate in doses (mean 118 mmol; range 83-320 mmol) to maintain normal plasma phosphate; 10 untreated controls</td>
<td>Red-cell 2,3-diphosphoglycerate (DPG) concentration; tissue oxygenation</td>
<td>Significantly lower red-cell 2,3-DPG concentrations were found between 2 and 6 days after admission in controls vs treated patients; no difference in tissue oxygenation was found between groups.</td>
<td>Cohort study</td>
<td></td>
</tr>
<tr>
<td>Wilson 1982</td>
<td>44 patients with DKA (39/44 IDDM, five patients are newly diagnosed) Mean age 26.8 ± 11.6 years (range</td>
<td>A: No phosphate replacement</td>
<td>Length of time in DKA Total insulin dose required to treat DKA DKA was considered corrected when the pH was &gt; 7.3, bicarbonate &gt; 15 mEq/L and serum</td>
<td>No significant difference seen between groups of admission biochemical data. Serum phosphate is slightly different at outset in the patients treated with sodium phosphate compared to</td>
<td>Randomisation: Blinding: RCT Not stated</td>
<td></td>
</tr>
<tr>
<td>Study (Year)</td>
<td>No.</td>
<td>Type</td>
<td>Intervention Details</td>
<td>Outcomes</td>
<td>Follow-up Comments</td>
<td></td>
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<tr>
<td>Becker 1983</td>
<td>58</td>
<td>35</td>
<td>IV potassium replacement as phosphate (4.7 to 28.5 mg/kg, N = 13) or chloride (N = 13), or no potassium replacement other than normal diet (N = 9)</td>
<td>Serum calcium and phosphate; Phosphate excretion</td>
<td>Significantly lower serum phosphorus concentrations at 24 and 36 hours occurred in patients treated with phosphate, significantly more phosphorus was and excreted during the first 12 hours of the study than either of the other two groups of patients. The use of phosphorus</td>
<td>Cohort study III-2</td>
</tr>
</tbody>
</table>

Diagnosis of DKA: blood pH < 7.25, plasma glucose > 250 mg/dL, bicarbonate level < 14 mEq/L, serum ketones positive at a dilution > 1:2

ketones were negative.

untreated controls, but this difference is not significant. At 4 hours there was no significant difference in the serum phosphate between the intervention groups. At 8 hours the serum phosphate level was significantly higher in group B treated with 1 dose of 15 mmol phosphate replacement therapy at 4 hours, compared to no phosphate treatment. The serum phosphate level remained raised in the group but raise was not significantly for 16 and 24 hours. At 8, 16 and 24 hours serum phosphate level was significantly higher in group C, treated with 3 dose of 15 mmol phosphate replacement therapy at 2, 6 and 10 hours, compared to no phosphate treatment. Time course to development of DKA did not correlate with any admission biochemical data. The rate of correction of arterial blood pH and the mean duration of time required to correct the DKA was no different in any of the three groups. No difference among the three groups in the total amount of insulin necessary to correct the DKA. No clinical benefit of phosphate therapy found.
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No.</th>
<th>Characteristics</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soler 1972</td>
<td>59</td>
<td>25 patients, age range 13 to 84 years, severe DKA (pH &lt; 7.2, bicarbonate &lt; 10 mEq/L)</td>
<td>All patients treated with saline (8 saline alone; 11 also received bicarbonate (up to 250 meq), 7 received bicarbonate (&gt; 250 meq))</td>
<td>Hypokalemia and hyperkalemia diagnosis; potassium requirements during first 24 hours of treatment for DKA</td>
<td>3/25 patients had hypokalemia (&lt; 3.5 mEq/L) and 5/25 hyperkalemia (&gt; 5.5 mEq/L) at diagnosis. Potassium requirement was significantly greater in those receiving higher dose of bicarbonate.</td>
<td>Case series IV</td>
</tr>
<tr>
<td>Hale 1984</td>
<td>60</td>
<td>32 patients with DKA, age range 15 to 80 years, all treated with normal saline and IM insulin</td>
<td>16 treated with 150 mmol bicarbonate; 16 treated with normal saline alone</td>
<td>Rate of fall of BGL; change in biochemical parameters</td>
<td>No difference in rate of fall of BGL; significantly slower fall in blood lactate, lactate: pyruvate ratio, and total ketones in patients treated with bicarbonate compared with saline group.</td>
<td>RCT II</td>
</tr>
<tr>
<td>Morris 1986</td>
<td>61</td>
<td>21 adults with severe DKA (pH 6.9–7.14)</td>
<td>Mean age: Bicarbonate: 34 ± 5 years, Controls: 28 ± 4. USA</td>
<td>Intravenous bicarbonate infused over 30 min: 133.8 mEq for arterial pH of 6.9–6.99, or 89.2 mEq for arterial pH 7.1–7.14), Repeated every 2 hours until pH was 7.15 or more.</td>
<td>Comparison of patients before and after bicarbonate therapy. At randomisation there was no difference in the biochemical profile between the two groups. No significant differences were seen in the rate of change of pH, ketone bodies, bicarbonate levels, and plasma lactate levels. No significant differences were noted in the recovery time in the two groups in terms of the number of hours required for glucose levels to reach 250 mg/dL (4.9 ± 1.3 h vs. 4.2 ± 1.0 h in the bicarbonate vs. control group respectively) and for bicarbonate to reach 15 mEq/L (21 ± 4.3 vs. 21 ± 4.0 h, respectively). No statistically significant differences in CSF glucose, bicarbonate, pH, lactate and ketones at three time points (0, 6–8, 10–12 h). There was no effect of mental status. Initially there appeared to be a greater decline in BGLs.</td>
<td>RCT II</td>
</tr>
<tr>
<td>Study</td>
<td>n</td>
<td>Participants</td>
<td>Intervention</td>
<td>Outcomes</td>
<td>Randomisation: Method of randomisation not described</td>
<td>Summarised Findings</td>
</tr>
<tr>
<td>------------------</td>
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<td>------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Kitabchi 1976</td>
<td>63</td>
<td>48 patients with DKA</td>
<td>Treatment with low-dose IM insulin vs high dose SC or IV insulin</td>
<td>Rates of hypoglycaemia and hypokalaemia</td>
<td>RCT II</td>
<td>Lower incidence of hypokalaemia in low dose group; higher rate of hypoglycaemia in high dose group; no difference in rate of drop of BGL or change in other biochemical parameters (NS)</td>
</tr>
<tr>
<td>Edwards 1977</td>
<td>64</td>
<td>22 children with DKA, aged 21 months to 16 years USA</td>
<td>Treatment with insulin: low-dose IV insulin infusion (0.1 U/kg/hr, n=11) or high-dose intermittent subcutaneous injections (1 to 2.2 U/kg/hr, n=11)</td>
<td>Rate of correction of ketoacidosis and change in biochemical parameters</td>
<td>RCT III-2</td>
<td>There were no statistically significant differences in rate of correction of ketoacidosis, rate of reduction of plasma glucose, or decline in plasma osmolality. The incidence and severity of hypokalaemia were higher in patients receiving SC insulin. Statistical significance not reported for comparison of hypokalaemia between groups</td>
</tr>
<tr>
<td>Drop 1977</td>
<td>65</td>
<td>14 children with DKA, aged 5 to 17 years, with 18 episodes of DKA</td>
<td>Treatment with 0.1 U/kg/hr IV insulin infusion vs SC insulin</td>
<td>Rate of clearance of ketones and fall in BGL</td>
<td>RCT II</td>
<td>Serum ketones persisted longer in the IV group; “both regimens of insulin administration are equally effective”</td>
</tr>
</tbody>
</table>

Appendix 2: Evidence Tables
Australian Clinical Practice Guidelines: Type 1 Diabetes in Children and Adolescents
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Methodological Characteristics</th>
<th>Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baum 1975</td>
<td>17</td>
<td>17 children (mean age 7.4 years) with newly diagnosed T1DM and DKA; 3 children with established T1DM and DKA</td>
<td>Treatment with “low-dose” IM insulin (mean dose 0.29 U/kg)</td>
<td>IM insulin resulted in gradual fall in blood glucose; 2-hour plasma insulin values were within the range which in adults has been associated with a maximum fall in blood glucose concentration. No adverse effects</td>
<td>No control group</td>
<td>Cohort study (two single arms)</td>
</tr>
<tr>
<td>Burghen 1980</td>
<td>67.</td>
<td>32 children with DKA (range 6.2 to 15.8 years)</td>
<td>Low-dose (0.1 U/kg/h) vs high-dose (1.0 U/kg/h) insulin</td>
<td>Time to correction of hyperglycaemia, ketosis</td>
<td>Reduction in glucose was slower in low-dose group (P &lt; 0.01) Reduction in ketones, bicarbonate, cortisol, and glucagon was similar in both groups (NS) Hypokalemia (K &lt; 3.4 meq/L) occurred in 3/16 low-dose and 10/16 high-dose patients</td>
<td>Randomisation: Method of randomisation not stated</td>
</tr>
<tr>
<td>Soler 1975</td>
<td>69.</td>
<td>51 patients in severe DKA</td>
<td>IM insulin (n=18); IV infusion (n=18); IV bolus insulin (n=25)</td>
<td>Time to correction of hyperglycaemia and acidosis</td>
<td>Slower fall in blood glucose with IM regimen</td>
<td>Not randomised</td>
</tr>
<tr>
<td>Franklin 1982</td>
<td>70.</td>
<td>Single case of CE and DKA</td>
<td>Mannitol</td>
<td>Resolution of CE and ophthalmoplegia after mannitol therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Curtis 2001</td>
<td>71.</td>
<td>Single case of CE and DKA</td>
<td>Adolescent female with life-threatening DKA-related CE who responded to combination of mannitol and hypertonic saline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linares 1996</td>
<td>73.</td>
<td>Children admitted with DKA over a 4 year period: 132 patient visits in 45 patients (newly diagnosed cases excluded) Mild DKA (pH ≥ 7.20, bicarbonate</td>
<td>Time to correction of acidosis; prediction of patients suitable for outpatient management</td>
<td>Acidosis was corrected within 6 hours in 33/72 (46%) of mild DKA episodes vs 3/80 (5%) of moderate-severe DKA (P &lt; 0.0001) Acidosis was corrected within 6 hours in 69% of mild and 11% of moderate-severe DKA (P &lt; 0.0001)</td>
<td>Authors concluded that initial laboratory values can help predict patients who may be considered for outpatient management (mild DKA), but the study design cannot address this adequately because of retrospective design</td>
<td>Case series</td>
</tr>
</tbody>
</table>
### Appendix 2: Evidence Tables

<table>
<thead>
<tr>
<th>Ref No</th>
<th>Technical Reports/Consensus Statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>72</td>
<td>International Society for Pediatric and Adolescent Diabetes: ISPAD Consensus Guidelines for the Management of Type 1 Diabetes Mellitus in Children and Adolescents. Zeist, Netherlands, Medforum, 2000</td>
</tr>
</tbody>
</table>

### 9.2 Technical Reports and Consensus Statements used to formulate the recommendations and principles of clinical practice.

### Chapter 10: Surgery and Fasting

#### 10.1 Management of surgery and fasting in children and adolescents with diabetes

As only one study was found the majority of the suggested protocol in the Surgery and Fasting chapter is based on consensus.

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref No</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Comments</th>
<th>Design</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaufman</td>
<td>3</td>
<td>19 peri operative children and adolescents with type 1 diabetes mellitus</td>
<td>Intravenous insulin infusion (n=9, gp 1) versus subcutaneous insulin (n=10, gp 2)</td>
<td>Blood glucose levels</td>
<td>The mean bedside BGL were higher 1 h prior to surgery and during the intraoperative period (p &lt; 0.05) in those receiving sc insulin. In the postoperative period, BGL were higher at multiple times for up to 3 days in those treated with sc compared to IV.</td>
<td>On the day of surgery and during postoperative days 1 and 2, patients in group 1 received a greater insulin dosage than group 2 subjects (p &lt; 0.025). In group 1, insulin dosage was increased 23% and 15% over baseline for postoperative days 1 and 2, respectively, then, by day 3, was decreased back toward the baseline. Infusion give better BGL control than sc. To achieve glycaemic control, insulin dosage needs to be increased on the day of surgery and for approximately 2 postoperative days</td>
<td>Retrospective case series</td>
<td>III-3</td>
</tr>
</tbody>
</table>
Chapter 11: Sick Day Management

Insulin adjustment during “sick days”/intercurrent illnesses in children and adolescents with Type 1 diabetes

No studies were identified. One review article was found, others included advice, personal practice. Therefore the regimen suggested in the Sick Day Management chapter is based on current consensus guidelines.

