Evidence-based Paediatric and Adolescent Diabetes

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Foreword

There appear to be a number of irrefutable facts about diabetes in childhood: some to do with aetiology and others related to the management of this group of disorders [1]. First, type 1 diabetes mellitus (T1DM) accounts for the vast majority of children and youths with diabetes. T1DM is increasing in incidence worldwide at the rate of 2–5% per year, with immigrant populations relatively quickly assuming the higher incidence in their new countries. Second, there has been a staggering increase in childhood obesity worldwide, bringing with it a significant increase in earlier onset of T2DM, probably not yet of the epidemic proportions in the youth that many have threatened. Third, molecular genetic technologies have helped unravel the mysteries of an increasing number of monogenic types of diabetes, both neonatal and childhood/young adult onset. Finally, the data derived from two sentinel randomised control trials, namely the Diabetes Control and Complications Trial (DCCT) and its extension observation study Epidemiology of Diabetes Interventions and Complications (EDIC) in T1DM, and the United Kingdom Prospective Diabetes Study (UKPDS) in T2DM inform the current approach to the control of hyperglycaemia in order to prevent the onset or slow the progression of diabetes-related complications.

While certain 'facts' may seem irrefutable, what is less robust are the data needed to fill in the details about the why's, when's, what's and how-to's about the cause, course and complications of all types of diabetes. This is where a careful distillation of the available information is required and decisions are made based on the most convincing evidence. The discipline of evidence-based medicine has arisen and rapidly evolved as a means of accomplishing this as accurately and reproducibly as possible in order to provide the state-of-the-art recommendations for diagnosis, treatment and prognosis of the condition under review. There are several caveats that warrant attention here. First, the recommendations can only be as strong as the data that underpin them. Second, there is in the field of diabetes in children and the youth a paucity of data on which to make the highest grade recommendations. This is a fact of life in most areas of paediatric medicine. Finally, the evidence changes, and it may do so quite rapidly with the emergence of new therapeutic agents (e.g. insulin analogues and oral hypoglycaemic agents). Hopefully, this means that as steadily as the evidence accumulates and improves, so does the treatment and outcome of the condition.

A couple of sobering thoughts are in order here. First, a study from the Centers for Disease Control in Atlanta, USA [2], in 2003 reported a loss of almost 20 life years for 10-year-old children diagnosed with diabetes in the year 2000. And Gale from Bristol [3] has pointed out that the majority of children with diabetes worldwide will *not* achieve levels of control commensurate with reasonable protection from microvascular complications. Furthermore, '*the individual and communal legacy of poor glucose control will remain with us for the next thirty years, even if an effective means of preventing new cases of the disease*

were to be introduced tomorrow.' Gale concluded that '*the greatest need is for more effective implementation of what is already known*' [3].

In this book, editor Jeremy Allgrove has marshalled the energies and expertise of a highly qualified and accomplished international group of childhood diabetes specialists to sift carefully through the evidence ('what is already known') and make the best possible recommendations for the care of children and the youth with diabetes. The result is an outstanding addition to the literature in this field. This has been a gargantuan, but highly worthwhile, task at a number of levels. First, it helps the reader understand just how strong (or not) the evidence is for recommending one approach over another. Then, it highlights the areas where the evidence is not based on the type of studies needed to provide high-grade recommendations, but in which there is general consensus as to a most sensible approach. In many of these instances, the gold-standard study, a randomised controlled trial, is unlikely to be performed. Finally, it lays bare the issues that remain inadequately addressed such that no definitive recommendations can be made.

Undoubtedly, both the editor and the chapter authors as well as the readers hope that the recommendations will soon be out of date with the emergence of 'newer and better' approaches to diabetes prediction and prevention in both T1DM and T2DM, management that facilitates achievement and maintenance of normoglycaemia without the ever-present threat of hypoglycaemia and prevention or reversal of complications. Until such time as these advances become reality, this volume will stand as a wonderful navigator for health-care professionals involved in the care of children with all types of diabetes. My heartiest congratulations to Dr Allgrove and his contributors for their superb efforts.

