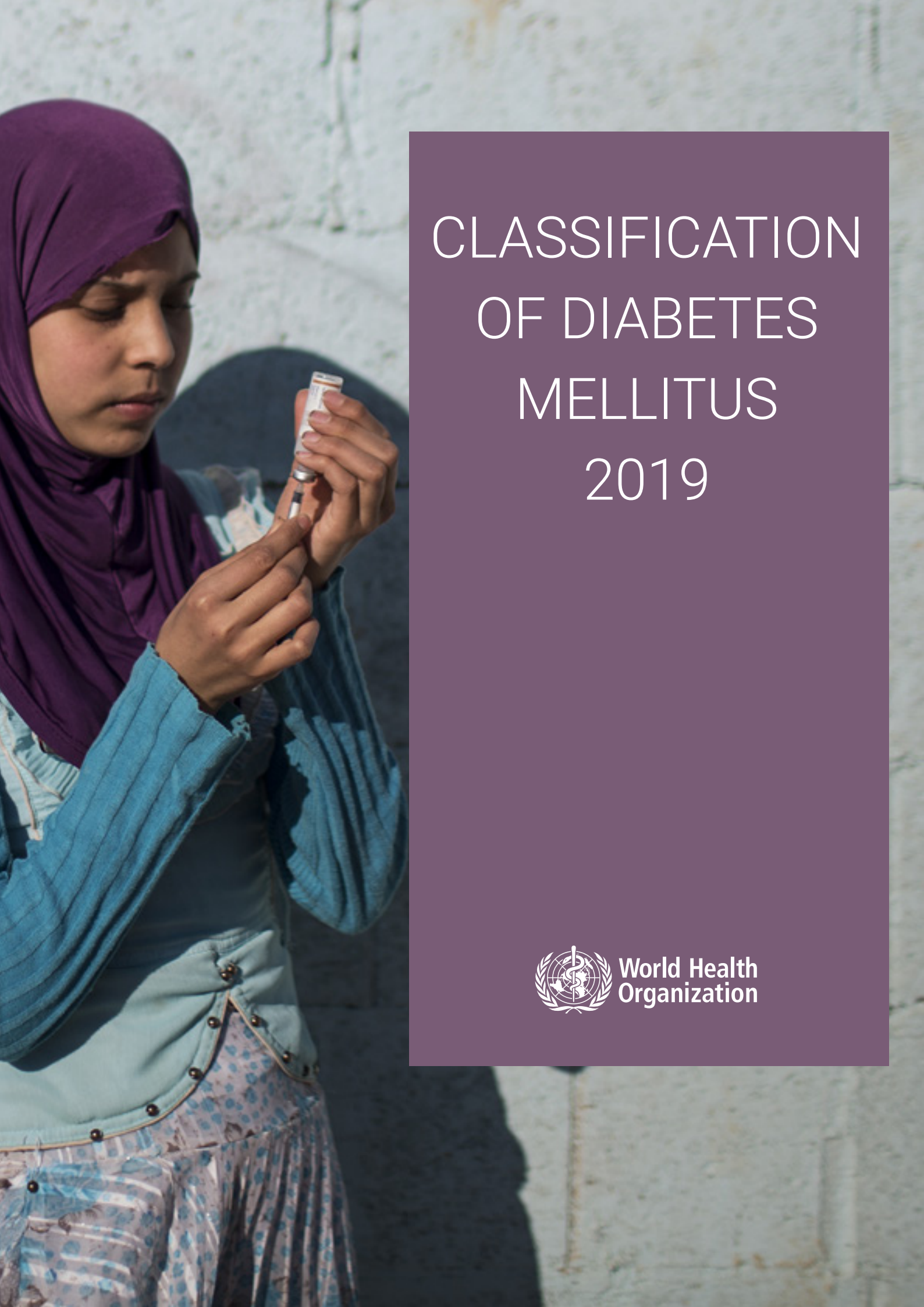


CLASSIFICATION OF DIABETES MELLITUS 2019

World Health Organization

Classification of diabetes mellitus

ISBN 978-92-4-151570-2

Suggested citation. Classification of diabetes mellitus. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

Design and layout by Hélène Dufays.

Photo credits:

Cover: © WHO/Tania Habjouqa

Pages 5, 37: © WHO/Eduardo Martino

Pages 7, 28: © WHO/Atul Loke

Page 12, 17: © WHO/Frederik Naumann

Table of contents

Acknowledgements

WHO gratefully acknowledges the technical input and expert advice provided by the following external experts.