### 11.1 Management of severe hypoglycaemia: to treat with intravenous glucose or intramuscular/intravenous glucagon

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref No</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Comments</th>
<th>Design</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patrick 1990</td>
<td>10</td>
<td>29 adult patients attending an accident and emergency department in hypoglycaemic coma</td>
<td>Randomized to treatment with either intravenous dextrose (25g); n=14 or intramuscular glucagon (1mg); n=15, administered into the right thigh</td>
<td>Recovery after hypoglycaemia</td>
<td>Normal conscious level slower after glucagon than dextrose (9.0 (range 5-30) vs 3.0 (range 2-15) min, p &lt;0.01)</td>
<td>IM glucagon is valuable in severe hypoglycaemia outside hospital. The slightly slower and less predictable recovery may make it a less attractive option than IV dextrose in the emergency department. Should be balanced against the advantages of ease of administration and a lower incidence of serious adverse effects</td>
<td>RCT II</td>
<td>II</td>
</tr>
<tr>
<td>Collier 1987</td>
<td>11</td>
<td>52 adult insulin-treated patients attending an emergency department with severe hypoglycaemia</td>
<td>Intravenous glucagon (1 mg); n=25 was compared with intravenous dextrose (25g); n=24</td>
<td>Recovery after hypoglycaemia</td>
<td>Intravenous glucagon and dextrose were effective in the treatment of hypoglycaemic coma. There was a difference in the glycaemic profile after intravenous glucagon compared with intravenous dextrose. Recovery of a normal level of consciousness after glucagon was slower than after dextrose (6.5 (range 2-16) vs. 4.0 min (range 1-15), respectively; P &lt;0.001). Although IV glucagon is an option, IM glucose is faster</td>
<td>Randomisation: Method not stated Consciousness assessed throughout the study by the same observer Losses to follow-up: 1 patient with coexisting Addison’s disease excluded from analysis (received both glucagon and dextrose but only regained normal consciousness after receiving hydrocortisone)</td>
<td>RCT II</td>
<td>II</td>
</tr>
</tbody>
</table>
11.2 Consensus Statements used to formulate the recommendations and principles of clinical practice.

<table>
<thead>
<tr>
<th>Ref No</th>
<th>Technical Reports/Consensus Statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>Australasian Paediatric Endocrine Group: APEG Handbook on Childhood and Adolescent Diabetes. Sydney, Australasian Paediatric Endocrine Group, 1996</td>
</tr>
<tr>
<td>17</td>
<td>International Society for Pediatric and Adolescent Diabetes: ISPAD Consensus Guidelines for the Management of Type 1 Diabetes Mellitus in Children and Adolescents. Zeist, Netherlands, Medforum, 2000</td>
</tr>
</tbody>
</table>

Chapter 12: Hypoglycaemia

12.1 Effects of intensive diabetes management on the incidence of hypoglycaemia.

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref No</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Comments</th>
<th>Design</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCCT</td>
<td>1994</td>
<td>23</td>
<td>Adolescent subgroup of (n=95)</td>
<td>Intensive insulin therapy (by multiple daily)</td>
<td>Development of diabetes complications</td>
<td>Retinopathy: Intensive therapy decreased the</td>
<td>Landmark study. See other DCCT references</td>
<td>RCT</td>
</tr>
</tbody>
</table>

1 patient had already received subcutaneous glucagon administered at home by a relative before arriving at the emergency dept.
<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Design</th>
<th>Outcome Measures</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DCCT trial. Age 13-17 years</strong>&lt;br&gt;125 adolescents with no retinopathy and 70 with mild retinopathy&lt;br&gt;Mean follow up 7.4 years (for adolescents)</td>
<td>DCCT trial. Age 13-17 years&lt;br&gt;125 adolescents with no retinopathy and 70 with mild retinopathy&lt;br&gt;Mean follow up 7.4 years (for adolescents)</td>
<td><strong>Episodes of hypoglycaemia</strong>&lt;br&gt;HbA1c</td>
<td><strong>risk of retinopathy by 53% (CI 1-78%, p=0.048) (in those with no retinopathy) and 70% (CI 25-88%, p=0.010) (in those with mild retinopathy)</strong>&lt;br&gt;Nephropathy: Intensive therapy group had 10% reduction in microalbuminuria (95% CI 4-22%); p=0.049 in those with no retinopathy; and by 55% (95% CI 3% to 9%); p=0.042 in those with mild retinopathy&lt;br&gt;Diabetic ketoacidosis: RR 0.2 (95% CI 0.32-1.23)&lt;br&gt;Severe hypoglycaemia: RR 2.96 (95% CI 1.90-4.62)&lt;br&gt;Hypoglycaemia resulting in coma or seizure: RR 2.93 (95% CI 1.75-4.90)&lt;br&gt;Overweight: RR 2.11 (95% CI 1.31-3.40)&lt;br&gt;HbA1c (%±SE): 8.06±0.13 vs 9.76±0.12 (reduction of 1.7% ±SE 0.18)</td>
<td><strong>Blinding:</strong>&lt;br&gt;Standard therapy group blinded to HbA1c results; intensive therapy group could not be blinded to HbA1c as they were using it as a management tool;&lt;br&gt;Research group blinded to the effects of the two treatment regimens;&lt;br&gt;Investigators and patients unaware of outcome data unless predetermined ‘alert’ criteria (e.g. development of retinopathy) were reached;&lt;br&gt;Retinopathy assessed by operators who were unaware of treatment group assignment&lt;br&gt;Loses to follow-up: No patients voluntarily withdrew; 2 patients died; 2 patients assigned to inactive status for some time&lt;br&gt; &gt;95% of scheduled examinations were completed; overall time spent in assigned treatment was 95%;&lt;br&gt;Independent data monitoring committee determined that study results warranted terminating trial after mean follow-up of 6.5 years (overall)</td>
</tr>
<tr>
<td>Handelsman 2001</td>
<td>26</td>
<td>Audit of 1,190 children with T1D. Case attainment based on Diabetes Register was 67% of children in NSW and ACT. Compared urban with rural children.</td>
<td>Severe hypoglycaemia</td>
<td>Median HbA1c 8.2% (IQ range 7.6-9.1%) in both urban and rural group.</td>
</tr>
<tr>
<td>Davis 1998</td>
<td>27</td>
<td>A large population based sample of T1D children and adolescents. Rates of severe (coma, convulsion) and moderate (requiring assistance for treatment) hypoglycaemia were studied prospectively over a four year period. 709 patients were studied yielding 2027 patient years (mean (SD) age: 12.3 (4.4); range 0-18 years, duration IDDM: 4.9 (3.8) years). Details of hypoglycaemia were recorded at clinic visits every three months when glycated haemoglobin (HbA1c) was also measured.</td>
<td>Incidence of severe hypoglycaemia was 7.8 and moderate was 15.4 episodes/100 patient years. Over the four years mean (SD) clinic HbA1c steadily fell from 10.2 (1.6)% in 1992 to 8.8 (1.5)% in 1995 (p&lt;0.01). In parallel with this there was an increase in the rate of hypoglycaemia, especially in the fourth year of the study, when severe hypoglycaemia increased from 4.8 to 15.6 episodes/100 patient years. This increase was particularly marked in younger children (&lt; 6 years) in whom severe hypoglycaemia increased from 14.9 to 42.1 episodes/100 patient years in 1995. Attempts to achieve improved metabolic control must be accompanied by efforts to minimise the effects of significant hypoglycaemia, particularly in the younger age group.</td>
<td>Australian study (Perth)</td>
</tr>
<tr>
<td>DCCT</td>
<td>29</td>
<td>1441 patients with Intensive insulin therapy (by Development of diabetes Retinopathy: intensive therapy</td>
<td>Landmark study.</td>
<td>RCT</td>
</tr>
<tr>
<td>1993</td>
<td>TID aged 13-39 years. 726 with no retinopathy at baseline (primary intervention group) and 715 with mild retinopathy (secondary intervention group)</td>
<td>complications</td>
<td>reduced the risk of retinopathy by 76% (95% CI 62-85) in patients with no retinopathy at baseline (p&lt;0.002), and by 54% (95% CI 39-66) in those with mild retinopathy at baseline (p&lt;0.001); combined 63% (95% CI 52-71), p&lt;0.002. Neuropathy: At 5 years, intensive therapy reduced incidence of clinical neuropathy by 69%; 95% CI 24-87 (3% in intensively treated group vs 10% in conventionally treated group) p=0.006 in patients with no retinopathy at baseline; and by 57% (95% CI 29-73); p&lt;0.002 in those with mild retinopathy at baseline; combined 60% (95% CI 38-74), p&lt;0.002 Neuropathy: Intensive therapy reduced risk of microalbuminuria by 39% (95% CI 21-52) and albuminuria by 54% (95% CI 19-74); Intensive therapy reduced the mean adjusted risk of microalbuminuria by 34% (p=0.04) in in patients with no retinopathy at baseline and by 43% in those with mild retinopathy at baseline (p&lt;0.001) Adverse events: Incidence of hypoglycaemia increase 2-3 fold on intensive therapy (19 versus 62 hypoglycaemic episodes per 100 patient years, p&lt;0.001).</td>
<td>Rigorous multicentre study supervised by NIH, USA See other DCCT references Follow up period of 6.5 years (trial terminated by independent monitoring committee) Blinding: Standard therapy group blinded to HbA1c results; intensive therapy group could not be blinded to Hba1c because they were using it as a management tool Research group blinded to effects of the two treatment regimens Losses to follow-up: 99% of patients completed study; &gt;95% of all scheduled examinations completed; 11 patients died; 32 patients assigned to inactive status for some time during trial due to unavailability or investigator’s decision that continuation of treatment would be hazardous Compliance: Average time spent receiving assigned treatment = 97%, including 95 women assigned to conventional therapy who received intensive therapy during pregnancy or while planning a pregnancy</td>
</tr>
</tbody>
</table>
### 12.2 Management of severe hypoglycaemia: to treat with intravenous glucose or intramuscular/intravenous glucagon?

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref No</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Comments</th>
<th>Design</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patrick</td>
<td>49</td>
<td>Adult patients attending an accident and emergency department in hypoglycaemic coma</td>
<td>Randomized to treatment with either intravenous dextrose (25g); n=14 or intramuscular glucagon (1mg); n=15, administered into the right thigh</td>
<td>Recovery after hypoglycaemia</td>
<td>Normal conscious level slower after glucagon than dextrose (9.0 (range 5-30) vs 3.0 (range 2-15) min, p &lt;0.01)</td>
<td>IM glucagon is valuable in severe hypoglycaemia outside hospital. The slightly slower and less predictable recovery may make it a less attractive option than IV dextrose in the emergency department. Should be balanced against the advantages of ease of administration and a lower incidence of serious adverse effects</td>
<td>RCT</td>
<td>II</td>
</tr>
<tr>
<td>Collier</td>
<td>50</td>
<td>Insulin-treated patients attending an emergency department with severe hypoglycaemia</td>
<td>Intravenous glucagon (1 mg); n=25 was compared with intravenous dextrose (25 g); n=24</td>
<td>Recovery after hypoglycaemia</td>
<td>Intravenous glucagon and dextrose were effective in the treatment of hypoglycaemic coma. There was a difference in the glycaemic profile after intravenous glucagon compared with intravenous dextrose. Recovery of a normal level of consciousness after glucagon was slower than after dextrose (6.5 (range 2-16) vs 4.0 min (range 1-15), respectively; P &lt;0.001). Although IV glucagon is an option, IM glucose is faster</td>
<td>Randomisation: Method not stated Consciousness assessed throughout the study by the same observer Losses to follow-up: 1 patient with coexisting Addison’s disease excluded from analysis (received both glucagon and dextrose but only regained normal consciousness after receiving hydrocortisone) 1 patient had already received subcutaneous glucagon administered at home by a relative before arriving at the emergency dept.</td>
<td>RCT</td>
<td>II</td>
</tr>
</tbody>
</table>