Denis Daneman
Past President, ISPAD

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Preface

This book is intended to be part of a series of evidence based publications on a variety of topics. It is particularly intended as a companion volume to 'Evidence-Based Diabetes' which will deal in a similar manner with the field of adult diabetes. It is not intended to be yet another guideline to the treatment of diabetes as several of these have already been published, but rather to concentrate on the evidence that is available in the paediatric field to support the development of those guidelines. Whilst we have tried to be as comprehensive as possible, there are certain topics that have not yet had a significant impact on paediatric practice and are therefore not covered. These include inhaled insulins, the artificial pancreas and pancreatic cell transplantation. Nevertheless, there are topics covered, not least the chapter on Type 2 Diabetes, which are unlikely to have been included in a similar publication even five years ago but which are of increasing importance today.

It has been an enormous privilege to have been asked to edit this edition of 'Evidence-Based Paediatric and Adolescent Diabetes' and a great pleasure to be able to work with my co-authors, Peter Swift and Stephen Greene, both of them long-standing colleagues and good friends. I wish to thank them and all of our co-authors for their hard work and effort in seeing this book through to its final stages. I also wish to thank the publishers, Blackwell's, for their unstinting support and encouragement in making it possible.

Many thanks also to all of the authors who have contributed to the book and for their efforts in getting manuscripts in on time so that publication can go ahead within the time frame originally envisaged. Finally I wish to thank my wife, Natalie, for her patience and understanding in tolerating my slaving over a hot computer when other attractions beckoned.

When one is responsible for editing a book that is dependent upon evidence, it is, of course, necessary to ensure that the evidence presented is as was originally published, even if the conclusions reached in those papers were dubious. Martin Routh (1755–1854), British academic and President of Magdalen College, Oxford from 1791 until his death in 1854, was once asked by an admiring student, towards the end of his life, to supply a precept which might serve as a guiding principle in a young man's life. *'I think, sir,'* he replied, after a moment's thought, *'since you come for the advice of an old man, you will find it a very good practice always to verify your references!'* I hope that all of the references quoted here have been verified.

Jeremy Allgrove,
Editor-in-Chief

CHAPTER 1
Methodology of evidence-based medicine

Jeremy Allgrove

When one admits that nothing is certain one must, I think, also admit that some things are much more nearly certain than others.

—Bertrand Russell. 'Am I an Atheist or an Agnostic?' 1947
British author, mathematician and philosopher (1872–1970)

Introduction

Over the past two decades evidence-based medicine has become increasingly important in determining the way in which medicine is practised. The medical profession has always had a reputation for questioning its own practices, as demonstrated by the number of scientific publications that have appeared since medical journals were invented. As a result, considerable advances in health care have been achieved.

Nevertheless, it is not always the case that ideas that have developed are necessarily correct, and dogmatic statements or assumptions that have been made have sometimes turned out to be false when re-examined more rigorously. Although it has been suggested that 'it is curious, even shocking, that the adjective "evidence-based" is needed' [1], it is nevertheless the purpose of evidence-based medicine to limit these false assumptions and incorrect dogma so that patients may be treated in the best possible way with the tools available.

What is evidence-based health care?

The Cochrane library [2] quotes three slightly different definitions of evidence-based health care:

• Evidence-based health care is the conscientious use of current best evidence in making decisions about the care of individual patients or the delivery of health services. Current best evidence is up-to-date information from relevant, valid research about the effects of different forms of health care, the potential for harm from exposure to particular agents, the accuracy of diagnostic tests and the predictive power of prognostic factors [3].

• Evidence-based clinical practice is an approach to decision-making in which the clinician uses the best evidence available, in consultation with the patient, to decide upon the option which suits that patient best [4].

• Evidence-based medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients. The practice

of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research [5].

All of these definitions are very similar but differ slightly in emphasis on such matters as patient involvement and reliance on diagnostic tests.

What constitutes proof?

Scientific proof has always depended on probabilities rather than absolute proof and is determined by observation and perception. Both of these are open to misinterpretation and can be refuted by other observations that may be made under different circumstances. Statistical analysis is frequently used to 'verify' observations and it has become usual practice to accept that a probability of something being true with 95% certainty ($p < 0.05$) means that observation is 'true'. By definition, it also means that there is a 5% chance that it will not be true.

