# HANDBOOK OF DIABETES

5TH EDITION

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WILEY Blackwell

# Handbook of Diabetes

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Rudy Bilous would like to dedicate this book firstly, to all of the people with diabetes for whom he has had the privilege of caring in over 40 years of practice; and to his DSN partner and wife Mary who showed him how to practice patient centred care over many years of joint practice, and whose forbearance, encouragement, patience and advice were crucial to his chapters.

# Contents

# Preface

It is more than 10 years since the last edition and much has changed in diabetes understanding and therapy. Advances in diabetes technologies such as continuous glucose monitoring have made the use of closed-loop insulin infusion devices commonplace in many countries. New therapies for type 2 diabetes have led to the concept of personalised management algorithms for patients based upon individual circumstances such as age, weight and presence of complications or comorbidities. Large randomised trials of these treatments have shown benefit in terms of reduction of cardiovascular and renal risk. Diabetic retinopathy is no longer the leading cause of blindness in the working age population in the UK. Bariatric surgery and very low calorie diets have demonstrated the reversibility of type 2 diabetes.

Some things are sadly the same, however, such as the seemingly inexorable rise in prevalence, with the 2019 global figures already exceeding the 2025 predictions of the last edition. Others have fallen short of initial promise, such as islet cell transplantation, and while genetic research into the causes of diabetes has increased our understanding it has not yet been translated into new treatments.

This latest version of the Handbook has been revised and updated incorporating all of these developments and more, and there are new chapters on Cancer and Liver disease. We have tried to maintain the standards and ethos of previous editions. References are again selective but focus on reviews that are freely available wherever possible; key guidance from NICE, SIGN, ADA and other specialist bodies is also included.

Iskandar Idris is a new member of the editorial team and we would like to thank Alistair Lumb for his contribution to the chapters on type 1 diabetes treatment and psychological problems.

The team at Wiley have been notable for their patience. We would like to thank Priyanka Gibbons, Anupama Srikanth, and Jennifer Seward. Their forbearance during the long gestation of this edition is much appreciated. Any errors of commission or omission are, of course, the responsibility of the editors.

The goal with this latest edition is to continue to provide a useful desktop reference for all involved in providing care to people with diabetes.

*Rudy Bilous*
*Richard Donnelly*
*Iskandar Idris*

# Key to the boxes

**KEY POINTS**

These points summarise important learning topics, things to remember and/or areas that are sometimes misunderstood by healthcare professionals.

**CASE HISTORY**

This is a typical case summary that illustrates a number of learning topics from the chapter.

**LANDMARK CLINICAL TRIALS**

These are often major trials underpinning the evidence base for clinical practice and decision-making in the area.

**KEY WEBSITES**

Websites that contain further information, practice guidelines and/or learning topics to supplement the information in the chapter.

**FURTHER READING**

Published reviews, original research or meta-analyses relevant to the chapter.

# List of abbreviations

| | |
|---|---|
| ABPI | Ankle Brachial Pressure Index |
| ABPM | ambulatory blood pressure measurement |
| ACCORD | Action to Control Cardiovascular Risk in Diabetes |
| ACE | angiotensin-converting enzyme |
| ACEI | angiotensin-converting enzyme inhibitors |
| ACR | albumin creatinine ratio |
| ADA | American Diabetes Association |
| ADVANCE | Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation |
| AGE | advanced glycation endproduct |
| AKI | acute kidney injury |
| ALT | alanine aminotransferase |
| AMI | acute myocardial infarction |
| ARB | angiotensin type 1 receptor blocker |
| AST | aspartate aminotransferase |
| ATP | adenosine triphosphate |
| BB | BioBreeding |
| BMI | Body Mass Index |
| BP | blood pressure |
| CABG | coronary artery bypass grafting |
| CBT | cognitive behavioural therapy |
| CCB | calcium channel blockers |
| CETP | cholesterol ester transfer protein |
| CF | cystic fibrosis |
| CGM | continuous glucose monitoring |
| CHD | coronary heart disease |
| CI | confidence interval |
| CIDP | chronic inflammatory demyelinating polyneuropathy |
| CKD | chronic kidney disease |
| CSF | cerebrospinal fluid |
| CSII | continuous subcutaneous insulin infusion |
| CT | computed tomography |
| CVD | cardiovascular disease |
| DAFNE | Dose Adjustment for Normal Eating |
| DAG | diacylglycerol |
| DCCT | Diabetes Control and Complications Trial |
| DESMOND | Diabetes Education and Self-Management Ongoing and Newly Diagnosed |
| DIDMOAD | diabetes insipidus diabetes mellitus optic atrophy deafness |
| DKA | diabetic ketoacidosis |
| DME | diabetes-related macular oedema |
| DPP-4 | dipeptidyl peptidase-4 (IV) |
| DSN | diabetes specialist nurse |
| DVA | Driving and Vehicle Agency |
| DVLA | Driving and Vehicle Licensing Authority |
| eAG | estimated average glucose |
| ED | erectile dysfunction |
| EDIC | Epidemiology of Diabetes Complications |
| eGFR | estimated glomerular filtration rate |
| eNOS | endothelial nitric oxide synthase |
| EPO | erythropoietin |
| ESRD | end-stage renal disease |
| ETDRS | Early Treatment Diabetic Retinopathy Study |
| EURODIAB | European Diabetes complications |
| FATP | study group<br>fatty acid transporter protein |
| FDA | Food and Drug Administration |
| FFA | free fatty acids |
| FPG | fasting plasma glucose |
| FSD | female sexual dysfunction |
| GAD | glutamic acid decarboxylase |
| GBM | glomerular basement membrane |
| GCK | glucokinase |
| GDM | gestational diabetes mellitus |
| GFAT | glutamine:fructose-6-phosphate amidotransferase |
| GFR | glomerular filtration rate |
| GI | gastrointestinal |
| GIP | gastric inhibitory polypeptide |
| GIR | glucose infusion rate |
| GKI | glucose potassium insulin infusion |
| GLP-1 | glucagon-like peptide-1 |