### 12.3 Effects of hypoglycaemia on cognitive function in children and adolescents with type 1 diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref No</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Comments</th>
<th>Design</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northam</td>
<td>6</td>
<td>Follow up study from Northam 98</td>
<td>None</td>
<td>WISC-III and subs tests of WISC-III used for IQ.</td>
<td>Six years after onset of diabetes, children with T1D</td>
<td>Subjects enrolled from Royal Children’s Hospital,</td>
<td>Comparative cohort study</td>
<td>III-2</td>
</tr>
<tr>
<td>Study</td>
<td>N</td>
<td>Patients</td>
<td>Controls</td>
<td>Details</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Hannonen 2003</td>
<td>7</td>
<td>21 children with T1D (age 5.5-11.8yrs) and 10 healthy controls</td>
<td>Divided into 3 groups: T1D and one episode of severe hypo (n=11), T1D with no hypo (n=10), Normal controls</td>
<td>WISC-R, NEPSY (dev. Neuropsych assessment)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rovet 1997</td>
<td>8</td>
<td>103 T1D (50 boys, 53 girls) Mean age 13.5 yrs +/-2.3 years</td>
<td>100 controls (50 boys, 50 girls) mean age 13.1 +/- 2.5 years</td>
<td>Attentional functioning (WISC-R and WAIS-R IQ)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Hannonen 2003**
- **Rovet 1997**

**Appendix 2: Evidence Tables**

**Australian Clinical Practice Guidelines: Type 1 Diabetes in Children and Adolescents**
<table>
<thead>
<tr>
<th>Study/Year</th>
<th>Sample Size</th>
<th>Sample Description</th>
<th>Follow up</th>
<th>Primary Outcome</th>
<th>Results</th>
<th>Study Design</th>
<th>Strengths/Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rovet 1999</td>
<td>9</td>
<td>16 Children With Type 1 Diabetes Mean Age 12.1 +/-2.6 Years (Range 9.4-17.7 Years) Mean age at diagnosis was 4.5 years +/- 3.9 years. mean HbA1c 8.4% (range 7.5-9.4) 9 had hypoglycaemic seizure Follow up at 1, 3, 7 years</td>
<td>Verbal IQ</td>
<td>At 7 years those with hypoglycaemic seizures more likely to have verbal IQ decline (67% vs 14%, p=0.05) Hypo seizure patients scored lower (p=0.01) There were no effects on full-scale IQ, performance IQ, supplementary spatial or achievement tests.</td>
<td>The study's strengths were its extended time frame and detailed testing 7 years after diagnosis. Limiting factors include small sample size, lack of longitudinally assessed controls, and possible bias within groups and recall inaccuracies of diabetes data management.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hershey 1999</td>
<td>10</td>
<td>Nondiabetic children (n = 16) and 25 children with type 1 diabetes Randomised at diagnosis to either intensive (IT) (n = 13) or conventional (CT) (n = 12) diabetes therapy</td>
<td>Episodes of severe hypoglycaemia were prospectively ascertained. All children were tested on memory tasks that have been closely linked to medial temporal functioning and on reaction time measures</td>
<td>IT had a threefold higher rate of severe hypoglycaemia than the CT group; and performed less accurately on a spatial memory task, performed more slowly (p=0.01), but not less accurately, on a pattern recognition task than did the CT group or control subjects. Larger studies needed, but extreme caution in imposing overly strict standards for glucose control in young patients with type 1 diabetes would be indicated because of the increased risk of hypoglycaemia associated with IT regimens.</td>
<td>Randomisation: Method of randomisation not stated Comparison with nondiabetic participants was not randomised</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Holmes 1985</td>
<td>39</td>
<td>41 children with T1D Divided in 4 groups depending upon age of onset and length of duration</td>
<td>WISC-R Verbal subtests</td>
<td>IQ scores lower in early onset and longer duration Reading and memory impairment in early onset groups</td>
<td>Cohort study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sansbury 1997</td>
<td>40</td>
<td>28 T1D children Age at onset Duration HbA1c</td>
<td>WISC-R Matching figures Behaviour checklist</td>
<td>Increased age assoc with decreased IQ score Inc duration assoc with lower matching figures score. Poor metabolic control assoc with lower vocab subtest scores.</td>
<td>Cohort study</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Appendix 2: Evidence Tables

#### Australian Clinical Practice Guidelines: Type 1 Diabetes in Children and Adolescents

#### 12.4 Consensus Statements used to formulate the recommendations and principles of clinical practice.

<table>
<thead>
<tr>
<th>Ref No</th>
<th>Technical Reports/Consensus Statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>International Society for Pediatric and Adolescent Diabetes: ISPAD Consensus Guidelines for the Management of Type 1 Diabetes Mellitus in Children and Adolescents. Zeist, Netherlands, Medforum, 2000</td>
</tr>
<tr>
<td>57</td>
<td>Australasian Paediatric Endocrine Group: APEG Handbook on Childhood and Adolescent Diabetes. Sydney, Australasian Paediatric Endocrine Group, 1996</td>
</tr>
</tbody>
</table>

#### Chapter 13: Psychosocial Aspects

#### 13.1 The incidence and risk factors for non-adherence with treatment regimens in children and adolescents with type 1 diabetes.

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref No/Year</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Comments</th>
<th>Design</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kovacs 1992 and 1996</td>
<td>16 and 41</td>
<td>88 youths, 8 to 13 years old at onset of IDDM, 83 were white (94%), 5 were black (6%)</td>
<td>None</td>
<td>Evaluated repeatedly during a 9-year follow-up period, on average, using a standardized psychiatric protocol. Levels of HbA1 were also assessed repeatedly. Psychiatric diagnoses were derived independently of HbA1 values</td>
<td>The cumulative risk for non-adherence over the 9 years was 0.4. Non-compliance tended to emerge in middle adolescence and was found to be protracted. Social competence, self-esteem, and aspects of family functioning at IDDM onset and initial psychiatric status did not predict non-compliance. However, non-compliance was associated with having major psychiatric disorder later in the course of IDDM. In univariate longitudinal analyses, the psychiatric diagnosis of non-compliance with medical treatment was significantly related to HbA1 level. There was a trend of an association between any major psychiatric disorder, as well as non-depressive disorder, and HbA1. Interaction terms between IDDM duration (or age) and psychiatric variables were significantly related to metabolic control. According to the final multivariate model of repeatedly assessed HbA1, non-compliance with medical treatment (irrespective of duration) and the interaction between non-depressive psychiatric disorder and IDDM duration contributed to worse metabolic control. During observation period 44 patients (50%) had one or more episode of psychiatric disorder and 35 (40%) received the diagnosis of non-compliance with medical treatment.</td>
<td>Sample derived from patients sequentially admitted to Pittsburgh 1978-1985. Approx 75% of suitable families were recruited. Those who declined did not differ significantly.</td>
<td>Longitudinal Observational study.</td>
<td>IV</td>
</tr>
<tr>
<td>Tubiana</td>
<td>27</td>
<td>165 French</td>
<td>A standardized scale (FACES III) was</td>
<td>More diabetic families than comparison families fell into</td>
<td></td>
<td>Cross-sectional</td>
<td>IV</td>
<td></td>
</tr>
</tbody>
</table>

Appendix 2: Evidence Tables
Australian Clinical Practice Guidelines: Type 1 Diabetes in Children and Adolescents
<table>
<thead>
<tr>
<th>Name</th>
<th>Year</th>
<th>Study Details</th>
<th>Methodology</th>
<th>Study Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruffi 1998</td>
<td></td>
<td>Used to determine if family cohesion and adaptability (i) differed in diabetic children's families, as compared to other families; (ii) were related to an adherence measure; or (iii) were related to metabolic control.</td>
<td>the categories of disengaged with low levels of cohesion, and rigid with low levels of adaptability. Scores of cohesion and adaptability were significantly and positively correlated with both children's and parents' adherence scores, but not with HbA1c levels. Children from rigidly disengaged families had a more hypoglycaemias and 6 times more ketoacidosis than the other diabetic children. Family adaptation significantly and positively correlated to parent's education level.</td>
<td>multcentre study</td>
</tr>
<tr>
<td>Frank 1996</td>
<td>28</td>
<td>Compared compliant with non compliant patients.</td>
<td>Compliant patients more likely to have tertiary education, fewer hospitalisations.</td>
<td>Retrospective medical record audit plus telephone interview</td>
</tr>
<tr>
<td>Ott 2000</td>
<td>30</td>
<td>Self-efficacy, Adherence, Personal responsibility, Parental responsibility</td>
<td>Self efficacy was the mediating variable for mastery experience.</td>
<td>Questionnaire</td>
</tr>
<tr>
<td>Hentinen 1992</td>
<td>31</td>
<td>Insulin treatment, Diet, Monitoring, Co-operation</td>
<td>Showed best adherence, Diet and monitoring are problem areas.</td>
<td>Cross sectional survey</td>
</tr>
<tr>
<td>Burroughs 1993</td>
<td>32</td>
<td>Predictors of compliance</td>
<td>Dietary compliance is best predictor of metabolic control.</td>
<td>Questionnaire</td>
</tr>
<tr>
<td>Kyngas 2000</td>
<td>33</td>
<td>Compliance</td>
<td>Compliance with insulin treatment 81%. Only 19% reported complete compliance with all aspects of diabetes management. Adherence was lowest for diet and home blood glucose monitoring. Names selected from Finnish Insurance Register.</td>
<td>Cross sectional</td>
</tr>
<tr>
<td>Littlefield 2000</td>
<td>34</td>
<td>Participants completed the Rosenberg</td>
<td>Adolescents reporting lower adherence tended to report.</td>
<td>Questionnaire</td>
</tr>
<tr>
<td>Year</td>
<td>Study</td>
<td>Patients</td>
<td>Methods</td>
<td>Findings</td>
</tr>
<tr>
<td>---------</td>
<td>------------------------------------------------------------------------</td>
<td>---------------------------------</td>
<td>-------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>1992</td>
<td>Jacobson 1987</td>
<td>57 children, Joslin Clinic, Boston</td>
<td>Psychological predictors of compliance</td>
<td>Adolescents (13-15yrs) less compliant than children (9-12yrs). Patients with higher self reported self esteem, and parent reported confidence, adjustment and social functioning were more adherent.</td>
</tr>
<tr>
<td>1992-90</td>
<td>Johnston 1992 and 1990</td>
<td>140 children with T1D and their mothers</td>
<td>Interviews 3 times over 2 week period</td>
<td>Older patients were less adherent and had worse HbA1c.</td>
</tr>
<tr>
<td>1997</td>
<td>Morris 1997</td>
<td>DARTS/MEMO Collaboration</td>
<td>Associations between glycaemic control (HbA1c), episodes of diabetic ketoacidosis, and all hospital admissions for acute complications and the adherence index were modelled.</td>
<td>Insulin was prescribed at 48IU/day and mean insulin collected from pharmacies was 58IU/day. However, 25 (28%) of the 89 patients obtained less insulin than their prescribed dose (mean deficit 115 (68; range 9-246) insulin days/annum).</td>
</tr>
</tbody>
</table>

**Self-Esteem Scale**, the Children's Depression Inventory, an assessment of the frequency of binging in the past 3 mo, and parallel forms of an adherence scale and a self-efficacy scale that were developed for use in this study.

lower self-esteem ($r = 0.45$, $P < 0.001$) and self-efficacy ($r = 0.57$, $P < 0.001$), more depressive symptoms ($r = -0.50$, $P < 0.001$), more binging ($r = -0.36$, $P < 0.001$), and had higher HbA1c ($r = -0.24$, $P < 0.001$) than those with higher adherence scores.

Together, the psychological variables accounted for 50% of the variance in adherence.

There was no sex difference in reported binging, but, as expected, adolescent females reported less adherence overall ($F[7,184] = 2.5$, $P = 0.018$).