In contrast, there is a fundamental difference between a scientific proof and a mathematical proof [6, pp. 21–2]. In the latter, proof is absolute and remains so forever. If proof is not absolute, i.e. if a flaw can be found in the logic, then proof does not exist. A simple example of this is the proof of the well-known formula of Pythagoras:

$$a^2 + b^2 = c^2$$

where a, b and c are the values of the sides of a right-angled triangle, c being the hypotenuse. The proof of this theorem is straightforward [6, pp. 333–4] and it can be shown that the relationship is true under *all* circumstances. Thus, if the values of any two numbers are known, the third can always be calculated.

However, this relationship can be rewritten as:

$$a^x + b^x = c^x$$

where the value of x is any whole number greater than 2. The French mathematician Pierre de Fermat (1601–1665) postulated that there is *no* solution to this equation. This has become known as Fermat's last theorem. He died having claimed that he had found a proof that there is no solution, but the proof was lost and the challenge to rediscover it became the most exciting in the field of mathematics for the next 329 years until finally solved by Andrew Wiles in 1994.

Fermat's last theorem is fiendishly difficult to prove. Initial attempts resulted in proofs that the postulate is true for values of $x = 4$ and $x = 3$. The problem is that even if it is possible to show that for all values between, say, 3 and 1000 the postulate is also true, this does not prove the theorem, as there could still be values greater than 1000 that do satisfy the equation. This is shown by another conjecture, that of the Swiss mathematician Leonhard Euler, which states that there are also no solutions to the equation:

$$x^4 + y^4 + z^4 = \omega^4$$

Initial attempts to solve it proved fruitless and the lack of a counter-example was taken as proof of its truth until a solution* was eventually found in 1988 some two centuries after it was postulated [6]. Therefore, Euler's postulate is absolutely not true in mathematical

*$2{,}682{,}440^4 + 15{,}365{,}639^4 + 18{,}796{,}760^4 = 20{,}615{,}673^4$

terms, although in scientific terms it had been taken to be so. Thus, to obtain an absolute proof, it is necessary to go back to first mathematical principles and demonstrate that the conditions apply to *all* numbers.

Scientific proof is not so rigorous and only demands that there is a sufficient body of evidence to suggest very strongly that a fact is 'true'. Medicine is no different in this respect from other scientific disciplines and, particularly because one is dealing with a biological rather than a physical system, is particularly open to variations in response. The most rigorous method available to scientists, in the realm of medicine, for determining the effectiveness of a treatment is the double-blind, placebo-controlled trial, properly conducted under clearly defined conditions with sufficient numbers of patients and with removal of bias. Some treatments have fulfilled these criteria, although others that are regularly used have never been tested under such circumstances. There has, for instance, never been such a trial of the use of insulin in type 1 diabetes mellitus (T1DM). It would, of course, be totally unethical to conduct such a trial now and yet there is little or no doubt that insulin therapy is effective in treating T1DM. The statement 'insulin is an effective treatment of T1DM' is taken to be true. Evidence-based medicine depends upon scientific observation rather than mathematical proof and is always open to some degree of doubt, however small. It is therefore necessary to have some means of gauging how reliable a piece of evidence is in scientific terms.

Grading of evidence

Several methods of grading evidence have been used and different guideline development groups (GDGs) have used different methods of classifying evidence. The classification used by the Scottish Intercollegiate Guideline Network (SIGN) is the most detailed [7]. The 'levels of evidence' are then converted into 'grades of recommendation' (A–D). In addition, they list 'good practice points' (GPPs).

The National Institute for Clinical Excellence (NICE), an independent body set up by the UK Department of Health, uses a similar, though not quite so detailed, classification [8]. It gives grades A–D and GPPs, and also recommendations from NICE technology appraisals.

The American Diabetes Association (ADA) has the simplest classification. This does not describe a level of evidence which is then converted into a grade but assigns a grade directly to a study [9]. The classification is shown in Table 1.1.