| | |
|---|---|
| GLUT | glucose transporter |
| GWAS | genome wide association study |
| HBPM | home blood pressure measurement |
| HDL | high-density lipoprotein |
| HHS | hyperosmolar hyperglycaemic state |
| HL | hepatic lipase |
| HLA | human leukocyte antigen |
| HOMA | Homeostasis Model Assessment |
| HPLC | high-pressure liquid chromatography |
| HR | hazard ratio |
| hsCRP | high-sensitivity C-reactive protein |
| IAA | insulin autoantibody |
| IAPP | islet amyloid polypeptide |
| ICA | islet cell antibody |
| | insulin-dependent diabetes mellitus |
| IFG | impaired fasting glycaemia |
| IGF | Insulin-like growth factor |
| IGT | impaired glucose tolerance |
| IM | intramuscular |
| IPPV | intermittent positive pressure ventilation |
| IQR | interquartile range |
| IRMA | intraretinal microvascular abnormality |
| IRS | insulin receptor substrate |
| ITU | intensive therapy unit |
| IV | intravenous |
| KATP | ATP-sensitive potassium channel |
| LADA | latent autoimmune diabetes of adults |
| LDL | low-density lipoprotein |
| LH | luteinising hormone |
| MAP | mitogen-activated protein |
| MAPK | mitogen-activated protein kinase |
| MDI | multiple daily injection |
| MHC | major histocompatibility complex |
| MI | myocardial infarction |
| MODY | maturity-onset diabetes of the young |
| mTOR | mammalian target of rapamycin |
| NADH | nicotinamide adenine dinucleotide |
| | plus hydrogen |
| NADPH | nicotinamide adenine dinucleotide |
| NDIP | phospate hydrogen |
| | National Diabetes in Pregnancy audit |
| NEFA | non-esterified fatty acid |
| NDIP | National Diabetes in Pregnancy audit |
| NFκB | nuclear factor kappa-light-chain-enhancer |
| | of activated B cells |
| NGT | normal glucose tolerance |
| NICE | National Institute of Health and Clinical |
| | Excellence |
| NK | natural killer |
| NKCF | natural killer cell factor |
| NLD | necrobiosis lipoidica diabeticorum |
| NO | nitric oxide |
| NOD | non-obese diabetic |
| NPH | neutral protamine Hagedorn |
| NPY | neuropeptide Y |
| NVD | new vessels on the disc |
| NVE | new vessels elsewhere |
| OCT | optical coherence tomography |
| OGTT | oral glucose tolerance test |
| OR | odds ratio |
| PAD | peripheral arterial disease |
| PAI-1 | plasminogen activator inhibitor-1 |
| PCI | percutaneous coronary intervention |
| PCOS | polycystic ovary syndrome |
| PG | plasma glucose |
| PI | phospatidylinositol |
| PKC | Protein kinase C |
| PNDM | permanent neonatal diabetes mellitus |
| PP | pancreatic polypeptide |
| PPARγ | peroxisome proliferator-activated receptor-γ |
| PRP | panretinal laser photocoagulation |
| PTDM | post-transplant diabetes mellitus |
| QALY | quality-adjusted life-year |
| RAGE | receptor for AGE |
| RAS | renin-angiotensin system |
| RCT | randomised controlled trial |
| ROS | reactive oxygen species |
| RRR | relative risk reduction |
| RRT | renal replacement therapy |
| RXR | retinoid X receptor |
| SC | subcutaneous |
| SGLT2 | sodium-glucose transporter 2 |
| SMI | severe mental illness |
| SPK | simultaneous pancreas and kidney |
| | transplantation |
| SU | sulfonylurea |
| TCC | total contact casting |
| TCF7L2 | transcription factor 7-like 2 gene |
| TG | triglyceride |
| TGF | transforming growth factor |
| TIA | transient ischaemic attack |
| TNF | tumour necrosis factor |
| TZD | Thiazolidinediones |
| UKPDS | UK Prospective Diabetes Study |
| UTI | urinary tract infections |
| VCAM | vascular cell adhesion molecule |
| VDT | vibration detection threshold |
| VEGF | vascular endothelium-derived growth factor |
| VIP | vasoactive intestinal peptide |
| VLDL | very low-density lipoprotein |
| VRIII | variable rate intravenous insulin infusion |
| WESDR | Wisconsin epidemiologic study of diabetic |
| | retinopathy |
| WHO | World Health Organization |

# Part 1 Introduction to diabetes

Chapter 1

# Introduction to diabetes

**KEY POINTS**

- Diabetes is common, and its incidence is rising.
- Type 2 diabetes is by far the most common accounting for 85–95% of cases.
- Complications in the microvasculature (eye, kidney and nerve) and the macrovasculature are responsible for considerable morbidity and excess mortality.
- Mortality from some complications is decreasing but absolute numbers for many are still rising.

Diabetes mellitus is a condition of chronically elevated blood glucose concentrations which give rise to its main symptom of passing large quantities of sweet–tasting urine (*diabetes* from the Greek word meaning 'a siphon', as the body acts as a conduit for the excess fluid, and *mellitus* from the Greek and Latin for honey). The fundamental underlying abnormality is a net (relative or absolute) deficiency of the hormone insulin. Insulin is essentially the only hormone that can lower blood glucose.

There are two main types of diabetes: type 1 is caused by an autoimmune destruction of the insulin-producing β cell of the islets of Langerhans in the pancreas (absolute deficiency); and type 2 is a result of both impaired insulin secretion and resistance to its action – often secondary to obesity (relative deficiency).

The precise level of blood glucose that defines diabetes has been revised several times and is covered in more detail in Chapter 3. Diabetes is common and is becoming more common. In absolute numbers, globally there are 463 million people aged 20–79 with known diabetes in 2019, projected to rise to 700 million in 2045. Alarmingly it is thought that there are almost as many again with undiagnosed diabetes. World-wide, age-adjusted prevalence is set to rise from 9.3 to 10.9% in 2045. The numbers of those with impaired glucose tolerance are equally startling with a prevalence of 7.5% in 2019, projected to rise to 8.6% in 2045 (Figure 1.1). The relative proportions of type 1 to type 2 vary from 15 : 85% for Western populations to 5 : 95% in developing countries.

It is the short- and long-term complications of diabetes which make it a major public health problem. Absolute deficiency of insulin leads to ketoacidosis and coma with an appreciable mortality even in the UK and other Western countries. Hyperglycaemic hyperosmolar state is less common but remains an equally serious problem for people with type 2 diabetes (see Chapter 12).

Long-term hyperglycaemia affects the microvasculature of the eye, kidney, and nerve as well as the larger arteries, leading to accelerated atherosclerosis. Diabetes is the most common cause of blindness in those of working age, the most common single cause of end-stage renal failure worldwide, and the consequences of neuropathy and peripheral vascular disease make it the most common cause of non-traumatic lower limb amputation. Diabetes and its complications are estimated to account for 11.3% of all cause mortality in adults aged 20–79 years in 2019 and nearly 50% of these are in people of working age (< 60 years).

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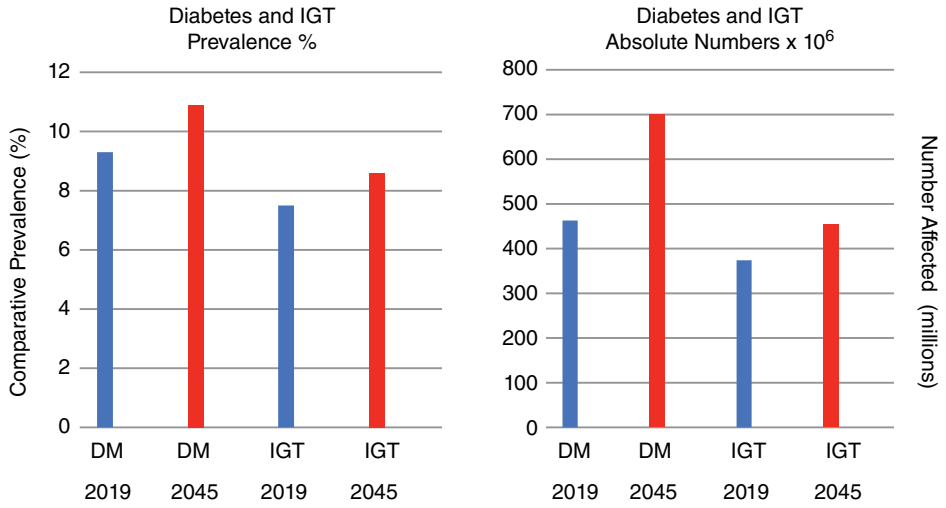



**Figure 1.1** Estimated comparative raw prevalence of diabetes and impaired glucose tolerance (IGT) together with numbers affected for the global population age 20–79 years for 2019 (BLUE) and 2045 (RED). Data from *Diabetes Atlas*, 9th edn, International Diabetes Federation.