**Adherence in adolescents with insulin-dependent diabetes mellitus is associated with behavioural and psychological variables.**
### Appendix 2: Evidence Tables

**Australian Clinical Practice Guidelines: Type 1 Diabetes in Children and Adolescents**

<table>
<thead>
<tr>
<th>Wysocki</th>
<th>1996</th>
<th>43</th>
<th>100 T1D youths</th>
<th>Hospital pediatric or young-adult diabetes clinic in 1993 and 1994 (mean age 16 (SD 7) years, diabetes duration 8 (4) years, and glycosylated haemoglobin (HbA1c) 8.4 (1.9)%)</th>
<th>with insulin therapy.</th>
<th>Scottish study</th>
<th>Scottish study</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldston</td>
<td>1997</td>
<td>45</td>
<td>91 adolescents attending diabetes outpatient clinic appointments</td>
<td>Semistructured and structured interview instruments and self-report questionnaires were used to determine history of suicidal thoughts and behaviour, serious non-compliance with the</td>
<td>The rate of suicidal ideation among the diabetic adolescents was higher than expected, but the rate of suicide attempts was comparable with that reported for the general population. Suicidal thoughts were strongly associated with serious non-compliance with the medical regimen. Duration of IDDM and psychiatric diagnosis were related to both suicidal ideation within the previous year and lifetime suicidal ideation. Diagnosable psychiatric disorder and not living in a two-parent home were related to non-compliance with medical treatment.</td>
<td>Semistructured and structured interview instruments and self-report questionnaires</td>
<td>Semistructured and structured interview instruments and self-report questionnaires</td>
<td>IV</td>
</tr>
</tbody>
</table>

**Scottish study**

**IV**
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Sample Size</th>
<th>Age</th>
<th>Type of Eating Disorder</th>
<th>Methodology</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rodin 1991</td>
<td>46</td>
<td>103 Female T1D patients attending diabetes clinic in Toronto, Canada</td>
<td>Mean age 15.1 years, Mean duration of T1D 6.4 years</td>
<td>Incidence of anorexia nervosa 1%, Incidence of bulimia nervosa 12%, Mean age of eating disorder patients 16.2 years</td>
<td>Questionnaire survey, HbA1c level, Clinical information from hospital notes</td>
<td>12% reported intentional insulin under treatment as a method of weight control, Incidence of anorexia nervosa 1%, Incidence of bulimia nervosa 12%, Mean age of eating disorder patients 16.2 years. Those with eating disorders were less likely to follow food plan or perform blood glucose monitoring. Mean HbA1c in eating disorder group was significantly higher than those without eating disorders (10% compared with 8.9%, p&lt;0.02).</td>
</tr>
<tr>
<td>Peveler 1992</td>
<td>47</td>
<td>A cross-sectional survey of eating habits and attitudes conducted in 76 adolescents with IDDM, and age- and sex-matched non-diabetic control subjects</td>
<td></td>
<td>Adolescent girls with IDDM were heavier than non-diabetic female control subjects and were dieting more intensively to control their shape and weight. However, clinical eating disorders were no more common among adolescent girls with IDDM than among non-diabetic control subjects. Nine percent of the IDDM girls met diagnostic criteria for an operational version of 'Eating disorder not otherwise specified.' Fifteen percent had omitted or reduced their dose of insulin to influence their shape and weight. Eating disorder features and insulin misuse for shape and weight control were not found in IDDM or non-diabetic boys, and these two groups did not differ in their body weight.</td>
<td>Assessed by standardized research interview adapted for use with patients with diabetes (EDE), Glycaemic control was assessed by GHb assay</td>
<td>High incidence of insulin omission in girls.</td>
</tr>
<tr>
<td>Ry dall 1997</td>
<td>48</td>
<td>91 young women with IDDM mean age 15+/2 years</td>
<td>Studied at base line and 5 yrs later</td>
<td>At base line, 26 of 91 young women (29 percent) had highly or moderately disordered eating behaviour, which persisted in 16 (18 percent) and improved in 10 (11 percent). Of the 65 women with normal eating behaviour at base</td>
<td>Prevalence and persistence of disordered eating behaviour (on the basis of self-reported eating and weight-loss practices, including the intentional omission or underdosing of insulin to control weight) and the</td>
<td>High incidence of intentional insulin omission to control.</td>
</tr>
</tbody>
</table>
and the duration of diabetes was 7±4 years.

association of such eating disorders with metabolic control, diabetic retinopathy, and urinary albumin excretion.

line (71 percent), 14 (15 percent) had disordered eating at follow-up.

Omission or underdosing of insulin lose weight was reported by 12 of 88 young women (14 percent) at base line and 30 (34 percent) at follow-up (P=0.003).

At base line, the mean (+/−SD) haemoglobin A(1c) value was higher in the group with highly disordered eating behaviour (11.1+/−1.2 percent) than in the groups whose eating behaviour was moderately disordered (8.9+/−1.7 percent) or nondisordered (8.7+/−1.6 percent, P<0.001).

Disordered eating at base line was associated with retinopathy four years later (P=0.004), when 86 percent of the young women with highly disordered eating behaviour, 43 percent of those with moderately disordered eating behaviour, and 24 percent of those with nondisordered eating behaviour had retinopathy.

13.2 The effect of psychosocial interventions on metabolic and psychological outcomes in children and adolescents with type 1 diabetes.

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref No.</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Comments</th>
<th>Design</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hampson 2001</td>
<td>52</td>
<td>Systematic review of 62 studies from Health Technology Assessment Program UK.</td>
<td>Question asked “Do educational and psychosocial interventions for adolescents with type 1 diabetes have beneficial effects on biological and psychosocial outcomes?”</td>
<td>Psychosocial Self or parent reports of changes in psychological or interpersonal constructs (e.g. self-efficacy, diabetes-specific stress)</td>
<td>Metabolic measures Small to medium effect on HbA1c, and psychosocial outcome of educational and psychosocial intervention. Mean of 12 pooled effect sizes for psychosocial outcomes was 0.37 (95% CI 0.19-0.55)</td>
<td>Rigorous search strategy with appropriate inclusion criteria. 62 studies in total. 23 RCTs reviewed (16 with sufficient detail to enable effect sizes to be calculated). 37 other study designs eg non RCT’s without control groups, pre and post intervention studies</td>
<td>Systematic review</td>
<td>1</td>
</tr>
</tbody>
</table>

These studies demonstrate the variety of intervention and outcomes that have been studied. All the pre-, post
Other studies published after the Hampson 2001 Health Technology Appraisal Systematic Review

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Design</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wysocki 2001</td>
<td>53</td>
<td>RCT</td>
<td>119 families of adolescents with diabetes</td>
<td>BFST, education and support group</td>
<td>Family relationships, psychological adjustment to diabetes, treatment adherence and diabetic control assessed at baseline, after 6 and 12 months' treatment. Compared with CT and ES, BFST yielded lasting improvement in parent-adolescent relations and reduced diabetes-specific conflict (p&lt;0.05). At 12 months BFST effects on psychological adjustment to diabetes differed from CT group (p&lt;0.05) but not from the ES group. No significant differences on HbA1c between groups were noted. There were no effects on treatment adherence. BFST yielded some improvement in parent-adolescent relationship. Factors mediating the effectiveness of BFST need to be clarified.</td>
</tr>
<tr>
<td>Laffel 2003</td>
<td>55</td>
<td>RCT</td>
<td>105 children and adolescents, aged 8 to 17 years of age, with T1DM for &lt; or ≥6 years. Of 128 eligible families attending Joslin clinic (USA) 105 agreed to participate. Patients of families not participating were slightly older but otherwise not.</td>
<td>Family-focused teamwork (TW) intervention or to standard multidisciplinary diabetes care (SC).</td>
<td>Measures of family involvement in diabetes tasks, DFC, and quality of life were performed at baseline and after 1 year. Haemoglobin A1c was measured at each visit. Both groups had similar frequencies of blood glucose monitoring (BGM) and insulin dosing. After 1 year, A1c was 8.2% +/- 1.1% in TW compared with 8.7% +/- 1.5% in SC (P &lt;.05). Families exposed to the TW intervention maintained or increased family involvement significantly more than families exposed to SC (P = .05). In multivariate analysis, TW intervention and the daily frequency of BGM significantly predicted HbA1c (R (2) = 0.17, P = .05).</td>
</tr>
</tbody>
</table>
significantly different.
Patients (n = 100) completed follow-up, (50 in TW and 50 in SC).

At entry, HbA1c was 8.4% +/- 1.3% in TW and 8.3% +/- 1.0% in SC.

Despite increased family involvement, the TW group reported no increase in Diabetes Related Family Conflict or decrease in quality of life.
Ambulatory TW intervention prevented the expected deterioration in glycaemic control seen with SC in youths with TIDM of < or =6 years' duration.
Successful family involvement may assist in the preservation of health and the prevention of long-term diabetes complications for youth with diabetes.

CST subjects had lower glycosylated haemoglobin (P = .001) and better diabetes (P = .002) and medical (P = .04) self-efficacy, and less impact of diabetes on their quality of life (P = .005) than youth receiving IDM alone after 1 year.
In males, CST did not affect adverse outcomes of IDM hypoglycaemia, diabetic ketoacidosis, and weight gain, but CST decreased the incidence of weight gain (P = .05) and hypoglycaemia in females (P = .03).

Conclusion: The addition of behavioural intervention to IDM in adolescence results in improved metabolic control and quality of life over 1 year

<table>
<thead>
<tr>
<th>Ref No</th>
<th>Technical Reports/Consensus Statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT 11</td>
<td>Consensus Statements used to formulate the recommendations and principles of clinical practice.</td>
</tr>
</tbody>
</table>
Chapter 14: Diabetes Complications

14.1 Effect of intensive diabetes management on microvascular and macrovascular complications in adolescents.

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref No</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Comments</th>
<th>Design</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCCT 1994</td>
<td>2</td>
<td>Adolescent subgroup of DCCT trial. Age 13-17 years</td>
<td>Intensive insulin therapy (n=95) (by multiple daily injections or insulin pump) with frequent BG monitoring OR Conventional therapy with 1 or 2 insulin injections daily and once daily monitoring (n=114)</td>
<td>Development of diabetes complications</td>
<td>Retinopathy: Intensive therapy decreased the risk of retinopathy by 53% (CI 1-78%, p=0.048) (in those with no retinopathy) and 70% (CI 25-88%, p=0.010) (in those with mild retinopathy) Nephropathy: Intensive therapy group had 16% reduction in microalbuminuria (95% CI -70% to 52%; p=0.745 in those with no retinopathy; and by 55% (95% CI 3% to 9%); p=0.042 in those with mild retinopathy</td>
<td></td>
<td>RCT</td>
<td>II</td>
</tr>
</tbody>
</table>

**Landmark study:** See other DCCT references

**Blinding:** Standard therapy group blinded to HbA1c results; intensive therapy group could not be blinded to HbA1c as they were using it as a management tool; research group blinded to the effects of the two treatment regimens; investigators and patients unaware of outcome data unless predetermined 'alert' criteria (e.g. development of retinopathy) were reached; Retinopathy assessed by operators who were unaware of treatment group assignment.

**Losses to follow-up:** No patients voluntarily withdrew; 2 patients died; 2 patients assigned to inactive status for some time >95% of scheduled examinations were completed; overall time spent in assigned treatment was 95%; Independent data monitoring committee determined that study results warranted terminating trial after mean...
## Appendix 2: Evidence Tables

### Australian Clinical Practice Guidelines: Type 1 Diabetes in Children and Adolescents

| DCCT 1995 | 20 | 1441 patients with T1D aged 13-39 years. 726 with no retinopathy at baseline (primary intervention group) and 715 with mild retinopathy. Patients with recognised risk factors (other than diabetes) were excluded from the trial. | Intensive insulin therapy (by multiple daily injections or insulin pump) with frequent BG monitoring OR Conventional therapy with 1 or 2 insulin injections daily and once daily monitoring | Development of diabetes complications | No. of major macrovascular events was twice as high in conventional tx gp (40 events) as in intensive-treatment group (23 events). Differences were not statistically sig (p = 0.08). There were no differences in the cumulative incidence of hypertension. Mean total serum cholesterol, LDL cholesterol, and triglycerides were significantly reduced in intensive-tx gp (p < 0.01), as was the development of LDL cholesterol levels > 160 mg/dl. The reduction in some, but not all, cardiovascular risk factors suggests a potential beneficial effect of intensive therapy on macrovascular disease in insulin-dependent diabetes mellitus. | See other DCCT references. Blinding: Morbidity and Mortaity Committee classified deaths and cardiovascular events without knowledge of treatment assignment, according to pre-established criteria. Analysis: All analyses carried out on an intention-to-treat basis. Losses to follow-up: 11 patients died during the study and 8 dropped out. At the end of the study all 8 were determined to be alive and healthy, with no history of major macrovascular events; >95% of scheduled outcome date were obtained. Adherence: 49 patients deviated from intensive to conventional therapy for some period of the study; 104 deviated from conventional to intensive therapy (95 of these were pregnant women). Overall intensively-treated patients spent >98% of their time on the assigned treatment, and conventionally-treated patients spent 97% of their time on that therapy. | RCT | II |