All of these grading methods are similar but, since this book is not designed to be another guideline but rather to present the evidence, we have chosen to use the ADA classification which does not include any GPPs, etc. The new International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines also use the same gradings. Where relevant, gradings have been assigned to references within the text.

Guidelines

Since the beginning of the 1990s there has been a move away from professional consensus towards more rigorous scientific methods, such as systematic reviews and meta-analyses [10]. This has usually been done in the context of creating guidelines, although the quality of these guidelines has varied depending on how rigorously the methodology has been applied. In 2003, Burgers *et al.* published a study, on behalf of the Appraisal of Guidelines,

Table 1.1 ADA evidence grading system for clinical practice recommendations

Level	Description
A	Clear evidence from well-conducted, generalisable, randomised controlled trials that are adequately powered, including: • evidence from a well-conducted multicentre trial • evidence from a meta-analysis that incorporated quality ratings in the analysis • compelling non-experimental evidence, i.e. 'all-or-none' rule developed by Centre for Evidence-Based Medicine at Oxford Supportive evidence from well-conducted randomised controlled trials that are adequately powered, including: • evidence from a well-conducted trial at one or more institutions • evidence from a meta-analysis that incorporated quality ratings in the analysis
B	Supportive evidence from well-conducted cohort studies: • evidence from a well-conducted prospective cohort study or registry • evidence from a well-conducted meta-analysis of cohort studies • supportive evidence from a well-conducted case-control study
C	Supportive evidence from poorly controlled or uncontrolled studies: • evidence from randomised clinical trials with one or more major or three or more minor methodological flaws that could invalidate the results • evidence from observational studies with high potential for bias (such as case series with comparison to historical controls) • evidence from case series or case reports Conflicting evidence with the weight of evidence supporting the recommendation
E	Expert consensus or clinical experience

Note: There is no Grade **D**.

Research and Evaluation for Europe (AGREE) study group [11], in which they described the structures and working methods of 18 national GDGs from 13 different countries worldwide. These did not include guideline development by NICE since this organisation was formed only in 1999 and produced its first report in 2002. They concluded that '*principles of evidence-based medicine dominate current guideline programs*'. As a result, it can be concluded that most of the current guidelines that have been developed are reasonably well evidence based and well referenced.

However, this is not always the case. For instance, the Consensus Guidelines for the Management of Type 1 Diabetes in Children and Adolescents published by ISPAD in 2000 contained no references. It raises the question of how truly evidence-based they were and how much they depended on the views and opinions of the guideline development team. Having said that, they have proved invaluable as a resource. The situation is due to be rectified with the publication of the new ISPAD Clinical Practice Consensus Guidelines 2006/2007, which are heavily referenced. The first two chapters were published in 2006 (**E**) [12, 13], with the rest due to be published in 2007.

Bertrand Russell is quoted as saying [14], '*The fact that an opinion has been widely held is no evidence whatever that it is not utterly absurd; indeed in view of the silliness of the majority of mankind, a widespread belief is more likely to be foolish than sensible*'. Although he was referring to marriage, he could as easily have been referring to clinical guidelines. That is not to say that guidelines should not be followed, but it must be understood that, whilst

they are usually well researched, there are often aspects of the guidelines that are based solely on the personal opinions of those drawing them up with little or no hard evidence to support them and there may be individual circumstances where they do not necessarily apply.

There may also be a tendency, in some instances, for recommendations to be 'transferred' from one guideline to another by default. Let us examine, as an example, the statement made in all of the major national and international guidelines for the treatment of diabetic ketoacidosis (DKA) in children that the dose of insulin should be '0.1 unit per kilogram body weight per hour' **(E)** [8, 15–18]. The British Society for Paediatric Endocrinology and Diabetes (BSPED) guidelines **(E)** [16] state that '*Modifications (to their previous guideline) have been made in the light of the guidelines produced by the International Society for Pediatric and Adolescent Diabetes (2000) and the recent ESPE/LWPES consensus statement on diabetic ketoacidosis in children and adolescents*', and the NICE guidelines **(E)** [8] say that '*The current guidelines take account of recently published consensus statements developed by the European Society for Paediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society. The guidelines highlight the need for further research to investigate the effectiveness of different concentrations of rehydration fluid, the rate of rehydration and the concentration of insulin infusion in the management of diabetic ketoacidosis*'. The implication of these two statements is that they are merely following previous recommendations and have not re-examined the evidence.