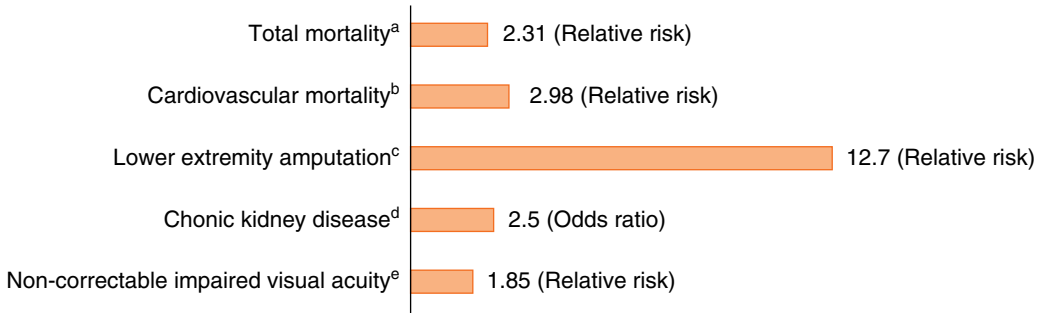
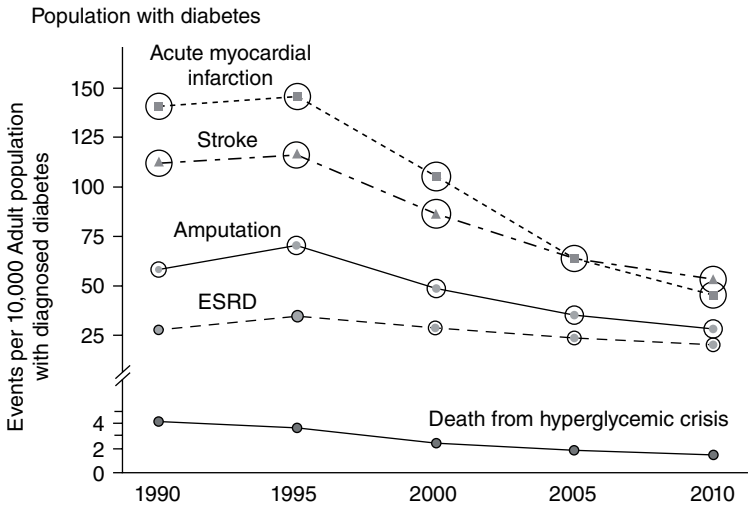



**Figure 1.2** Rates of major complications of diabetes for the US population derived from NHANES or Medicare data. [a]NHANES data 1988–2000; [b]Medicare population Minnesota 1993–5; [c]NHANES data, 1999–2006 (chronic kidney disease defined as estimated GFR <60 mL/min/1.73 $m^2$.); [d]NHANES data, 1999–2002.

Mortality from ischaemic heart disease and stroke is 2–4-fold higher than in the age- and sex-matched non-diabetic population (Figure 1.2). These relative rates have not substantially changed since the last edition, although, encouragingly, mortality rates from acute myocardial infarction and hyperglycaemic crises have reduced, at least in the USA and Sweden (Figure 1.3). Because of the increasing numbers of people with diabetes, however, absolute numbers experiencing stroke, amputation, and end stage renal disease are increasing with massive associated financial costs. In 2019 the IDF estimates total diabetes healthcare expenditure will be US$760 billion and predicts that this will rise to US$ 825 billion in 2030 and US$ 845 billion by 2045 (Figure 1.4).

This handbook sets out to cover the essentials of diagnosis, epidemiology and management of diabetes and its' distressingly many complications. By using case vignettes and summaries of key trials together with web links and suggestions for further reading, it will hopefully serve as a useful desktop reference for all healthcare professionals who provide diabetes care.




| Mortality rates per 10,000 adults with diabetes | 1990 | 1995 | 2000 | 2005 | 2010 |
|---|---|---|---|---|---|
| AMI | 8.5 | 10.1 | 9.6 | 7.3 | 5.7 |
| Stroke | 7.6 | 8.9 | 9.0 | 8.0 | 7.9 |
| Amputation | 3.0 | 4.2 | 4.0 | 3.2 | 3.0 |
| ESRD | 1.1 | 1.6 | 2.1 | 2.2 | 2.1 |
| Hypergly - caemia | 0.17 | 0.15 | 0.12 | 0.10 | 0.10 |

**Figure 1.3** Age standardised mortality rates from diabetes-related complications in the US population with known diabetes 1990–2010. Circle size is proportional to the absolute number of cases. The table shows the rate per 10,000 population with or without diabetes. AMI = acute myocardial infarction, ESRD = End Stage Renal Disease. Figure and data from Gregg, E.W. et al. *NEJM* 2014; 370:1514–23 with permission.

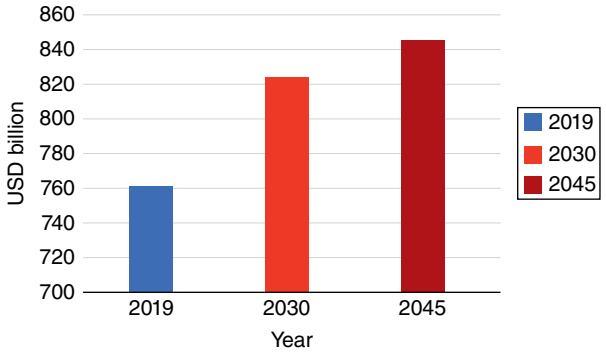



**Figure 1.4** Estimated global diabetes-related healthcare costs for adults aged 20–79 years in 2019, 2030 and 2045. Source: IDF Diabetes Atlas 9th Edition 2019.

**FURTHER READING**

International Diabetes Federation. *Diabetes Atlas*, 9th edn. Brussels: International Diabetes Federation, 2019.

**KEY WEBSITE**

- Diabetes Atlas: **www.diabetesatlas.org**

Chapter 2

# History of diabetes

**KEY POINTS**

- Diabetes has been known since ancient times.
- A link to the pancreas was established in 1889 culminating in the isolation of insulin in 1921.
- There have been five Nobel Prizes awarded to scientists researching diabetes and carbohydrate metabolism.
- The structure of insulin was finally elucidated in the 1960s.
- Insulin was the first therapy to be manufactured using genetic engineering techniques.
- There are now several biologically engineered designer insulin molecules approved for use in man.
- The range of oral and other therapies for type 2 diabetes has led to the concept of personalised medicine.

Diseases with the clinical features of diabetes have been recognised since antiquity. The Ebers papyrus (Figure 2.1), dating from 1550 BC, describes a polyuric state that resembles diabetes.

The word 'diabetes' was first used by Aretaeus of Cappadocia in the second century CE. Aretaeus gave a clinical description of the disease (Box 2.1), noting the increased urine flow, thirst, and weight loss, features that are instantly recognisable today.

The sweet, honey-like taste of urine in polyuric states, which attracted ants and other insects, was reported by Hindu physicians such as Sushrut (Susruta) during the fifth and sixth centuries CE. These descriptions even mention two forms of diabetes, the more common occurring in older, overweight, and indolent people, and the other in lean people who did not survive for long. This empirical subdivision predicted the modern classification into type 1 and type 2 diabetes.