<p>| DCCT 1993 | 63 | 1441 patients with T1D aged 13-39 years. 726 with no retinopathy at baseline and 715 with mild retinopathy. | Intensive insulin therapy (by multiple daily injections or insulin pump) with frequent BG monitoring (n=704; 348 primary and 366 secondary prevention) OR Conventional therapy with 1 or 2 insulin injections daily and once daily monitoring | Development of diabetes complications | Retinopathy: intensive therapy reduced the risk of retinopathy by 76% (95% CI 62-85) in patients with no retinopathy at baseline (p=0.002), and by 54% (95% CI 39-66) in those with mild retinopathy at baseline (p=0.001); combined 63% (95% CI 52-71), p=0.002. Landmark study. Rigorous multicentre study supervised by NIH, USA. See other DCCT references. Follow up period of 6.5 years (trial terminated by independent monitoring committee). | RCT | II |</p>
<table>
<thead>
<tr>
<th>Nathan 2003</th>
<th>95</th>
<th>Of 1441 patients who participated in the DCCT, 1229 patients participated in EDIC (Epidemiology of Diabetes Interventions and Complications) N = 611</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinopathy (secondary intervention group)</td>
<td>Conventional therapy with 1 or 2 insulin injections daily and once daily monitoring (n=704; 352 primary and 352 secondary prevention)</td>
<td>Neuroropathy: At 5 years, intensive therapy reduced incidence of clinical neuropathy by 69% (95% CI 24-87) vs 10% (95% CI 38-74), p&lt;0.006 in patients with no retinopathy at baseline; and by 57% (95% CI 29-73); p&lt;0.002 in those with mild retinopathy at baseline; combined 60% (95% CI 38-74), p&lt;0.002</td>
</tr>
<tr>
<td></td>
<td>Neuropathy: At 5 years, intensive therapy reduced incidence of clinical neuropathy by 69% (95% CI 24-87) vs 10% (95% CI 38-74), p&lt;0.006 in patients with no retinopathy at baseline; and by 57% (95% CI 29-73); p&lt;0.002 in those with mild retinopathy at baseline; combined 60% (95% CI 38-74), p&lt;0.002</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Nephropathy: Intensive therapy reduced the risk of microalbuminuria by 39% (95% CI 21-52) and albuminuria by 54% (95% CI 19-74): Intensive therapy reduced the mean adjusted risk of microalbuminuria by 34% (p&lt;0.04) in patients with no retinopathy at baseline and by 43% in those with mild retinopathy at baseline (p=0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adverse events: Incidence of hypoglycaemia increase 2-3 fold on intensive therapy (19 versus 62 hypoglycaemic episodes per 100 patient years, p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean progression of the intima-media thickness was significantly less in group that received intensive therapy during DCCT than in group that received conventional therapy (progression of the intima-media thickness of the common carotid artery, 0.032 vs. 0.046 mm; P=0.01; and progression of the combined intima-media)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>As for DCCT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blinding: Standard therapy group blinded to HbA1c results; intensive therapy group could not be blinded to HbA1c because they were using it as a management tool</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Research group blinded to effects of the two treatment regimens</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Losses to follow-up: 99% of patients completed study; &gt;95% of all scheduled examinations completed; 11 patients died; 32 patients assigned to inactive status for some time during trial due to unavailability or investigator’s decision that continuation of treatment would be hazardous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Compliance: Average time spent receiving assigned treatment = 97%, including 95 women assigned to conventional therapy who received intensive therapy during pregnancy or while planning a pregnancy</td>
</tr>
</tbody>
</table>

**As for DCCT**

**Blinding:** Assessment of intima-media thickness carried out by a single operator who was blinded to patient’s treatment assignments

**RCT II**
Appendix 2: Evidence Tables

Australian Clinical Practice Guidelines: Type 1 Diabetes in Children and Adolescents

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### Chapter 15: Other Complications and Associated Conditions

#### How frequently should children and adolescents with type 1 diabetes be screened for microvascular (retinopathy, nephropathy, neuropathy) complications?

Studies were included if they specifically addressed the frequency of screening for microvascular disease in children and adolescents with type 1 diabetes. While some studies described the prevalence of microvascular complications in children and adolescents with type 1 diabetes, we did not find any relevant studies that specifically addressed the frequency of screening. In the absence of other evidence the current consensus guidelines form the basis for the screening recommendations. Articles describing prevalence of microvascular complications in children with type 1 diabetes are mentioned in the text.

#### How frequently should children and adolescents with type 1 diabetes be screened for macrovascular complications?

Studies were included if they specifically addressed the frequency of screening for macrovascular disease in children and adolescents with type 1 diabetes. While some studies described the prevalence of macrovascular complications in children and adolescents with type 1 diabetes, we did not find any relevant studies that specifically addressed the frequency of screening. In the absence of other evidence the current consensus guidelines form the basis for the screening recommendations. Articles relating to macrovascular disease in children and adolescents with type 1 diabetes are mentioned in the text.

#### How frequently should children and adolescents with type 1 diabetes be screened for thyroid disease?

Studies were included if they specifically addressed the frequency of screening for thyroid disease in children and adolescents with type 1 diabetes. While many studies described the prevalence of autoantibodies in children and adolescents with type 1 diabetes, we did not find any relevant studies that specifically addressed the frequency of screening. In the absence of other evidence the current consensus guidelines form the basis for the screening recommendations. Articles describing prevalence of thyroid disease in children with type 1 diabetes are mentioned in the text.

#### How frequently should children and adolescents with Type 1 diabetes be screened for coeliac disease?

Studies were included if they specifically addressed the frequency of screening for coeliac disease in children and adolescents with type 1 diabetes. While many studies described the prevalence of autoantibodies in children and adolescents with type 1 diabetes, we did not find any relevant studies that specifically addressed the frequency of screening. In the absence of other evidence the current consensus guidelines form the basis for the screening recommendations. Articles describing prevalence of coeliac disease in children with type 1 diabetes are mentioned in the text.

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**Ref No | Technical Reports/Consensus Statements**
---
21 | International Society for Pediatric and Adolescent Diabetes: Consensus Guidelines for the Management of Type 1 Diabetes Mellitus in Children and Adolescents. Zeist, Netherlands, Medforum, 2000
110 | American Diabetes Association: Standards of Medical Care for Patients With Diabetes Mellitus. Diabetes Care 26:335, 2003
122 | Australasian Paediatric Endocrine Group: APEG Handbook on Childhood and Adolescent Diabetes. Sydney, Australasian Paediatric Endocrine Group, 1996

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**Chapter 15: Other Complications and Associated Conditions**

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Appendix 2: Evidence Tables

Australian Clinical Practice Guidelines: Type 1 Diabetes in Children and Adolescents
screening. In the absence of other evidence the current consensus guidelines form the basis for the screening recommendations. Articles describing the prevalence of coeliac disease in children with type 1 diabetes are mentioned in the text.

15.1 **Effect of a gluten free diet (GFD) in asymptomatic patients with type 1 diabetes found to have coeliac disease on routine screening.**

Articles chosen if they addressed the question of GFD in truly asymptomatic children and adolescents with type 1 diabetes detected on routine screening.

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref No</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Comments</th>
<th>Design</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saukkonen 2002</td>
<td>57</td>
<td>18 patients detected out of 776 children with T1D by retrospectively screening stored serum samples. Screened by anti-reticulin and anti-gliadin antibodies. Confirmed diagnosis by jejunal biopsy. Children and adolescents (mean age 11.4) with type 1 diabetes.</td>
<td>Exclusive GFD</td>
<td>Prevalence 2.4% of type 1 diabetics. Only one patient reported symptoms at the time of diagnosis. 2 patients had iron deficiency anaemia. However on retrospective questioning 9 reported GI symptoms (mostly flatulence, which resolved in all but 2 patients. GFD did not affect glycaemic control HbA1c. Height did not change before or after dx. Weight for height did not change before diagnosis, but there was a significant increase after dx and intro of GFD (p=0.02)</td>
<td>Nationwide screening programme for Childhood Diabetes in Finland (DiMe) study. Overt GI symptoms reported in 1 patient before disclosure of diagnosis. Short follow up period. Details up to one year post diagnosis of coeliac disease only. One patient died, cause of death not stated.</td>
<td>Retrospective case series</td>
<td>IV</td>
<td></td>
</tr>
<tr>
<td>Acerini 1998</td>
<td>63</td>
<td>167 children &amp; adolescents with TID screened with EMA and IgA (+/- AGA). 8 with diagnosed coeliac disease</td>
<td>Gluten free diet (GFD)</td>
<td>Eleven (6.6%) antibody positive, 9 had biopsies: 8 coeliac (1 'classical'; 1 anaemia; 3 'atypical'; 3 asymptomatic). Asymptomatic patients reported no change in wellbeing on the GFD, although trend for BMI SDS to increase was not significant (p=0.248). All had normal antibody tests after 3-6 months of GFD HbA1c reduction with gluten</td>
<td>Clinic population at John Radcliffe Hospital, Oxford. Serological screening is effective, although the therapeutic benefit of dietary therapy in asymptomatic cases remains uncertain</td>
<td>Case series longitudinal follow-up</td>
<td>IV</td>
<td></td>
</tr>
</tbody>
</table>
15.2 Consensus Statements used to formulate the recommendations and principles of clinical practice.

<table>
<thead>
<tr>
<th>Ref No</th>
<th>Technical Reports/Consensus Statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>International Society for Pediatric and Adolescent Diabetes: ISPAD Consensus Guidelines for the Management of Type 1 Diabetes Mellitus in Children and Adolescents. Zeist, Netherlands, Medforum, 2000</td>
</tr>
<tr>
<td>46</td>
<td>NSW Health Department: Principles of Care and Consensus Guidelines for the Management of Diabetes Mellitus in Children and Adolescents. 1998</td>
</tr>
<tr>
<td>59</td>
<td>Australasian Paediatric Endocrine Group: APEG Handbook on Childhood and Adolescent Diabetes. Sydney, Australasian Paediatric Endocrine Group, 1996</td>
</tr>
<tr>
<td>60</td>
<td>National Institute for Clinical Excellence. Type 1 Diabetes (Childhood): Diagnosis and Management of Type 1 Diabetes in Children and Young People (DRAFT). 2004.</td>
</tr>
</tbody>
</table>

Chapter 16: Foot Care

How frequently should children and adolescents with Type 1 diabetes be screened for foot complications?

Studies were included if they specifically addressed the frequency of screening for foot complications in children and adolescents with type 1 diabetes. While many studies described the prevalence we did not find any relevant studies that specifically addressed the frequency of screening. In the absence of other evidence the current consensus guidelines form the basis for the screening recommendations.

16.1 The effect of type 1 diabetes on joint mobility in the feet of young people.

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref No</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Comments</th>
<th>Design</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barnett 1995</td>
<td>1</td>
<td>67 diabetic children and a comparison group matched for age, sex, and social class.</td>
<td>N/A</td>
<td>Questionnaire, clinical examination, and biomechanical assessment for foot pathology (limited joint mobility, plantar callus, skin conditions) contact with podiatry services and knowledge</td>
<td>Increased foot pathology (limited joint mobility, plantar callus) in the children with diabetes (52 children) compared with comparison group (28 children); Increased biomechanical anomalies (limited joint mobility) (58 children with diabetes, 34 comparison group); Increased incidence of abnormal skin conditions (53 children with diabetes, 27 comparison group).</td>
<td>42 children with diabetes had received foot health education compared with 27 in the comparison group. Among the diabetic group there was ignorance and misconceptions, and previous contact with a podiatrist was minimal.</td>
<td>Comparative study</td>
<td>IV</td>
</tr>
<tr>
<td>Study</td>
<td>Ref No</td>
<td>Population</td>
<td>Intervention</td>
<td>Outcome</td>
<td>Results</td>
<td>Comments</td>
<td>Design</td>
<td>Level</td>
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<td>-------</td>
</tr>
<tr>
<td>Duffin 2002</td>
<td>14</td>
<td>216 young people with Type 1 diabetes mellitus and 57 controls</td>
<td>Thickness of the skin on the plantar surface of the foot and plantar aponeurosis were examined using ultrasound. Foot length, arch length, joint mobility, peak pressure and pressure time integrals were evaluated</td>
<td>Skin was not significantly thicker in the diabetic subjects. The plantar aponeurosis was significantly thicker in the diabetic subjects than controls. Thickened plantar aponeurosis was associated with foot size, male gender and subtalar joint limited joint mobility (P &lt; 0.01). Males were nearly 3 times more likely to have thickened plantar aponeurosis.</td>
<td>Any patients with known joint condition or arthritis was excluded</td>
<td>Comparative study</td>
<td>IV</td>
<td></td>
</tr>
<tr>
<td>Duffin 1999</td>
<td>19</td>
<td>302 diabetic adolescents and 51 non-diabetic controls (aged 11.5-20 years)</td>
<td>Hands, feet and hips were examined. Also screened for diabetes complications (retinopathy and nephropathy) Limited joint mobility was defined as less than the fifth percent reference for controls</td>
<td>Reduced motion was found in diabetic adolescents at the: subtalar (ST) joint in 35%, first metatarsophalangeal (MTP) joint in 18% fifth metacarpophalangeal (MCP) joint in 26% 13% of diabetics had limited passive extension of the interphalangeal (IP) joints of the hands compared to 0% in controls. Limited active IP joint extension, a positive 'prayer sign', occurred in 35% of diabetic adolescents and 14% of controls. Diabetic adolescents showing LJM in any of these areas, except the prayer sign, were more likely to have retinopathy (odds ratio 2.53, CI: 1.53-4.18). Those with LJM in the foot were more likely to have albumin excretion rates &gt;7.5 microg/min (OR 2.06, CI: 1.16-3.68).</td>
<td>Clinic population. Referred for diabetes complications screening. Any patients with known joint condition or arthritis was excluded</td>
<td>IV</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