Despite claims to the contrary [15], the evidence for the stated dose of insulin is weak. The Lawson Wilkins Pediatric Endocrine Society/British Society of Paediatric Endocrinology and Diabetes (LWPES/BSPED) guidelines state that '*Physiologic studies indicate that IV insulin at a dose of 0.1 unit/kg per hour, which achieves steady state plasma insulin levels of ~100 to 200 μU/mL within 60 minutes, is effective*'. However, as stated by Edge and Spinks in Chapter 4 of this book, '*there is a body of opinion that a dose of 0.05 units/kg/hour is sufficient to reverse the metabolic abnormalities and overcome any insulin resistance whilst reducing the blood glucose at a steadier rate*', and many units in the UK ignore the national and international guidelines and routinely use this lower dose.

The statement, which is given an **A** grading, is based on a study conducted in six adults with established diabetes who were rendered ketotic by the administration of two doses of dexamethasone and cessation of insulin in the 24 hours prior to the study [19]. They were then given insulin infusions at varying rates (0.01, 0.1 and 1 U/kg/h) in random order. Steady-state levels of insulin were measured and the rates of fall of glucose and ketones, as measured by β-hydroxybutyric acid and acetoacetate, observed with the different doses. The principal conclusions were as follows:

1 An infusion rate of 0.1 U/kg/h achieves a steady-state insulin concentration between 100 and 200 μU/mL (an increase between 90 and 112 μU/mL over baseline).

2 Logarithmic increases in infusion rates resulted in logarithmic increases in insulin concentration.

3 The effect of insulin on reducing ketones was maximal at 0.1 U/kg/h but the effect on reducing blood glucose had no such plateau effect; i.e. the rate of fall of blood glucose continues to increase with larger doses of insulin.

Unfortunately, an infusion rate of 0.05 U/kg/h was not tested but it can be deduced from the above that this lower rate of infusion would be likely to result in a steady-state concentration of insulin of ~55 μU/mL, which may well be sufficient to switch off ketogenesis (the principal aim of insulin therapy in the treatment of DKA) whilst reducing

the rate of fall of blood glucose. This is supported by another study, also conducted in adults [20], and also quoted in the LWPES/BSPED guidelines, in which patients with newly diagnosed diabetes were admitted with DKA and treated with insulin at a rate of 1 mU/kg/min (≡0.06 U/kg/h). This resulted in a steady fall in blood glucose at an acceptable rate of 3.3 mmol/L/h and correction of the acidosis.

In some units it is considered important to control the rate of fall of blood glucose with the use of systems that involve the use of solutions of different strengths of dextrose, used at different rates depending upon circumstances, a situation that arguably increases the risk of error. Even so, in one such study [21], which was conducted in children, the recommended dose of 0.1 U/kg/h was used and the blood glucose fell initially, when no glucose was being infused, by approximately 33 mmol/L in the first 5 hours (6.6 mmol/h), a rate which is now regarded as being too rapid. Although there is little evidence to support it, a maximum of 5 mmol/L/h is recommended by the ISPAD guidelines (**E**) [17].

It is therefore clear that the evidence for the recommended dose of insulin is weak and has never been properly tested in children. It is possible that this dose *is* correct (although it may be different at different ages) but, as stated in the NICE guidelines, '*further research to investigate the effectiveness of different concentrations of . . . insulin infusion in the management of diabetic ketoacidosis*' is required (see above). Evidence-based medicine should ultimately be able to provide an answer.

Guidelines are widely quoted throughout this book and in many instances, the recommendations are clearly evidence based and have a high degree of validity. Nevertheless, in view of the fact that they are all consensus documents, they are always given an **E** grading. Whilst there is clearly a hierarchy of validity between **A** and **C**, an **E** grading does not necessarily mean that this is the lowest level since consensus documents do often contain systematic reviews or meta-analyses, which, under other circumstances, might be rated **A**. Having said that, some **C**-graded articles, particularly those that are case reports, may still carry quite a lot of weight if they contain, for instance, convincing genetic data.