Diabetes was largely neglected in Europe until a seventeenth-century English physician, Thomas Willis (1621–75) (Figure 2.2), rediscovered the sweetness of diabetic urine. Willis, who was physician to King Charles II, thought that the disease had been rare in ancient times, but that its frequency was increasing in his age 'given to good fellowship'. Nearly a century later, the Liverpool physician Matthew

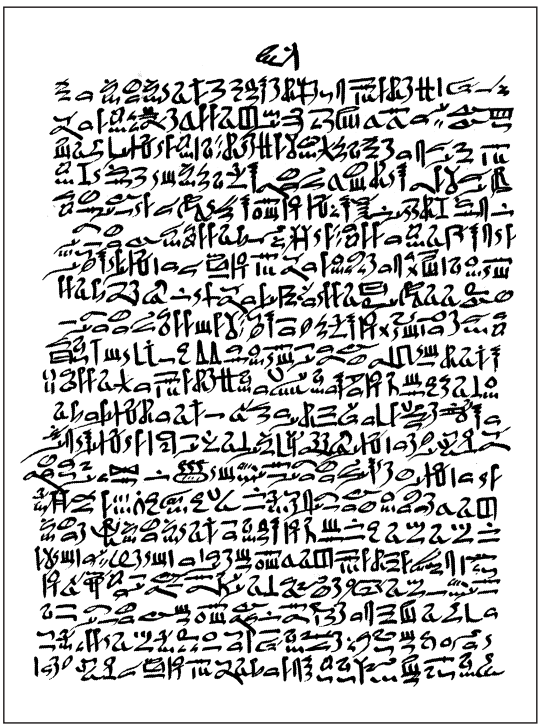


**Figure 2.1** The Ebers papyrus. The Wellcome Institute Library, London, UK.

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**Box 2.1** Description of diabetes by Aretaeus.

Diabetes is a dreadful affliction, not very frequent among men, being a melting down of the flesh and limbs into urine. The patients never stop making water and the flow is incessant, like the opening of aqueducts. Life is short, unpleasant and painful, thirst unquenchable, drinking excessive, and disproportionate to the large quantity of urine, for yet more urine is passed. One cannot stop them either from drinking or making water. If for a while they abstain from drinking, their mouths become parched and their bodies dry; the viscera seem scorched up, the patients are affected by nausea, restlessness and a burning thirst, and within a short time, they expire.

Adapted from Papaspyros S. *The History of Diabetes Mellitus*, 2nd edn. Stuttgart: Thieme, 1964.


**Figure 2.2** Thomas Willis. The Wellcome Institute Library, London, UK.

Dobson (1735–84) showed that the sweetness of urine and serum was caused by sugar. John Rollo (d. 1809) was the first to apply the adjective 'mellitus' to the disease.

In the 19th century, the French physiologist Claude Bernard (1813–78) (Figure 2.3) made many discoveries relating to diabetes. Among these was the finding that the sugar that appears in the urine was stored in the liver as glycogen. Bernard also demonstrated links between the central nervous system and diabetes when he observed temporary hyperglycaemia (piqûre diabetes) when the medulla of conscious rabbits was transfixed with a needle.

In 1889, Oskar Minkowski (1858–1931) and Joseph von Mering (1849–1908) from Strasbourg removed the pancreas

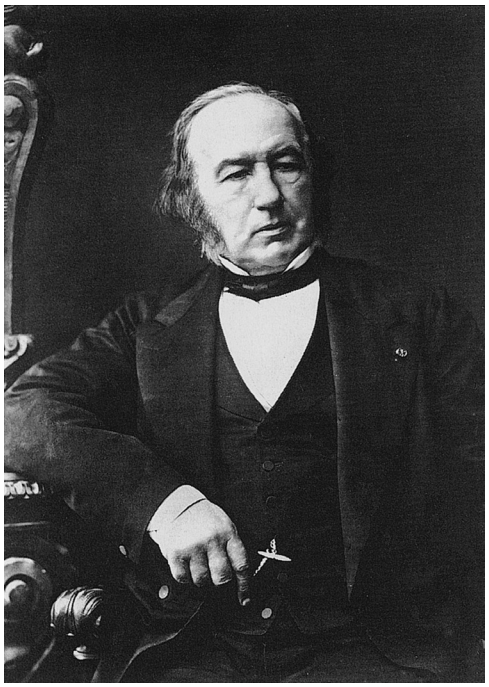

**Figure 2.3** Claude Bernard. The Wellcome Institute Library, London, UK.

from a dog to see if the organ was essential for life. The animal displayed typical signs of diabetes, with thirst, polyuria, and wasting, which were associated with glycosuria and hyperglycaemia. This experiment showed that a pancreatic disorder causes diabetes, but they did not follow up on their observation.

Paul Langerhans (1847–88) (Figure 2.4) from Berlin, in his doctoral thesis of 1869, was the first to describe small clusters of cells in teased preparations of the pancreas. He did not speculate on the function of the cells, and it was Edouard Laguesse in France who later (1893) named the cells 'islets of Langerhans' and suggested that they were endocrine tissue of the pancreas that produced a glucose-lowering hormone.

In the early twentieth century, several workers isolated impure hypoglycaemic extracts from the pancreas, including the Berlin physician Georg Zuelzer (1840–1949), the Romanian Nicolas Paulesco (1869–1931), and the Americans Ernest Scott (1877–1966) and Israel Kleiner (1885–1966).

Insulin was discovered in 1921 at the University of Toronto, Canada, through a collaboration between the surgeon Frederick G Banting (1891–1941), his student assistant Charles H Best (1899–1978), the biochemist James B Collip (1892–1965) and the physiologist JJR Macleod (1876–1935). Banting and Best made chilled extracts of dog pancreas, injected them into pancreatectomised diabetic dogs, and showed a fall in blood glucose concentrations (Figure 2.5).

**Figure 2.4** Paul Langerhans. The Wellcome Institute Library, London, UK.

**Figure 2.5** Charles Best and Frederick Banting in Toronto in 1922 (the dog is thought to have been called Marjorie). The Wellcome Institute Library, London, UK.

Banting and Best's notes of the dog experiments refer to the administration of 'isletin', later called insulin at the suggestion of Macleod. They were unaware that the Belgian Jean de Meyer had already coined the term 'insuline' in 1909. (All these names ultimately derive from the Latin for 'island'.)

Collip improved the methods for the extraction and purification of insulin from the pancreas, and the first person with diabetes, a 14-year-old boy called Leonard Thompson, was treated on 11 January 1922. A commercially viable extraction procedure was then developed in collaboration with chemists from Eli Lilly and Co. in the USA, and insulin became widely available in North America and Europe from 1923. The 1923 Nobel Prize for Physiology or Medicine was awarded to Banting and Macleod, who decided to share their prizes with Best and Collip.

The American physician Elliot P Joslin (1869–1962) was one of the first doctors to gain experience with insulin. Working in Boston, he treated 293 patients in the first year after August 1922. Joslin also introduced systematic education for his diabetic patients.

In the UK, the discovery of insulin saved the life of the London physician Robin D Lawrence (1892–1968), who had recently developed type 1 diabetes. He subsequently played a leading part in the founding of the British Diabetic Association now Diabetes UK.

Among the many major advances since the introduction of insulin into clinical practice was the elucidation in 1955 of its primary structure (amino acid sequence) (Figure 2.6) by the Cambridge UK scientist Frederick Sanger (b. 1918), who received the Nobel Prize for this work in 1958.

Oxford-based Dorothy Hodgkin (1910–1994), another Nobel Prize winner, and her colleagues described the three-dimensional structure of insulin using X-ray crystallography (1969). In total, there have been five Nobel Prizes awarded for scientific discoveries related to diabetes and carbohydrate metabolism.