16.2 The management of high plantar pressure and callus in adolescents with type 1 diabetes.
Appendix 2: Evidence Tables

Australian Clinical Practice Guidelines: Type 1 Diabetes in Children and Adolescents

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref No</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Comments</th>
<th>Design</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duffin 2003</td>
<td>3</td>
<td>211 adolescents with diabetes and 57 non-diabetic controls 17 diabetic subjects with high peak plantar pressure and 17 diabetic subjects with plantar callus</td>
<td>Treatment with foot orthosis, cushioning or combination of both</td>
<td>Peak plantar pressure 12 months after intervention</td>
<td>Cushioning alone: significant decrease in peak plantar pressure (p=0.001) Orthosis alone: significant decrease in peak plantar pressure (p=0.05) Combination of cushioning and orthosis: significant decrease (p&lt;0.001)</td>
<td>Clinic population. Referred for diabetes complications screening. Any patients with known joint condition or arthritis was excluded</td>
<td>Case series study with interventional phase (pre-test, post test).</td>
<td>IV</td>
</tr>
</tbody>
</table>

16.3 Consensus Statements used to formulate the recommendations and principles of clinical practice.

<table>
<thead>
<tr>
<th>Ref No</th>
<th>Technical Reports/Consensus Statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>Australasian Paediatric Endocrine Group. APEG Handbook on Childhood and Adolescent Diabetes. Sydney, Australasian Paediatric Endocrine Group, 1996</td>
</tr>
</tbody>
</table>

Chapter 17: Dental Health

How frequently should children and adolescents with Type 1 diabetes have a dental review?

Studies were included if they specifically addressed the frequency of screening for dental complications in children and adolescents with type 1 diabetes. While many studies described the prevalence we did not find any relevant studies that specifically addressed the frequency of screening. In the absence of other evidence the current consensus guidelines form the basis for the screening recommendations.

17.1 The effect of type 1 diabetes on dental health in children and adolescents.

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref No</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Comments</th>
<th>Design</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twetman 2002</td>
<td>4</td>
<td>64 children and adolescents (8-15 years of age) with diabetes treated and monitored according to a standard medical protocol and receiving extensive preventive oral health care based on individual needs.</td>
<td>N/A</td>
<td>Data on blood glucose and glycosylated haemoglobin (Hb A1c) were collected from the medical records. Whole saliva was collected every 3rd month and secretion rate, buffer capacity, glucose concentration, mutans streptococci and lactobacilli counts were determined. Dental examinations, including radiographs, were carried out once a year.</td>
<td>Patients with less good metabolic control (&gt;8.0% Hb A1c) had higher glucose levels in resting saliva (p &lt; 0.05) Patients with less good metabolic control (&gt;8.0% Hb A1c) had significantly higher caries incidence (p &lt; 0.05) compared to those with good metabolic control. The most influential determinants for high caries development during the 3-year follow-up period were metabolic control (odds ratio, OR = 5.7), poor oral hygiene (OR = 6.5), previous caries</td>
<td>Observational case series and retrospective medical note survey</td>
<td>IV</td>
<td></td>
</tr>
</tbody>
</table>
### Appendix 2: Evidence Tables

**Australian Clinical Practice Guidelines: Type 1 Diabetes in Children and Adolescents**

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Design</th>
<th>Outcome Measures</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miralles-Jorda 2002</td>
<td>Thirty juvenile diabetics and 30 healthy individuals</td>
<td>N/A</td>
<td>Evaluated for dental caries and oral mucosal lesions, with the performance of basal and stimulated sialometry, periodontal variables such as the presence of bacterial plaque, gingival status and attachment losses</td>
<td>Diabetics had significantly more periodontal attachment loss than non diabetics. No difference between groups for salivary flow, dental caries or mucosal lesions. The diabetic group had better oral hygiene habits.</td>
</tr>
<tr>
<td>Pinson 1995</td>
<td>26 type I diabetic patients and 24 control subjects (average age 13.4 years)</td>
<td>N/A</td>
<td>Glycosylated haemoglobin (GHb) to obtain a measure of diabetic control. Clinical periodontal details: plaque index, gingival fluid flow, gingival index, probing depths, clinical attachment levels, recession, and bleeding on probing</td>
<td>No statistically significant differences in the overall mean for the 2 groups for average attachment loss, probing depths, recession, gingival index, plaque index, gingival fluid flow, or bleeding on probing. There was no significant association between the level of control of diabetes (GHb) and clinical variables. However, comparisons based on site-specific measurements showed the gingival index to be somewhat higher among the diabetics (p = 0.0002), and examination of interaction effect plots showed the diabetic group to have higher average gingival index for most teeth and higher or the same plaque index levels on all teeth relative to controls.</td>
</tr>
<tr>
<td>Marin 2002</td>
<td>Twenty diabetic patients with good metabolic control, twenty diabetic patients with poor metabolic control and forty healthy subjects</td>
<td>N/A</td>
<td>Glycosylated haemoglobin Periodontal markers: Plaque, gingival, mobility, probing depth, attachment level, bleeding on probing, and marginal bone loss.</td>
<td>Poor glycaemic control associated with periodontal disease (p=0.05)</td>
</tr>
</tbody>
</table>
| Takahashi 2001 | 117 Japanese T1DM subjects (53 male, 64 female, mean age +/- SD, 16 +/- 6.5 years) Thirty-nine periodontally | N/A | Clinical examination for signs of periodontitis, gingivitis. Microbiological tests for four periodontal pathogens, Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans, Prevotella intermedia and Capnocytophaga | T1DM subjects: 12 had periodontitis, 32 had gingivitis and 73 were periodontally healthy. In the T1DM subjects, the Periodontitis group had a significantly longer mean duration of diabetes and a higher percentages of subjects harbouring P. gingivalis and P. intermedia than the
17.2 Consensus Statements used to formulate the recommendations and principles of clinical practice.

<table>
<thead>
<tr>
<th>Ref No</th>
<th>Technical Reports/Consensus Statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>Australasian Paediatric Endocrine Group: APEG Handbook on Childhood and Adolescent Diabetes. Sydney, Australasian Paediatric Endocrine Group, 1996</td>
</tr>
</tbody>
</table>

Chapter 18: Adolescent Health Issues

18.1 Difficulties in glycaemic control in adolescents compared with adults.

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref No</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Comments</th>
<th>Design</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCCT 1994</td>
<td>2</td>
<td>Adolescent subgroup of DCCT trial. Age 13-17 years, 125 adolescents with no retinopathy and 70 with mild retinopathy. Mean follow up 7.4 years (for adolescents)</td>
<td>Intensive insulin therapy (n=95) (by multiple daily injections or insulin pump) with frequent BG monitoring OR Conventional therapy with 1 or 2 insulin injections daily and once daily monitoring (n=114)</td>
<td>Development of diabetes complications</td>
<td>Retinopathy: Intensive therapy decreased the risk of retinopathy by 53% (CI 1-78%, p=0.048) (in those with no retinopathy) and 70% (CI 25-88%, p=0.010) (in those with mild retinopathy)</td>
<td>Landmark study. See other DCCT references</td>
<td>RCT</td>
<td>II</td>
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<td>Nephropathy: Intensive therapy group had 10% reduction in microalbuminuria (95% CI -70% to 52%; p=0.745 in those with no retinopathy; and by 55% (95% CI 3% to 9%); p=0.042 in those with mild retinopathy)</td>
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<td></td>
<td>Diabetic ketoacidosis: RR 0.2 (95% CI 0.32-1.23)</td>
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<td>Severe hypoglycaemia: RR 2.96 (95% CI 1.90-4.62) Hypoglycaemia resulting in coma or seizure: RR 2.93 (95% CI 1.75-4.90)</td>
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<td></td>
<td>Overweight: RR 2.11 95% CI</td>
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</tbody>
</table>

Blinding:
Standard therapy group blinded to HbA1c results; intensive therapy group could not be blinded to HbA1c as they were using it as a management tool; Research group blinded to the effects of the two treatment regimens; Investigators and patients unaware of outcome data unless predetermined 'alert' criteria (e.g. development of retinopathy) were reached; Retinopathy assessed by operators who were unaware of treatment group assignment.

Losses to follow-up:
No patients voluntarily withdrew; 2 patients died; 2 patients assigned to inactive status for some time.
## Appendix 2: Evidence Tables

### Australian Clinical Practice Guidelines: Type 1 Diabetes in Children and Adolescents

| DCCT 1993 | 3 | 1441 patients with T1D aged 13-39 years. 726 with no retinopathy at baseline (primary intervention group) and 715 with mild retinopathy (secondary intervention group) | Intensive insulin therapy (by multiple daily injections or insulin pump) with frequent BG monitoring (n=704; 348 primary and 366 secondary prevention) | Development of diabetes complications | Retinopathy: Intensive therapy reduced the risk of retinopathy by 76% (95% CI 62-85) in patients with no retinopathy at baseline (p<0.002), and by 54% (95% CI 39-66) in those with mild retinopathy at baseline (p<0.001); combined 63% (95% CI 52-71), p<0.002. Neuropathy: At 5 years, intensive therapy reduced incidence of clinical neuropathy by 69%; 95% CI 24-87 (3% in intensively treated group vs 10% in conventionally treated group) p=0.006 in patients with no retinopathy at baseline; and by 57% (95% CI 29-73); p=0.002 in those with mild retinopathy at baseline; combined 60% (95% CI 38-74), p<0.002. Nephropathy: Intensive therapy reduced risk of microalbuminuria by 39% (95% CI 21-52) and albuminuria by 54% (95% CI 19-74); Intensive therapy reduced the mean adjusted risk of microalbuminuria by 34% (p=0.04) in in patients with no retinopathy at baseline and by 43% in those with mild retinopathy at baseline (p=0.001). | >95% of scheduled examinations were completed; overall time spent in assigned treatment was 95%; Independent data monitoring committee determined that study results warranted terminating trial after mean follow-up of 6.5 years (overall) | Landmark study. Rigorous multicentre study supervised by NIH, USA. See other DCCT references. Follow up period of 6.5 years (trial terminated by independent monitoring committee). Blinding: Standard therapy group blinded to HbA1c results; intensive therapy group could not be blinded to HbA1c because they were using it as a management tool. Research group blinded to effects of the two treatment regimens. Losses to follow-up: 99% of patients completed study; >95% of all scheduled examinations completed; 11 patients died; 32 patients assigned to inactive status for some time during trial due to unavailability or investigator’s decision that continuation of treatment would be hazardous. Compliance: Average time spent receiving assigned treatment = 97%, including 95 women assigned. | RCT II | 200 |
## 18.2 Current transition processes and outcomes for adolescents with type 1 diabetes moving to the adult care system.