Sources of data

Electronic databases, such as MEDLINE, have proved enormously helpful in searching for relevant studies. Not only do they make the searches much faster than previously, but they are inevitably more thorough. We have made use of all the available databases including:

- Allied & Complementary Medicine – 1985 to date
- British Nursing Index – 1994 to date
- CINAHL (R) – 1982 to date
- DH-DATA – 1983 to date
- EMBASE – 1974 to date
- King's Fund – 1979 to date
- MEDLINE – 1950 to date
- PsycINFO – 1806 to date.

These have all been available either via KA24, the National Health Service (NHS) portal available to NHS employees (accessible via http://www.hilo.nhs.uk/ to registered personnel) [22], or via PUBMED, a service of the National Library of Medicine and the National Institutes of Health (accessible via http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=Pager&DB=pubmed).

In addition, the relevant Cochrane databases have been examined. These are a series of systematic reviews based on available publications and are also available via http://www.hilo.nhs.uk/ [22]. (This requires no special permissions.) Cochrane describes a systematic review as follows:

• To help identify which forms of health-care work, which do not and which are even harmful, Results from similar randomised trials need to be brought together. Trials need to be assessed and those that are good enough can be combined to produce both a more statistically reliable result and one that can be more easily applied in other settings. This combination of trials needs to be done in as reliable a way as possible. It needs to be systematic. A systematic review uses a predefined, explicit methodology. The methods used include steps to minimise bias in all parts of the process: identifying relevant studies, selecting them for inclusion and collecting and combining their data. Studies should be sought regardless of their results.

• A systematic review does not need to contain a statistical synthesis of the results from the included studies. This might be impossible if the designs of the studies are too different for an averaging of their results to be meaningful or if the outcomes measured are not sufficiently similar. If the results of the individual studies are combined to produce an overall statistic, this is usually called a meta-analysis. A meta-analysis can also be done without a systematic review, simply by combining the results from more than one trial. However, although such a meta-analysis will have greater mathematical precision than an analysis of any one of the component trials, it will be subject to any biases that arise from the study-selection process and may produce a mathematically precise, but clinically misleading, result.

The Cochrane databases deal mainly with adult practice and have little relevance to paediatrics. There is only one systematic review relating directly to children listed on their website [23]. Nevertheless, the principles of systematic reviews and meta-analyses are important and apply equally to children as to adults.

Summary and conclusions

Evidence-based medicine is becoming increasingly important in determining how best patients should be treated. There is an element of cost-effectiveness built into the system but this is not the principal aim of the process. Unfortunately, in paediatric practice, there is a certain paucity of studies in many areas and it has been necessary to rely on studies in adults which are then extrapolated into paediatrics. Whilst this is valid in some areas, it may not be so in others and one has to retain a certain degree of scepticism in doing so. The aim of this book is to present the data that are available in the hope that they will shed some light on why paediatricians treat their patients as they do and to highlight some of the areas where knowledge is lacking and which require further research.

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CHAPTER 2

Definition, epidemiology and classification of diabetes and structure of the diabetes team

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Accurate knowledge is the basis of correct opinions; the want of it makes the opinions of most people of little value.

—Charles Simmons, American Writer (1924–)

Definition, epidemiology and classification

Diabetes mellitus is a group of metabolic diseases characterised by chronic hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. The abnormalities in carbohydrate, fat and protein metabolism that are found in diabetes are due to deficient action of insulin on target tissues. If ketones are present in blood or urine, treatment is urgent, because ketoacidosis can evolve rapidly.

Diagnostic criteria for diabetes in childhood and adolescence

Diabetes in children usually presents with the characteristic symptoms of polyuria, polydipsia and weight loss, in association with glycosuria and ketonuria. In its most severe form ketoacidosis or, rarely, a non-ketotic hyperosmolar state may develop and lead to stupor, coma and, without treatment, death. The diagnosis is usually confirmed quickly by measurement of a markedly elevated blood glucose level. If ketones are also present in blood or urine, treatment is urgent. Waiting another day to confirm the hyperglycaemia is dangerous as ketoacidosis can evolve rapidly (**E**).