Amanda Adler, Addenbrooke's Hospital, Cambridge, UK

Peter Bennett, Phoenix Epidemiology & Clinical Research Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Phoenix, USA

Stephen Colagiuri (Chair), Boden Institute, University of Sydney, Australia

Edward Gregg, Centers for Disease Control and Prevention, Atlanta, USA

KM Venkat Narayan, the Rollins School of Public Health, Emory University, Atlanta, USA

Maria Inês Schmidt, University of Rio Grande do Sul, Porto Alegre, Brazil

Eugene Sobngwi, Faculté de Medecine et des Sciences Biomedicales et Centre de Biotechnologie, Université de Yaounde 1, Cameroon

Naoko Tajima, Jikei University School of Medicine, Tokyo, Japan

Nikhil Tandon, All India Institute of Medical Sciences, New Delhi, India

Nigel Unwin, Chronic Disease Research Centre, The University of the West Indies, Bridgetown, Barbados, and MRC Epidemiology Unit, University of Cambridge, UK

Sarah Wild, University of Edinburgh, UK

John Yudkin, University College London, UK

The suggestions and contributions of the following peer reviewers are gratefully acknowledged:

Naomi Levitt, Diabetic Medicine and Endocrinology, Department of Medicine at Groote Schuur Hospital and University of Cape Town, South Africa

Viswanathan Mohan, Dr Mohan's Diabetes Specialities Centre, Chennai, India

Sarah Montgomery, Primary Care International, Oxford, UK

Moffat J Nyirenda, Medical Research Council/Uganda Virus Research Institute/London School of Hygiene and Tropical Medicine, Uganda Research Unit, Entebbe, Uganda

Jaakko Tuomilehto, Dasman Diabetes Institute, Kuwait

Special thanks to Saskia Den Boon (consultant) and Samantha Hocking (Boden Institute, University of Sydney, Australia) for the preparation of background documents.

WHO expresses special appreciation to US Centers for Disease Control and Prevention for financial support through grant GH14-1420.

Executive summary

This document updates the 1999 World Health Organization (WHO) classification of diabetes. It prioritizes clinical care and guides health professionals in choosing appropriate treatments at the time of diabetes diagnosis, and provides practical guidance to clinicians in assigning a type of diabetes to individuals at the time of diagnosis. It is a compromise between clinical and aetiological classification because there remain gaps in knowledge of the aetiology and pathophysiology of diabetes.

While acknowledging the progress that is being made towards a more precise categorization of diabetes subtypes, the aim of this document is to recommend a classification that is feasible to implement in different settings throughout the world. The revised classification is presented in Table 1.

Unlike the previous classification, this classification does not recognize subtypes of type 1 diabetes and type 2 diabetes and includes new types of diabetes (“hybrid types of diabetes” and “unclassified diabetes”).

Table 1 : Types of diabetes

Type of diabetes	Brief description	Change from previous classification
Type 1 diabetes	β-cell destruction (mostly immune-mediated) and absolute insulin deficiency; onset most common in childhood and early adulthood	Type 1 sub-classes removed
Type 2 diabetes	Most common type, various degrees of β-cell dysfunction and insulin resistance; commonly associated with overweight and obesity	Type 2 sub-classes removed
Hybrid forms of diabetes		New type of diabetes
Slowly evolving, immune-mediated diabetes of adults	Similar to slowly evolving type 1 in adults but more often has features of the metabolic syndrome, a single GAD autoantibody and retains greater β-cell function	Nomenclature changed – previously referred to as latent autoimmune diabetes of adults (LADA)
Ketosis-prone type 2 diabetes	Presents with ketosis and insulin deficiency but later does not require insulin; common episodes of ketosis, not immune-mediated	No change
Other specific types		
Monogenic diabetes - Monogenic defects of β-cell function - Monogenic defects in insulin action	Caused by specific gene mutations, has several clinical manifestations requiring different treatment, some occurring in the neonatal period, others by early adulthood Caused by specific gene mutations; has features of severe insulin resistance without obesity; diabetes develops when β-cells do not compensate for insulin resistance	Updated nomenclature for specific genetic defects
Diseases of the exocrine pancreas	Various conditions that affect the pancreas can result in hyperglycaemia (trauma, tumor, inflammation, etc.)	No change
Endocrine disorders	Occurs in diseases with excess secretion of hormones that are insulin antagonists	No change
Drug- or chemical-induced	Some medicines and chemicals impair insulin secretion or action, some can destroy β-cells	No change
Infection-related diabetes	Some viruses have been associated with direct β-cell destruction	No change
Uncommon specific forms of immune-mediated diabetes	Associated with rare immune-mediated diseases	No change
Other genetic syndromes sometimes associated with diabetes	Many genetic disorders and chromosomal abnormalities increase the risk of diabetes	No change
Unclassified diabetes	Used to describe diabetes that does not clearly fit into other categories. This category should be used temporarily when there is not a clear diagnostic category especially close to the time of diagnosis	New types of diabetes
Hyperglycaemia first detected during pregnancy		
Diabetes mellitus in pregnancy	Type 1 or type 2 diabetes first diagnosed during pregnancy	No change
Gestational diabetes mellitus	Hyperglycaemia below diagnostic thresholds for diabetes in pregnancy	Defined by 2013 diagnostic criteria
Diagnostic criteria for diabetes: fasting plasma glucose ≥ 7.0 mmol/L or 2-hour post-load plasma glucose ≥ 11.1 mmol/L or Hba1c ≥ 48 mmol/mol **Diagnostic criteria for gestational diabetes**: fasting plasma glucose 5.1–6.9 mmol/L or 1-hour post-load plasma glucose ≥ 10.0 mmol/L or 2-hour post-load plasma glucose 8.5–11.0 mmol/L		

Introduction

Since 1965 the World Health Organization has periodically updated and published guidance on how to classify diabetes mellitus (hereafter referred to as "diabetes") *(1)*. This document provides an update on the guidance last published in 1999 *(2)*.