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref No</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Comments</th>
<th>Design</th>
<th>Level</th>
</tr>
</thead>
</table>
| Court 1993  | 15     | 105 T1D patients Australia Age (15-18)         | Patient questionnaire             | Preferred source of further adult care                                  | 72.3% Public hospital  
42.9% Private specialist  
14.3% GP only  
1.9% Don’t know  
1.9% Don’t care  
5.7% before age of 17 yrs  
48.6% between ages of 17 & 20 yrs  
44.8% any age up to 25 yrs | 105 responses out of 152 questionnaires sent | Survey                        | IV                 |
| Eiser 1993  | 16     | 69 T1D patients UK                             | Patient questionnaire             | Mean age of transfer  
Pt knowledge of transfer reasons  
Importance of visits before transfer | 15.9 yrs  
27.3% offered reason  
rated about 3.4 out of 5 (0=not important, 5=very important) |                           | Survey                        | IV                 |
| Kipps 2002  | 17     | 229 subjects T1D >18 and ≤ 16 between the years of 1985 and 1995 Oxford, UK | 222 audit of notes.  
164 interviewed by a single nurse | Mean age of transfer  
Rate of clinical attendance (at least 6 monthly) | 17.9 years range (13.3 - 22.4 years)  
2 years pre transfer: 98%  
1 year pre transfer: 87%  
2 years post transfer: 81%  
2 years post transfer: 61%,  
p < 0.0005 2 years pre transfer vs. 2 years post transfer |                           | Survey                        | IV                 |
| Rate of clinical attendance (3-4 monthly) |  |  |  |
| 2 years pre transfer: 77%  
1 year pre transfer: 54%  
2 years post transfer: 45%  
2 years post transfer: 24%,  
p < 0.0005 2 years pre transfer vs. 2 years post transfer |
| Transfer letter identified in clinical record |  |  |  |
| 86% |
| Attendance of first appointment in new clinic |  |  |  |
| 79% |
| Age at transfer |  |  |  |
| Unrelated to transfer outcome (attendance clinic) |
| Mean HbA1c at 2 yrs before tx comparing patients at clinic 2 yrs post tx. |  |  |  |
| 9.9 ± 1.9 vs. 11.4 ± 1.9%, p = 0.0004 |
| Satisfaction with transfer |  |  |  |
| 57% satisfied  
20% not sat.  
24% indifferent |
| Patients perception of importance of meeting adult clinic staff prior to transfer |  |  |  |
| 10% very important  
43% important  
46% not important  
1% discouraging |

| Pacaud 1996 | 18 | 212 subjects with type 1 diabetes  
Two different hospitals  
Canada |  |  |  |
| Mean age of transfer (mean ± SEM) |  |  |  |
| 18.5 ± 0.1 years |
| Suggested age of transfer (mean ± SEM) |  |  |  |
| 18.8 ± 0.2 years  
21% felt should have had transfer earlier  
39% felt transfer was at correct time  
65% felt later transfer would be better  
30% diabetes clinic |
| Adult care services now used |  |  |  |
| 54% endocrinologist |
| Patient Questionnaire |  |  |  |
| Survey IV |  |  |  |
| Datta 2003 | 19 | 42 young people with T1D Attending adolescent or transition clinic | Patient Questionnaire | Problem with transition from paediatric to adult care: A delay of more than 6 months between last visit at paed. clinic and first visit at adult clinic | 3% family physician 13% no regular contact 32.8% responded yes 27.5% (17% delay was more than 1 year) |
| --- | --- | --- | --- | --- |
| Jefferson 2003 | 20 | 302 paediatricians surveyed in UK | questionnaire | Age of transfer | 14% at 14-16 yrs 31% at 16 yrs 45% at 16-20 yrs 53% transfer young people into a young adult service | Survey | IV |
### Appendix 2: Evidence Tables

#### Australian Clinical Practice Guidelines: Type 1 Diabetes in Children and Adolescents

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref No</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>Sahni 1986</td>
<td></td>
<td>61 cases of adolescent T1D followed one yr before and 1 yr after transfer 1980-1983 Finland</td>
<td>Hba1c measured at 3 monthly intervals</td>
<td>Mean Hba1c</td>
<td>1 year before transfer: 11.2 ± 2.2 (n = 49)</td>
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<td>1st visit at the adult clinic 11.2 ± 2.3 (n = 49)</td>
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<td></td>
<td>1 year after transfer: 9.9 ± 1.7 (n = 49)</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean age of transfer</td>
<td></td>
<td>17.5 ± 0.5 years (range 16.5-18.8)</td>
</tr>
</tbody>
</table>

**18.3 The effect of type 1 diabetes on driving performance.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref No</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cox 2003</td>
<td></td>
<td>341 adults with type 1 diabetes, 332 with type 2 diabetes, and 363 non-diabetic spouse control subjects. Diabetes clinics in seven U.S. and four European cities,</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
<td>Driving mishaps</td>
<td>T1D drivers reported significantly more crashes, moving violations, episodes of hypoglycaemic stupor, required assistance, and mild hypoglycaemia while driving as compared with T2D drivers or spouse control subjects (P &lt; 0.01-0.001).</td>
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<td>T2D drivers had driving mishap rates similar to nondiabetic spouses, and the use of insulin or oral agents for treatment had no effect on the occurrence of driving mishaps.</td>
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<td></td>
<td>Crashes among T1D drivers were associated with more frequent episodes of hypoglycaemic stupor while driving, less frequent blood glucose monitoring before driving, and the use of insulin injection therapy as compared with pump therapy.</td>
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<td></td>
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<td></td>
<td>One-half of the T1D drivers and three-quarters of the T2D drivers had never discussed hypoglycaemia and driving with their physicians.</td>
</tr>
</tbody>
</table>

Type and severity of driving mishaps not described

Questionnaire IV
Cox 2000  23  37 adults with type 1 diabetes who drove a simulator during continuous euglycaemia and progressive hypoglycaemia. 16 men, 21 women. Mean age 35.3 +/- 7.1 years. Mean duration of diabetes 17.5 +/- 10.0 years. Mean HbA1c 8.5 +/- 1.8%  0/0 During testing, driving performance, EEG, and corrective behaviours (drinking a soda or discontinuing driving) were continually monitored, and BG, symptom perception, and judgement concerning impairment were assessed every 5 min. Mean +/- SD euglycaemia performance was used to quantify z scores for performance in 3 hypoglycaemic ranges (4.0-3.4, 3.3-2.8, and <2.8 mmol/l). During all three hypoglycaemic BG ranges, driving was significantly impaired, and subjects were aware of their impaired driving. Compared with euglycaemia hypoglycaemic subjects engaged in more driving across the midline (P<0.01 for BG<2.8 mmol/l), more speeding (P<0.01 for BG 2.8-4.0 mmol/l) and inappropriate braking (P<0.01 for BG 2.8-4.0 mmol/l). Corrective actions did not occur until BG was <2.8 mmol/l (P<0.05). Driving impairment was related to increased neurogenic symptoms and increased theta-wave activity. Awareness of impaired driving was associated with neuroglycoaemic symptoms, increased beta-wave activity, and awareness of hypoglycaemia. High beta and low theta activity and awareness of both hypoglycaemia and the need to treat low BG influenced corrective behaviour.

Recruited through advertisements. Simulated driving experience, not real life  Case series  IV

### 18.4 Eating disorders in children and adolescents with type 1 diabetes.

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref No</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Comments</th>
<th>Design</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nielsen 2002</td>
<td>47</td>
<td>Patients with type 1 diabetes and eating disorders</td>
<td>N/A</td>
<td>Data were extracted from the relevant case-control and follow-up studies</td>
<td>Incidence of anorexia nervosa not significantly increased in TID. Bulimia Nervosa is increased (OR = 2.9) in TID.</td>
<td>Meta-analysis of all relevant case-control and follow-up studies</td>
<td>IV</td>
<td></td>
</tr>
<tr>
<td>Source</td>
<td>Study Year</td>
<td>Participants</td>
<td>Methodology</td>
<td>Findings</td>
<td>Notes</td>
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<tr>
<td>Nielsen 2002</td>
<td>48</td>
<td>Patients with type 1 diabetes and eating disorders (age range 0-29 years)</td>
<td>Source of data: 1. Diabetes database and 2 previous population based studies 2. Danish nationwide psychiatric admission case register</td>
<td>Co-existing ED in T1D increases the overall common OR for retinopathy to 4.8 Insulin misuse (IM) is increased when ED co-exists with T1D (OR 12.6)</td>
<td>Population register based follow up study</td>
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</tr>
<tr>
<td>Neumark-Sztainer 2002</td>
<td>49</td>
<td>70 adolescent females and 73 adolescent males with type 1 diabetes. Mean age 15.3 +/- 2.3 years (12-21 years)</td>
<td>AHEAD (Assessing Health and Eating among Adolescents with Diabetes) survey. Data on BMI and glycosylated haemoglobin (HbA1c) were drawn from medical records.</td>
<td>More females (92.4%) than males (53.6%) reported weight control behaviours to lose weight or prevent weight gain (P&lt;0.001). Unhealthy weight control practices: in 37.9% of the females and 15.9% of the males. Among the females, 10.3% reported skipping insulin and 7.4% reported taking less insulin to control their weight. Only one male reported doing either of these behaviours. Weight control/disordered eating behaviours were not associated with age, parental level of education, family structure, or race/ethnicity. Higher levels of weight dissatisfaction tended to be associated with unhealthy weight control/disordered eating. associations with BMI were inconsistent. Family cohesion was negatively associated with disordered eating among females (r = -0.52; P &lt; 0.001)</td>
<td>Questionnaire IV</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Study</td>
<td>Sample Size</td>
<td>Sample Description</td>
<td>Measures</td>
<td>Results</td>
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<tr>
<td>Svensson 2003</td>
<td>50 adolescent males with T1D compared with that of healthy age-matched male controls</td>
<td>Sweden</td>
<td>Eating Disorder Inventory for Children and an interview.</td>
<td>Male patients were heavier than controls males (p = 0.004). Male T1D patients had higher Drive for Thinness scores (p=0.002).</td>
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<tr>
<td>Affenito 1997</td>
<td>51 90 with T1D (18-46 years of age) Mean age 28.8 years Recruited from diabetes clinics throughout Connecticut and Massachusetts</td>
<td>Categorized into one of 3 groups according to the Diagnostic Statistical Manual of Mental Disorders (DSM-III-R) criteria for eating disorders: the clinical group (n = 14), the subclinical group (partially fulfilling the diagnostic criteria; n = 13), and the control group (n = 63).</td>
<td>Women with(p&lt;0.05) subclinical and clinical eating disorders had clinically elevated HbA1c results. The Control HbA1c was 8.3+/-1.6. subclinical group HbA1c 10+/-1.5%, clinical group HbA1c 10.4+/-2.6% (p=0.05) and more diabetes-related complications, compared with the control subjects (Control group 0.6, subclinical group 1.23, p=0.03, clinical group 1.23,p=0.05). The severity of bulimic behaviours, weight concerns, reduced BMI, and decreased frequency of blood glucose monitoring were associated with elevated HbA1c. Diabetes complications by self-report or chart review.</td>
<td>Cohort study. Questionnaire IV</td>
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<tr>
<td>Rydall 1997</td>
<td>52 91 young women with IDDM mean age 15+/-2 years and the duration of diabetes was 7+/-4 years. Studied at base line and 5 yrs later</td>
<td>Prevalence and persistence of disordered eating behaviour (on the basis of self-reported eating and weight-loss practices, including the intentional omission or underdosing of insulin to control weight) and the association of such eating disorders with metabolic control, diabetic retinopathy, and urinary albumin excretion.</td>
<td>At base line, 26 of 91 young women (29 percent) had highly or moderately disordered eating behaviour, which persisted in 16 (18 percent) and improved in 10 (11 percent). Of the 65 women with normal eating behaviour at base line (71 percent), 14 (15 percent) had disordered eating at follow-up. Omission or underdosing of insulin lose weight was reported by 12 of 88 young women (14 percent) at base line and 30 (34 percent) at follow-up (P=0.003). At base line, the mean (+/SD) haemoglobin A1c value was higher in the group with highly disordered eating behaviour (11.1+/-1.2 percent) than in the groups whose eating behaviour was High incidence of intentional insulin omission to control weight</td>
<td>Case series IV</td>
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</tbody>
</table>
Disordered eating at baseline was associated with retinopathy four years later \((P=0.004)\), when 86 percent of the young women with highly disordered eating behavior, 43 percent of those with moderately disordered eating behavior, and 24 percent of those with nondisordered eating behavior had retinopathy.

| Peveler, 1992 | A cross-sectional survey of eating habits and attitudes conducted in 76 adolescents with IDDM, and age- and sex-matched non-diabetic control subjects | Assessed by standardized research interview adapted for use with patients with diabetes (EDE). Glycaemic control was assessed by GHb assay | Adolescent girls with IDDM were heavier than non-diabetic female control subjects and were dieting more intensively to control their shape and weight. However, clinical eating disorders were no more common among adolescent girls with IDDM than among non-diabetic control subjects. Nine percent of the IDDM girls met diagnostic criteria for an operational version of 'Eating disorder not otherwise specified.' Fifteen percent had omitted or reduced their dose of insulin to influence their shape and weight. Eating disorder features and insulin misuse for shape and weight control were not found in IDDM or non-diabetic boys, and these two groups did not differ in their body weight. | High incidence of insulin omission in girls. | Cross-sectional survey | IV |

| Rodin, 1991 | 103 Female T1D patients attending diabetes clinic. Toronto, Canada | Questionnaire and medical note review | 12% reported intentional insulin under treatment as a method of weight control. Incidence of anorexia nervosa 1%. Incidence of bulimia nervosa 12%. Mean age of eating disorder patients 16.2 years. Those with eating disorders were less likely to follow food plan or perform blood glucose monitoring. Mean HbA1c in eating disorder group was significantly higher than those without eating disorders (10% compared with 8.9%, \(p=0.02\)). | Survey questionnaire and medical note review | IV |