In the 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 fasting and/or 2-hour postprandial blood glucose levels and/or an oral glucose tolerance test (OGTT) (**E**) [1, 2] (Table 2.1). In the absence of symptoms of diabetes, hyperglycaemia detected incidentally or under conditions of acute infection, trauma, circulation or other stress may be transitory and should not in itself be regarded as diagnostic of diabetes.

An OGTT should not be performed if diabetes can be diagnosed using fasting and random or postprandial criteria, as excessive hyperglycaemia can result. It is rarely indicated in making the diagnosis of type 1 diabetes mellitus (T1DM) in childhood and adolescence (**E**) [1]. If doubt remains, periodic retesting should be undertaken until the diagnosis is

Table 2.1 Criteria for the diagnosis of diabetes mellitus (**E**) [1, 2]

- Symptoms of diabetes plus casual plasma glucose concentration ≥11.1 mmol/L (200 mg/dL)*
  (Casual is defined as any time of day without regard to time since last meal.)
  or
- Fasting plasma glucose ≥7.0 mmol/L (≥126 mg/dL)
  (Fasting is defined as no caloric intake for at least 8 h.)
  or
- Two-hour post-load glucose ≥11.1 mmol/L (≥200 mg/dL) during an OGTT

The test should be performed as described by WHO [1], using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water or 1.75 g/kg of body weight to a maximum of 75 g.

*Corresponding values (mmol/L) are ≥10.0 for venous whole blood and ≥11.1 for capillary whole blood and ≥6.1 for both venous and capillary whole blood.

established. In the absence of unequivocal hyperglycaemia with acute metabolic decompensation, these criteria should be confirmed by repeat testing on a different day.

Impaired glucose tolerance and impaired fasting glycaemia

Impaired glucose tolerance (IGT) and impaired fasting glycaemia (IFG) are intermediate stages in the natural history of disordered carbohydrate metabolism between normal glucose homeostasis and diabetes (**E**) [1, 2]. IFG and IGT are not interchangeable and represent different abnormalities of glucose regulation; 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.

Patients with IFG and/or IGT are now referred to as having 'pre-diabetes', indicating their relatively high risk for development of diabetes (**A**) [3, 4]. Pre-diabetes can be observed as an intermediate stage in any of the disease processes given in Table 2.2. IFG and IGT may be associated with the metabolic syndrome, which includes obesity (especially abdominal or visceral obesity), dyslipidaemia of the high-triglyceride and/or low-high-density lipoprotein type and hypertension (**E**) [5].

Individuals who meet criteria for IGT or IFG may be euglycaemic in their daily lives as shown by normal or near-normal glycated haemoglobin levels, and those with IGT may manifest hyperglycaemia only when challenged with an OGTT. Recently, the European Diabetes Epidemiology Group has recommended revising the lower cut-off for IFG back to 6.1 mmol/L from the current value of 5.6 mmol/L due to the two- to fivefold increase in prevalence of IFG across the world (**E**) [6] but the American Diabetes Association (ADA) continues to recommend 5.6 mmol/L as the cut-off point for normal FPG [2].

Categories of fasting plasma glucose (FPG) are defined as follows [2]:

- FPG <5.6 mmol/L (100 mg/dL) = normal fasting glucose
- FPG 5.6–6.9 mmol/L (100–125 mg/dL) = IFG
- FPG ≥7.0 mmol/L (126 mg/dL) = provisional diagnosis of diabetes (The diagnosis must be confirmed, as described above in the section *Diagnostic criteria.*)

The corresponding categories for stimulated plasma glucose when the OGTT is used are as follows:

- 2-hour post-load glucose <7.8 mmol/L (140 mg/dL) = normal glucose tolerance
- 2-hour post-load glucose 7.8–11.1 mmol/L (140–199 mg/dL) = IGT
- 2-hour post-load glucose ≥11.1 mmol/L (200 mg/dL) = provisional diagnosis of diabetes (The diagnosis must be confirmed, as described above.)