By the 1950s, it was accepted that tissue complications, such as those that occur in the eye and kidney, continued to develop in long-standing diabetes, in spite of insulin treatment. The definitive proof that normalisation of glycaemia could prevent or delay the development of diabetic complications had to wait until 1993 for type 1 diabetes (the Diabetes Control and Complications Trial in North America) and 1998 for type 2 diabetes (the UK Prospective Diabetes Study – UKPDS).

Until the 1980s, insulin was derived only from animal pancreata, in increasingly more refined preparations. Using additives such as protamine or zinc, the subcutaneous absorption could be delayed, thus providing 24-hour availability using 2–4 injections a day of different preparations.

With the development of genetic engineering, it became possible to produce human insulin and subsequent further

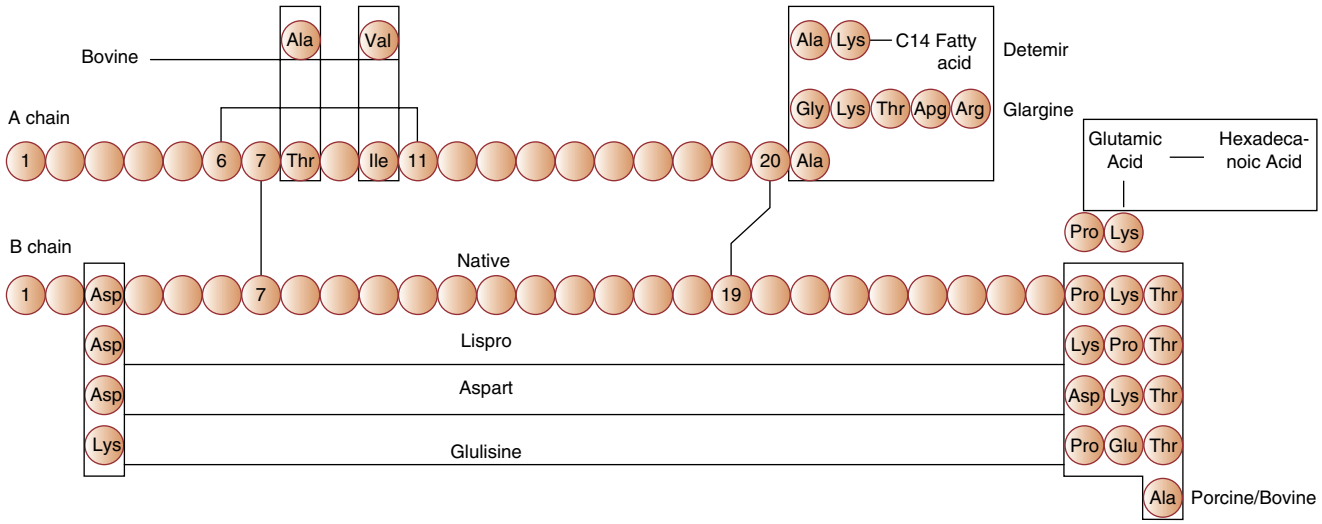


**Figure 2.6** Schematic amino acid sequence of human insulin; porcine and bovine insulin; the short-acting insulin analogues aspart, lispro, and glulisine; and the long-acting analogues glargine, detemir, and degludec.

manipulations of the molecule have led to a wide range of preparations (Figure 2.6) with different absorption profiles (Chapter 10). There has been extensive research into an orally effective form of insulin but a continuing dependence upon subcutaneous injection as the main route of administration is likely for the foreseeable future.

In the 1980s, capillary blood glucose testing was a major breakthrough for patients allowing them to precisely assess their blood glucose levels and check for hypoglycaemia. Modern meters allow downloading of results enabling better informed modification of insulin regimens.

The rapid evolution of insulin delivery devices and continuous subcutaneous glucose sensing over the last decade has led to the production of closed loop systems which are effectively acting as an artificial pancreas. These systems are revolutionising the management of type 1 diabetes, although their cost poses significant challenges for health care funders and has inevitably limited their use.

In type 2 diabetes oral agents have been available since the 1950s, bur the last few decades have seen the production of many different classes of compound that affect insulin secretion, its efficacy and sensitivity, as well as whole body glucose dispersal and excretion. This has led to the development of personalised diabetes therapy based upon the likely defect in the individual patient. This concept of personalised medicine forms the basis of recent guidelines for type 2 diabetes (Chapter 11).

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Chapter 3

# Diagnosis and classification of diabetes

Diabetes mellitus is diagnosed by identifying chronic hyperglycaemia. The World Health Organisation (WHO) and the American Diabetes Association (ADA) use a fasting plasma glucose (FPG) of 7 mmol/L or higher to define diabetes (Table 3.1). This originates from epidemiological studies in the 1990s which appeared to show that the risk of microvascular complications (e.g retinopathy) increases sharply at a FPG threshold of 7 mmol/L (Figure 3.1). Lately, the notion of a clear glycaemic threshold separating people at high and low risk of diabetic microvascular complications has been called into question. The relationship between plasma glucose and microangiopathy is likely to be continuous, thus a FPG of 7 mmol/L is an arbitrary cut-off for defining diabetes which may be lowered in the future.

There are currently 34.2 million people in the USA with diabetes (10.5% of the population). Approximately 7 million of these are not yet aware that they have diabetes. The total number of people with diabetes worldwide is projected to increase from 171 million in 2000 to 366 million in 2030. A key demographic change to the rising prevalence of diabetes worldwide is an increasing proportion of people >65 years of age.

FPG, 2-h PG after 75-g OGTT, and A1C are equally appropriate for diagnostic testing. It should be noted that the tests do not necessarily detect diabetes in the same individuals. The concordance between the FPG and 2-h PG tests is imperfect. The overlap depends on the ethnic and geographical population, and on other characteristics such as age and body mass index. Some individuals have asymptomatic, isolated post-challenge hyperglycaemia, while others

**Table 3.1** Diagnostic criteria for Type 2 diabetes.

Diabetes may be diagnosed based on plasma glucose criteria, either the fasting plasma glucose (FPG) or the 2-h plasma glucose (2-h PG) value after a 75-g oral glucose tolerance test (OGTT) or A1C criteria.

Criteria for the diagnosis of diabetes.

- FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
- 2-h PG ≥200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
- A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*

In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

* In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.

**Table 3.2** Use of HbA1c >6.5% (48 mmol/mol) as a cut-off for making the diagnosis of diabetes offers some advantages but there are several disadvantages.

| Advantages | Disadvantages |
|---|---|
| • Avoids the need for a fasting blood sample, and the pre-analytical instability of glucose measurements.<br>• HbA1c reflects glycaemia over several weeks.<br>• Lower biological variability of HbA1c compared with FPG or 2 h glucose.<br>• Virtual absence of significant retinopathy among people with HbA1c < 6.5%. | • HbA1c measurements can give spurious results in:<br>  ○ anaemia (Fe-deficiency)<br>  ○ haemoglobinopathies<br>  ○ renal failure<br>  ○ different ethnic groups.<br>• Diagnosis by HbA1c will identify a different population to that diagnosed by FPG.<br>• Distribution of HbA1c values varies in different ethnic groups.<br>• HbA1c increases with age<br>• Some patients and ethnic groups may be diagnosed with diabetes by some criteria but not others. |