18.5 Technical Reports and Consensus Statements used to formulate the recommendations and principles of clinical practice.
### Appendix 2: Evidence Tables

#### Australian Clinical Practice Guidelines: Type 1 Diabetes in Children and Adolescents

<table>
<thead>
<tr>
<th>Ref No</th>
<th>Technical Reports/Consensus Statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>International Society for Pediatric and Adolescent Diabetes: ISPAD Consensus Guidelines for the Management of Type 1 Diabetes Mellitus in Children and Adolescents. Zeist, Netherlands, Medforum, 2000</td>
</tr>
<tr>
<td>59</td>
<td>Australasian Paediatric Endocrine Group. APEG Handbook on Childhood and Adolescent Diabetes. Sydney, Australasian Paediatric Endocrine Group, 1996</td>
</tr>
<tr>
<td>60</td>
<td>National Institute for Clinical Excellence. <em>Type 1 Diabetes (Childhood): Diagnosis and Management of Type 1 Diabetes in Children and Young People (DRAFT)</em>. 2004.</td>
</tr>
</tbody>
</table>

### Chapter 19: School

#### 19.1 The effects of type 1 diabetes on cognitive function in children and adolescents.

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref No</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Comments</th>
<th>Design</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Puczyński 1990</td>
<td>5</td>
<td>24 school aged children with T1D (14 with hypo and 10 controls with no hypo)</td>
<td>14 tested immediately after complete symptom resolution of mild hypo episode</td>
<td>Neuropsych testing</td>
<td>Stat sig. decrease in 5/12 tasks following mild hypoglycaemic episode despite complete resolution of symptoms</td>
<td>Suggests time lag in resolution of cognitive function after mild hypo</td>
<td>Comparative</td>
<td>III-2</td>
</tr>
<tr>
<td>Davis 1996</td>
<td>9</td>
<td>12 children aged 12.4+/-2.6 years, age (range 11.1-15.4 years), duration of diabetes 5.9+/-3 years.</td>
<td>Hyperglycaemia or euglycaemia (Effect of hyperglycaemia using a modified glucose clamp to maintain BG between 5-10 mmol/l or between 20-30 mmol/l)</td>
<td>WISC-111 subtests</td>
<td>Analysis of variance demonstrated as significant decrease in performance IQ when hyperglycaemic (106+/-4.3 vs 112+/-4.5 IQ points, p=0.05) 8/12 had decreased IQ when hyperglycaemic, 2 remained the same and 2 had a slight increase</td>
<td>Patients were randomised to either euglycaemia or hyperglycaemia in the first instance, and then received the crossover treatment at least six months later</td>
<td>RCT (crossover)</td>
<td>II</td>
</tr>
<tr>
<td>Matyka 1999</td>
<td>10</td>
<td>29 prepubertal T1D</td>
<td>Cognitive function</td>
<td>No sig diff. bxn noct hypo nights and control nights</td>
<td></td>
<td></td>
<td>Comparative</td>
<td>III-2</td>
</tr>
<tr>
<td>Author(s)</td>
<td>Year</td>
<td>Study Design</td>
<td>Sample Details</td>
<td>Measures</td>
<td>Results</td>
<td>Methodology</td>
<td>Study Design</td>
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<tr>
<td>Holmes</td>
<td>1985</td>
<td>Case series</td>
<td>41 children with T1D divided into 4 groups depending on age of onset and length of duration</td>
<td>Mood assessment: WISC-R, WAIS-R, MMFFT for Attention</td>
<td>Higher depression score after hypo night (p=0.03)</td>
<td>Case series IV</td>
<td>IV</td>
<td></td>
</tr>
<tr>
<td>Rovet</td>
<td>1997</td>
<td>Case series</td>
<td>103 T1D (50 boys, 53 girls), mean age 13.5 +/- 2.3 years. 100 controls (50 boys, 50 girls), mean age 13.1 +/- 2.5 years</td>
<td>WISC-R, WAIS-R, MMFFT for Attention</td>
<td>IQ scores lower in early onset and longer duration. Reading and memory impairment in early onset groups.</td>
<td>Comparative III-2</td>
<td>II</td>
<td></td>
</tr>
<tr>
<td>Sansbury</td>
<td>1997</td>
<td>Case series</td>
<td>28 T1D children Age at onset, Duration, HbA1c</td>
<td>WISC-R, Matching figures, Behaviour checklist</td>
<td>Increased age assoc with decreased IQ score. Inc duration assoc with lower matching figures score. Poor met control assoc with lower vocab subtest scores.</td>
<td>Case series IV</td>
<td>IV</td>
<td></td>
</tr>
<tr>
<td>Rovet</td>
<td>1999</td>
<td>Case series</td>
<td>16 children with type 1 diabetes 9 had hypoglycaemic seizure Follow up at 1, 3, 7 years</td>
<td>Verbal IQ, Perceptual, fine motor, visuomotor, visual memory and attention</td>
<td>Hypo seizures more likely to have IQ decline (67% vs 14%, p&lt;0.05). Hypo seizure patients scored lower (p&lt;0.01)</td>
<td>Unclear methodology</td>
<td>IV</td>
<td></td>
</tr>
<tr>
<td>Hannonen</td>
<td>2003</td>
<td>Comparative</td>
<td>21 children with T1D and 10 healthy controls Divided into 3 groups T1D and one episode of severe hypo T1D with no hypo. Normal controls</td>
<td>WISC-R, NEPSY (dev. Neuropsych assessment)</td>
<td>Attention – T1D without hypox had test scores significantly lower than controls (p&lt;0.05). Phonological processes in T1D with hypox scored lower than controls (p&lt;0.05). Memory – Digit span</td>
<td>Comparative III-2</td>
<td>II</td>
<td></td>
</tr>
</tbody>
</table>
## Appendix 2: Evidence Tables

### Australian Clinical Practice Guidelines: Type 1 Diabetes in Children and Adolescents

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Population</th>
<th>Methodology</th>
<th>Measures</th>
<th>Results</th>
<th>Study Type</th>
<th>Case Series</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rovet 1990</td>
<td>16</td>
<td>63 new T1Ds, 40 sibling controls</td>
<td>Neurocog function examined at onset and 1 year later</td>
<td>WISC-R, Vocabulary decreased after 1 year (p=0.05)</td>
<td>Both T1D with &amp; without scored lower compared with controls (p&lt;0.01)</td>
<td>Comparative cohort study</td>
<td>III-2</td>
</tr>
<tr>
<td>Northam 1998</td>
<td>17</td>
<td>123 children (3-14 years) with recent T1D onset were compared with 129 community control subjects</td>
<td>Standardized measures of general intelligence, attention, speed of processing, memory, learning, executive skills and behavioural adjustment soon after diagnosis and 2 years later.</td>
<td>WPPSI-R, WISC-R and others</td>
<td>No differences in T1D and controls at initial assessment within 3 months of diagnosis. After 2 years significant decrease in vocabulary IQ (P&lt;0.01), block design P&lt;0.05) subtests. Multivariate group differences were apparent on speed of processing (p&lt;0.05) and learning (P&lt;0.01) subtests, reflecting smaller developmental gains in children with IDDM when compared with control subjects.</td>
<td>Comparative</td>
<td>III-2</td>
</tr>
<tr>
<td>Northam 2001</td>
<td>18</td>
<td>Follow up study from Northam 98 study</td>
<td>90 patients (aged 6-17 years, mean 12.1 +/- 2.9) who had been previously assessed soon after Dx and 2 years later were re-evaluated 6 years after onset of diabetes. 84 controls (12.1 +/- 2.8 years, p=NS).</td>
<td>Six years after onset of diabetes, children with T1D performed more poorly than controls on verbal IQ (F=8.07, p&lt;0.01), full scale IQ (F=5.33, P&lt;0.05), attention (F=2.63, P&lt;0.05), processing speed (F=4.81, P&lt;0.01), long-term memory (F=3.58, P&lt;0.01), and executive skills (F=4.57, P&lt;0.05).</td>
<td>Severe hypo assoc. with lower verbal and full-scale intelligence quotient scores.</td>
<td>Comparative</td>
<td>III-2</td>
</tr>
<tr>
<td>Schoenle 2002</td>
<td>19</td>
<td>64 T1D children between the ages of 7 and 16 years</td>
<td>Longitudinal study looking at long term metabolic control and hypoglycaemia on intellectual development.</td>
<td>Assessed at least 4 times using German version of the Hamburg Wechsler intelligence scale for preschool children, and by the Adaptive Intelligence Diagnosticum</td>
<td>Significant performance decline by 7yr and verbal IQ between age 7 and 16 years was observed in diabetic boys diagnosed before the age of 6 (not in those diagnosed later, not in diabetic girls).</td>
<td>Prospective longitudinal study. Cohort of 64 patients analysed out of a larger group of 164 patients being followed. Selection based on having had at least 4 out of 6 longitudinally applied tests between ages 7 to 16 yrs.</td>
<td>Prospective longitudinal case series</td>
</tr>
</tbody>
</table>

Appendix 2: Evidence Tables
Australian Clinical Practice Guidelines: Type 1 Diabetes in Children and Adolescents
The deterioration of performance in boys diagnosed at a very young age was not associated with the occurrence of severe hypoglycaemic episodes but was correlated with the degree of metabolic deterioration at diagnosis and with high long-term average of HbA1c. Male sex, diagnosis at a young age, metabolic condition at diagnosis and long-term metabolic control (p<0.001), rather than experienced hypoglycaemic attacks (p>0.21) are risk factors for intellectual development.

<table>
<thead>
<tr>
<th>Ref No</th>
<th>Technical Reports/Consensus Statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>International Society for Pediatric and Adolescent Diabetes: Consensus Guidelines for the Management of Type 1 Diabetes Mellitus in Children and Adolescents. Zeist, Netherlands, Medforum, 2000</td>
</tr>
</tbody>
</table>

Chapter 20: Diabetes Camps

No studies were identified specifically addressing the benefits on glycaemic control of diabetes camps.

### Consensus Statements used to formulate the recommendations and principles of clinical practice.

<table>
<thead>
<tr>
<th>Ref No</th>
<th>Technical Reports/Consensus Statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>Australasian Paediatric Endocrine Group: APEG Handbook on Childhood and Adolescent Diabetes. Sydney, Australasian Paediatric Endocrine Group, 1996</td>
</tr>
</tbody>
</table>

Chapter 21: Travelling and Holidays

### Insulin regimen during travel when crossing time zones.

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref No</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Comments</th>
<th>Design</th>
<th>Level</th>
</tr>
</thead>
</table>
## Appendix 2: Evidence Tables

### Australian Clinical Practice Guidelines: Type 1 Diabetes in Children and Adolescents

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th>No.</th>
<th>Study Details</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sane 90</strong></td>
<td>27 T1D patients</td>
<td>Advised to increase their insulin dose if travelling west, and decrease if travelling east. Also have 2-4 units of short-acting if BGL &gt; 15 mmol/L.</td>
<td>Total insulin dose required</td>
<td>Westward travel: increase in insulin 3.1% of total daily dose per time shift hour. Eastward travel reduced insulin dose 2.6% of total daily dose per time shift hour. Mean BGL same for east and west travel, but higher for travel days than days at home.</td>
</tr>
<tr>
<td><strong>Jones 94</strong></td>
<td>16 insulin treated patients (age range 9-69) 2 on basal bolus regimen, and 14 on BD injections</td>
<td>Individually advised to adjust insulin depending on flight and regimen. Basal bolus patients were advised to continue taking short-acting insulin with each meal during travel, but no intermediate acting. BD patients were advised to take between 15-20% of TDD before each meal.</td>
<td>Patient satisfaction</td>
<td>Patients were happy with this simple system and reported no problems.</td>
</tr>
</tbody>
</table>

| **21.2 Consensus Statements used to formulate the recommendations and principles of clinical practice.** |
|---|---|---|---|---|
| Ref No | Technical Reports/Consensus Statements |
| 6 | Australasian Paediatric Endocrine Group: APEG Handbook on Childhood and Adolescent Diabetes. Sydney, Australasian Paediatric Endocrine Group, 1996 |

**Chapter 22: Complementary and Alternative Medicine**

No Level I or II studies were identified for this chapter.

**22.1 Consensus Statements used to formulate the recommendations and principles of clinical practice.**

| Ref No | Technical Reports/Consensus Statements |
|---|---|---|---|---|