Table 2.2 Aetiological classification of disorders of glycaemia

I Type 1	
Beta-cell destruction, usually leading to absolute insulin deficiency	
Autoimmune	
Idiopathic	
II Type 2	
It may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with or without insulin resistance	
III Other specific types	
(a) Genetic defects of beta-cell development or function	
Chromosome 12, HNF-1_{α}	(MODY3)
Chromosome 7, glucokinase	(MODY2)
Chromosome 20, HNF-4_{α}	(MODY1)
Chromosome 13, insulin promoter factor-1	(IPF-1; MODY4)
Chromosome 17, HNF-1ß	(MODY5)
Chromosome 2, *NeuroD1*	(MODY6)
carboxyl exter lipase (CEL) gene	(MODY7)
Mitochondrial DNA mutation	DIDMOAD (Wolfram)
Chromosome 11	PNDM
Chromosome 11	PNDM/TNDM
Chromosome 6	TNDM
Chromosome 2	Wolcott—Rallison
Chromosome X	IPEX
Chromosome 10	PNDM and cerebellar agenesis
Others	
(b) Genetic defects in insulin action	
Type A insulin resistance	
Leprechaunism	
Rabson–Mendenhall syndrome	
Lipoatrophic diabetes	
Others	
(c) Diseases of the exocrine pancreas	
Pancreatitis	
Trauma/pancreatectomy	
Neoplasia	
Cystic fibrosis	
Haemochromatosis	
Fibrocalculous pancreatopathy	
Others	
(d) Endocrinopathies	
Acromegaly	
Cushing syndrome	
Glucagonoma	
Phaeochromocytoma	
Hyperthyroidism	
Somatostatinoma	
Aldosteronoma	
Others	
(e) Drug or chemical induced	
Vacor	
Pentamidine	
Nicotinic acid	
Glucocorticoids	
Thyroid hormone	

Continued

Table 2.2 *Continued*

Diazoxide
β-adrenergic agonists
Thiazides
Dilantin
Interferon alpha
Others
(f) Infections
Congenital rubella
Enterovirus
Cytomegalovirus
Others
(g) Uncommon forms of immune-mediated diabetes
'Stiff-man' syndrome
Anti-insulin receptor antibodies
Autoimmune polyendocrine syndromes (APS) I and II
Others
(h) Other genetic syndromes sometimes associated with diabetes
Down syndrome
Klinefelter syndrome
Turner syndrome
DIDMOAD (Wolfram) syndrome
Friedreich ataxia
Huntington chorea
Laurence–Moon–Biedl syndrome
Myotonic dystrophy
Porphyria
Prader–Willi syndrome
Others
IV Gestational diabetes

DIDMOAD, Diabetes insipidus, diabetes mellitus, optic atrophy and deafness; PNDM, permanent neonatal diabetes mellitus; TNDM, transient neonatal diabetes mellitus; IPEX, immune dysregulation, polyendocrinopathy, enteropathy X-linked syndrome.

Epidemiology of T1DM

Approximately 50–60% of individuals with T1DM are diagnosed before the age of 15 years (**B**) [7]. In most Western countries, T1DM accounts for over 90% of childhood and adolescent diabetes. However, T2DM is becoming more common and it accounts for a significant proportion of youth-onset diabetes in certain at-risk populations (**B**) [8, 9].

T1DM incidence varies greatly between different countries, within countries, and between different ethnic populations (**B**) [10]. Epidemiological incidence studies define the 'onset of T1DM' by the date of the first insulin injection because of the variable time between the onset of symptoms and diagnosis (**B**) [10]. Annual incidence rates for childhood T1DM (0–14 yr age group) comparing different countries of the world are shown in Figure 2.1 (0.1–43.9/100,000) [10–13]. Gender differences in incidence are found in some, but not all, populations (**B**) [10, 14–17].

Incidence rates show a close correlation with the frequency of human leucocyte antigen (HLA) susceptibility genes in the general population of white Caucasian ancestry; this locus confers approximately 50% of the genetic susceptibility to T1DM (**B**) [18–20] (see Chapter 3 for a more detailed discussion of this). In countries where the incidence of T1DM