*Handbook of Diabetes*, Fifth Edition. Rudy Bilous, Richard Donnelly, and Iskandar Idris.
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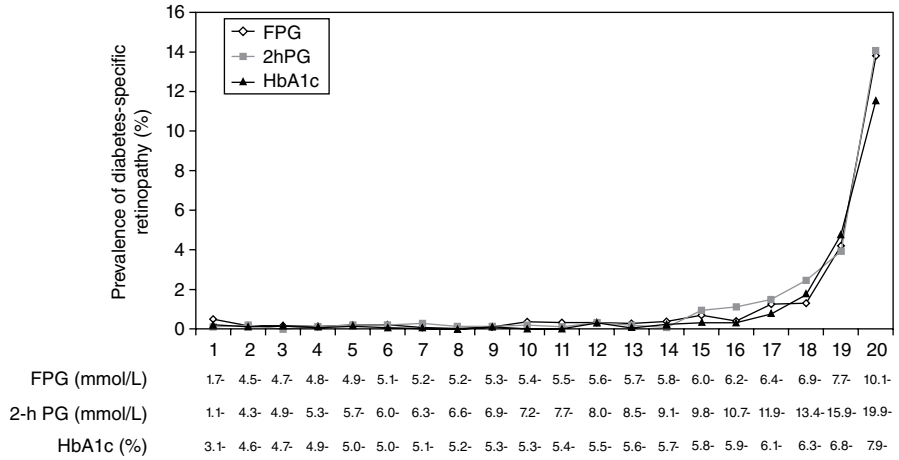


**Figure 3.1** Prevalence of diabetes-specific retinopathy (moderate or more severe retinopathy) by vigintiles of the distribution of FPG, 2-h PG, and A1C. Adapted from Colaguiri et al. Diabetes Care *2011; 34: 145-150.*

have fasting hyperglycaemia but normal post-load glycaemic responses. The fasting criteria for diabetes tend to pick out younger and more obese subjects.

Numerous studies have confirmed that, compared with FPG and A1C cut points, the 2-h PG value diagnoses more people with diabetes. When using A1C to diagnose diabetes, it is important to recognize that A1C is an indirect measure of average blood glucose levels and to take other factors into consideration that may impact haemoglobin glycation independently of glycaemia including age, race/ethnicity, and anaemia/haemoglobinopathies.

## Intermediate categories of hyperglycaemia: Pre-diabetes

During the natural history of all forms of diabetes, the disease passes through a stage of impaired glucose tolerance (IGT), defined as a plasma glucose of 7.8–11.0 mmol/L (140–200 mg/dL) 2 hours after an OGTT (Figure 3.2). Impaired fasting glucose (IFG) is an analogous category based on fasting glucose levels, and is defined as a FPG of 6.1–6.9 mmol/L (110–126 mg/dL).

IGT and IFG are intermediate metabolic stages between normal glucose homeostasis and diabetes. They are both risk factors for future diabetes and cardiovascular disease, but the 2-hour plasma glucose concentration is a particularly strong predictor of cardiovascular risk and mortality.

As with the glucose measures, several prospective studies that used A1C to predict the progression to diabetes as defined by A1C criteria demonstrated a strong, continuous

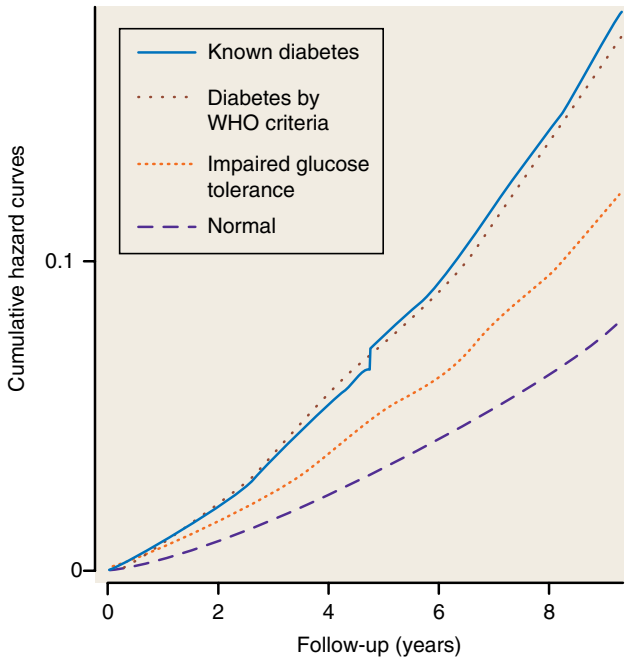


**Figure 3.2** The relationship between 2-hour plasma glucose and survival in patients with normal glucose tolerance, patients with IGT, those with newly-diagnosed diabetes by OGTT, and those with known diabetes, as shown by the DECODE study (combining data from 13 European cohort studies). From Glucose tolerance and mortality: comparison of WHO and American Diabetic Association diagnostic criteria. *The Lancet* 354(9179), 617–621.

association between A1C and subsequent diabetes. Based on numerous studies and meta-analysis, it is now considered

that A1C range of 5.7–6.4% (39–47 mmol/mol) as identifying individuals with prediabetes or with impaired glucose regulation IGR).

A proportion of patients with IFG, IGT and/or IGR (5-10% per annum) will deteriorate metabolically into overt diabetes. Lifestyle modification (diet, exercise and weight loss) is the best approach to diabetes prevention for these patients.

For an OGTT, the subject is tested in the morning after an overnight fast, in the seated position. After taking a fasting blood sample, 75 g of glucose is given by mouth, often in the form of a glucose drink such as Lucozade (843 mL based on the new formulation of 8.9g/100ml of glucose). For children, the glucose dose is calculated as 1.75 g/kg. A further blood sample is taken at 2 hours, and the fasting and 2 hour glucose values are interpreted as in Figure 3.3.

Glycosuria (the presence of glucose in the urine) is responsible for the classic diabetic symptoms and was previously regarded as a diagnostic hallmark of the disease. Nowadays, it indicates the need to test blood glucose, but cannot be used to diagnose diabetes because of the poor relationship between blood and urine glucose (Figure 3.6). This is for several reasons: the renal threshold for glucose reabsorption varies considerably within and between individuals, the urine glucose concentration is affected by the subject's state of hydration and the result reflects the average blood glucose during the period that urine has accumulated in the bladder. The average renal threshold is 10 mmol/L (i.e. blood glucose concentration above this level will 'spill over' into the urine), but a negative urine test can be associated with marked hyperglycaemia.

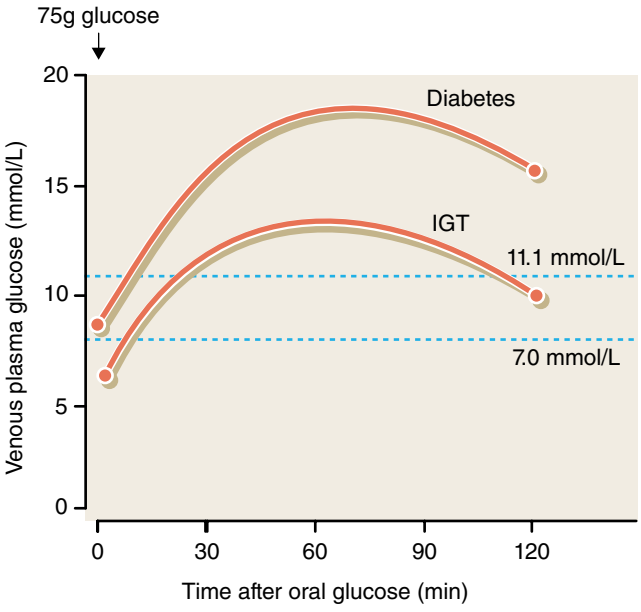


**Figure 3.3** *Diagnosis of diabetes and IGT by the oral glucose tolerance test.*

Longer term indices of hyperglycaemia include the HbA1c, a measure of integrated blood glucose control over the preceding few weeks. HbA1c is used primarily to assess glycaemic control among people with diabetes on treatment. HbA1c analyses are now being calibrated to the IFCC assay. Thus the units of HbA1c in many countries have changed from percent to mmol/mol (Table 3.3).

**Table 3.3** Historically, HbA1c has been reported in percentage values describing the proportion of haemoglobin that is glycated. The assay was aligned to that used in the Diabetes Control and Complications (DCCT) trial. The International Federation of Clinical Chemistry (IFCC) has now established a new reference system, and values will be reported in mmol HbA1c per mol haemoglobin without glucose attached. Conversion for HbA1c is shown below.

| DCCT (%) | IFCC (mmol/mol) | DCCT (%) | IFCC (mmol/mol) |
|---|---|---|---|
| 6.0 | 42 | 9.0 | 75 |
| 6.2 | 44 | 9.2 | 77 |
| 6.4 | 46 | 9.4 | 79 |
| 6.5 | 48 | 9.5 | 80 |
| 6.6 | 49 | 9.6 | 81 |
| 6.8 | 51 | 9.8 | 84 |
| 7.0 | 53 | 10.0 | 86 |
| 7.2 | 55 | 10.2 | 88 |
| 7.4 | 57 | 10.4 | 90 |
| 7.5 | 58 | 10.5 | 91 |
| 7.6 | 60 | 10.6 | 92 |
| 7.8 | 62 | 10.8 | 95 |
| 8.0 | 64 | 11.0 | 97 |
| 8.2 | 66 | 11.2 | 99 |
| 8.4 | 68 | 11.4 | 101 |
| 8.5 | 69 | 11.5 | 102 |
| 8.6 | 70 | 11.6 | 103 |
| 8.8 | 73 | 11.8 | 105 |

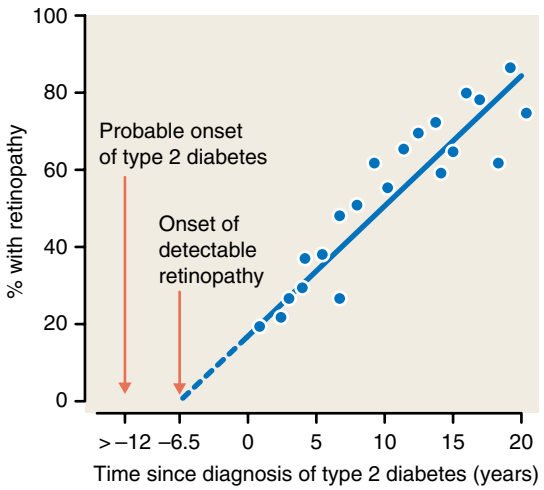


**Figure 3.4** *The prevalence of retinopathy in type 2 diabetes relative to the time of clinical diagnosis. Note the presence of retinopathy at diagnosis and the likely onset of retinopathy and diabetes some years before diagnosis.* From Paisey. Diabetologia 1980; 19: 31 – 34.

The potential value of screening for diabetes is to facilitate early diagnosis and treatment. About 20% of newly diagnosed type 2 diabetic subjects already have evidence of vascular complications, such as retinopathy, the prevalence of which increases with diabetes duration. This suggests that complications begin about 5–6 years before a diagnosis is made, and that the actual onset of (type 2) diabetes may be several years before the clinical diagnosis.

In most countries, there is no systematic screening policy for diabetes, yet there are estimates that up to 50% of patients with diabetes are undiagnosed. Ad-hoc screening of high-risk groups is becoming more common. The fasting

**High-risk patients who should be screened annually for type 2 diabetes**

- Metabolic syndrome
- Patients >45 years of age, especially the obese
- Those with parents or siblings with type 2 diabetes
- Ethnic minorities, e.g. South Indians, even if non-obese
- Patients with cardiovascular risk factors, e.g. hypertension or dyslipidaemia, and those with established atherosclerotic disease
- Women with previous gestational diabetes
- Women with polycystic ovary syndrome
- Patients with IFG/IGT

**Figure 3.5** *High-risk patients who should be screened annually for type 2 diabetes.*

**Classification of diabetes**

- Type 1 (β cell destruction, usually leading to absolute insulin deficiency)
  - Autoimmune
  - Idiopathic
- Type 2
  - Ranges from predominantly insulin resistant, with relative insulin deficiency, to a predominantly insulin-secretory defect, with or without insulin resistance
- Other specific types
  - Genetic defects of β cell function
  - Genetic defects of insulin action
  - Diseases of exocrine pancreas
  - Endocrinopathies
  - Drug induced or chemical induced, e.g. steroids
  - Infections
  - Uncommon forms of immune-mediated diabetes
  - Other genetic syndromes sometimes associated with diabetes
- Gestational diabetes

**Figure 3.6** *Classification of diabetes.*

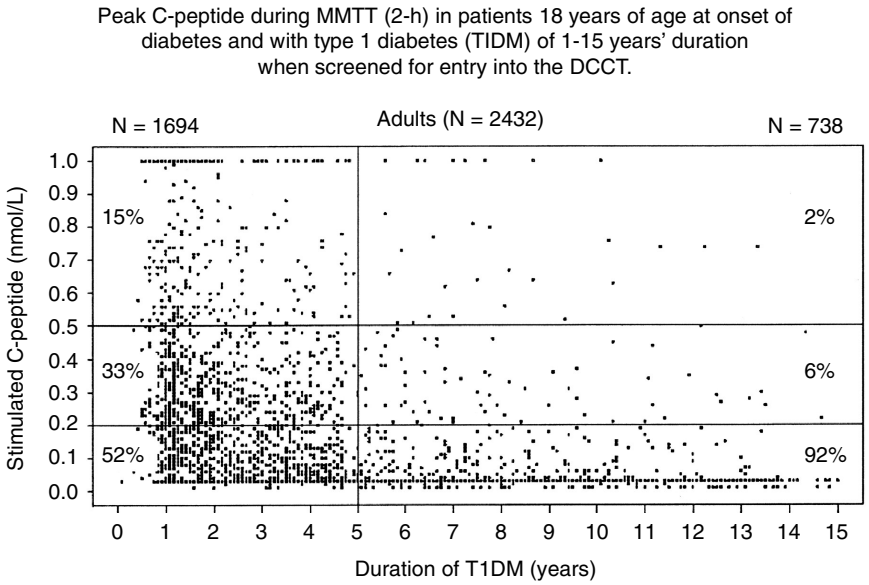


**Figure 3.7** Using C-peptide to confirm type 1 diabetes based on residual beta cell function. MMT-mixed meal tolerance test – i.e. patients ingested a standardized breakfast ingested over 10 min based on the total caloric need of the patient (25–30% of their daily caloric intake; 50% of the calories as carbohydrates). In routine practice this is utilised as a random 'c-peptide' level.

plasma glucose is simple, quick, acceptable to patients and of low cost, but can miss those with isolated post-challenge hyperglycaemia and requires patient to be fasted. The OGTT is more difficult to perform, impractical for large numbers and expensive, but is the only way to identify post-load hyperglycaemia. Screening should focus on high-risk groups. HbA1c is widely used to screen individuals at high risk of developing diabetes.

1 Severe Autoimmune Diabetes (SAID)
2 Severe Insulin Deficient Diabetes (SIDD)
3 Severe Insulin Resistance Diabetes (SIRD)
4 Moderate Obesity Diabetes (MOD)
5 Moderate Age Related Diabetes (MARD)

**Figure 3.8** Five replicable clusters of patients with diabetes. Source: Adapted from Ahlqvist et al. Lancet Diabetes & Endocrinology, 1 March 2018.

Clinical features of type 1 and type 2 diabetes

**Type 1 diabetes**

- Sudden onset with severe symptoms of thirst and ketoacidosis (vomiting, hyperventilation, dehydration)
- Recent, marked weight loss. Usually lean
- Spontaneous ketosis
- Life-threatening; needs urgent insulin replacement
- Absent C-peptide
- Markers of autoimmunity present (e.g. islet cell antibodies)

**Type 2 diabetes**

- Usually insidious onset of tiredness, thirst, polyuria, nocturia
- No ketoacidosis
- Usually overweight or obese; often no recent weight loss
- Frequent infections, e.g. urine, skin, chest
- Symptoms may be minimal and/or ignored by patient
- Often other features of 'metabolic syndrome' , e.g. hypertension
- C- peptide detectable

**Figure 3.9** Clinical features of type 1 and type 2 diabetes.

Other specific types of diabetes

**Genetic defects of β cell function**

- Chromosome 12, HNF-1a (formerly MODY-3)
- Chromosome 7, glucokinase (formerly MODY-2)
- Chromosome 20, HNF-4a (formerly MODY-1)
- Mitochondrial DNA
- Insulinopathies

**Genetic defects in insulin action**

- Type A insulin resistance
- Leprechaunism
- Rabson–Mendenhall syndrome
- Lipoatrophic diabetes

**Diseases of the exocrine pancreas**

- Pancreatitis
- Trauma/pancreatectomy
- Neoplasia
- Cystic fibrosis
- Haemochromatosis
- Fibrocalculous pancreatopathy

**Endocrinopathies**

- Acromegaly
- Cushing's syndrome
- Glucagonoma
- Phaeochromocytoma
- Hyperthyroidism
- Somatostatinoma
- Aldosteronoma

**Drug induced or chemical induced**

- Glucocorticoids
- Thiazides
- Pentamidine
- Nicotinic acid
- Thyroid hormone
- β- adrenergic agonists
- Interferon-α

**Infections**

- Congenital rubella
- Cytomegalovirus
- Others
- Uncommon forms of immune-mediated diabetes
- 'Stiff man' syndrome
- Anti-insulin receptor antibodies

**Other genetic syndromes sometimes a ssociated with diabetes**

- Down's syndrome
- Klinefelter' s syndrome
- Turner's syndrome
- Wolfram' s syndrome
- Friedreich' s ataxia
- Huntington' s chorea
- Lawrence–Moon–Biedl syndrome
- Myotonic dystrophy
- Porphyria
- Prader–Willi syndrome

**Figure 3.10** Other specific types of diabetes.

## Classification of diabetes

The current classification of diabetes is based on the aetiology of the disease. There are four categories:

- Type 1 diabetes (caused by pancreatic islet cell destruction);
- Type 2 diabetes (caused by a combination of insulin resistance and β-cell insulin secretory dysfunction);
- Other specific types of diabetes (caused by conditions such as endocrinopathies, diseases of the exocrine pancreas, genetic syndromes, steroid induced etc., see below);
- Gestational diabetes (defined as diabetes that occurs for the first time in pregnancy).

Type 1 diabetes is subdivided into two main types: 1a or autoimmune (about 90% of type 1 patients in Europe and North America, in which immune markers, such as circulating islet cell antibodies, suggest autoimmune destruction of the β-cells) and 1b or idiopathic (where there is no evidence of autoimmunity).

A steady increase (2.5–3% per annum) in the incidence of type 1 diabetes has been reported worldwide, especially among young children <4 years old. There are large differences between countries in the incidence of type 1 diabetes, e.g up to 10-fold differences among European countries.

This classification has now replaced the earlier, clinical classification into 'insulin-dependent diabetes mellitus' (IDDM) and 'non-insulin-dependent diabetes mellitus' (NIDDM), which was based on the need for insulin treatment at diagnosis. IDDM is broadly equivalent to type 1 diabetes and NIDDM to type 2 diabetes. One of the disadvantages of the old classification according to treatment was that subjects could change their type of diabetes – for example, some type 1a patients diagnosed after the age of 40 years masquerade as NIDDM, before eventually becoming truly insulin-dependent (this is now classified as latent autoimmune diabetes in adults, LADA). Where diagnostic uncertainty exists between type 1 versus non type 1 diabetes, c-peptide assessments can determine residual function beta cells (and insulin dependency to prevent ketoacidosis).

Various clinical and biochemical features can be used to decide whether the patient has type 1 or type 2 diabetes. The distinction may be difficult in individual cases.

A recent study have suggested a novel classification of adult onset diabetes according to patient characteristics (glutamate decarboxylase antibodies, age at diagnosis, BMI, HbA1c and homoeostatic model assessment 2 estimates of beta cell function and insulin resistance) and risk of diabetic complications.

1. Severe Autoimmune Diabetes (SAID)
2. Severe Insulin Deficient Diabetes (SIDD)
3. Severe Insulin Resistance Diabetes (SIRD)
4. Moderate Obesity Diabetes (MOD)
5. Moderate Age Related Diabetes (MARD)

Their study showed that individuals in cluster 3 (Most resistant to insulin) had significantly higher risk of diabetic kidney disease than individuals in cluster 4 and 5. Cluster 2 (insulin deficient) had the highest risk of diabetic eye disease. The largest cluster is cluster 5.

The category of 'other specific types of diabetes' is a large group of conditions, which includes genetic defects in insulin secretion [such as in maturity-onset diabetes of the young (MODY) and insulinopathies], genetic defects in insulin action (e.g. syndromes of severe insulin resistance), pancreatitis, steroid induced and other exocrine disorders, hormone-secreting tumours such as acromegaly (growth hormone) and Cushing's syndrome (cortisol). Some cases are caused by the administration of drugs such as glucocorticoids. Some genetic syndromes are sometimes associated with diabetes (e.g. Down syndrome, Klinefelter's syndrome and many more).

**CASE HISTORY**

A 66-year-old retired policeman attends his family doctor for a routine BP check. He has had hypertension for 4 years. He reports incidentally that he has been feeling generally tired and lethargic. On further questioning, he admits to nocturia x3 and volunteers that in recent months he has been taking a glass of water to bed since he often wakes feeling thirsty. The GP notices that he had a cutaneous boil lanced 6 weeks ago. Apart from hypertension, there is no other significant past medical history, but his body weight has gradually risen (95kg, BMI 32). He takes an ACE inhibitor, lisinopril 10mg, for hypertension. His mother had type 2 diabetes, he is a non-smoker and drinks 15 units of alcohol per week. His only exercise is golf, twice per week. The doctor takes a random venous blood sample, which shows a plasma glucose level of 13 mmol/L. Further blood tests show a normal haematology profile, normal electrolytes and renal function, HbA1c 8.3%, and fasting lipids show total cholesterol 6.6mmol/L, LDL-cholesterol 4.3mmol/L, triglycerides 3.9mmol/L and HDL-cholesterol 0.6mmol/L. Minor abnormalities of liver function are also noted (AST & ALT 2-3x upper limit).

**Comment:** This man presents with typical symptoms of type 2 diabetes and several risk factors (age, obesity, hypertension, family history). The random plasma glucose and HbA1c in the context of symptoms, is diagnostic. He has features of the metabolic syndrome, including hypertension, dyslipidaemia (high triglycerides and low HDL-cholesterol) and central obesity, and fatty infiltration of the liver is common in this scenario. Susceptibility to infections is typical.

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