Diabetes comprises many disorders characterized by hyperglycaemia. According to the current classification there are two major types: type 1 diabetes (T1DM) and type 2 diabetes (T2DM). The distinction between the two types has historically been based on age at onset, degree of loss of β cell function, degree of insulin resistance, presence of diabetes-associated autoantibodies, and requirement for insulin treatment for survival *(3)*. However, none of these characteristics unequivocally distinguishes one type of diabetes from the other, nor accounts for the entire spectrum of diabetes phenotypes.

There are several reasons for revisiting the diabetes classification. Firstly, the phenotypes of T1DM and T2DM are becoming less distinctive with an increasing prevalence of obesity at a young age, recognition of the relatively high proportion of incident cases of T1DM in adulthood and the occurrence of T2DM in young people. Secondly, developments in molecular genetics have allowed clinicians to identify growing numbers of subtypes of diabetes, with important implications for choice of treatment in some cases. In addition, increasing knowledge of pathophysiology has resulted in a trend towards developing personalized therapies and precision medicine *(3)*. Unlike the previous classification, this classification does not recognize subtypes of T1DM and T2DM, includes new types of diabetes ("hybrid types of diabetes" and "unclassified diabetes"), and provides practical guidance to clinicians for assigning a type of diabetes to individuals at the time of diagnosis.

1. Diabetes: Definition and diagnosis

The term diabetes describes a group of metabolic disorders characterized and identified by the presence of hyperglycaemia in the absence of treatment. The heterogeneous aetio-pathology includes defects in insulin secretion, insulin action, or both, and disturbances of carbohydrate, fat and protein metabolism. The long-term specific effects of diabetes include retinopathy, nephropathy and neuropathy, among other complications. People with diabetes are also at increased risk of other diseases including heart, peripheral arterial and cerebrovascular disease, obesity, cataracts, erectile dysfunction, and nonalcoholic fatty liver disease. They are also at increased risk of some infectious diseases, such as tuberculosis.

Diabetes may present with characteristic symptoms such as thirst, polyuria, blurring of vision, and weight loss. Genital yeast infections frequently occur. The most severe clinical manifestations are ketoacidosis or a non-ketotic hyperosmolar state that may lead to dehydration, coma and, in the absence of effective treatment, death. However, in T2DM symptoms are often not severe, or may be absent, owing to the slow pace at which the hyperglycaemia is worsening. As a result, in the absence of biochemical testing, hyperglycaemia sufficient to cause pathological and functional changes may be present for a long time before a diagnosis is made, resulting in the presence of complications at diagnosis. It is estimated that a significant percentage of cases of diabetes (30–80%, depending on the country) are undiagnosed *(4)*.

Four diagnostic tests for diabetes are currently recommended, including measurement of fasting plasma glucose; 2-hour (2-h) post-load plasma glucose after a 75 g oral glucose tolerance test (OGTT); HbA1c; and a random blood glucose in the presence of signs and symptoms of diabetes. People with fasting plasma glucose values of ≥ 7.0 mmol/L (126 mg/dl), 2-h post-load plasma glucose ≥ 11.1 mmol/L (200 mg/dl) *(5)*, HbA1c ≥ 6.5% (48 mmol/mol); or a random blood glucose ≥ 11.1 mmol/L (200 mg/dl) in the presence of signs and symptoms are considered to have diabetes *(6)*. If elevated values are detected in asymptomatic people, repeat testing, preferably with the same test, is recommended as soon as practicable on a subsequent day to confirm the diagnosis *(6)*.

A diagnosis of diabetes has important implications for individuals, not only for their health, but also because of the potential stigma that a diabetes diagnosis can bring may affect their employment, health and life insurance, driving status, social opportunities, and carry other cultural, ethical and human rights consequences.

1.1 Epidemiology and global burden of diabetes

Diabetes is found in every population in the world and in all regions, including rural parts of low- and middle-income countries. The number of people with diabetes is steadily rising, with WHO estimating there were 422 million adults with diabetes worldwide in 2014. The age-adjusted prevalence in adults rose from 4.7% in 1980 to 8.5% in 2014, with the greatest rise in low- and middle-income countries compared to high-income countries *(7)*. In addition, the International Diabetes Federation (IDF) estimates that 1.1 million children and adolescents aged 14–19 years have T1DM *(8)*. Without interventions to halt the increase in diabetes, there will be at least 629 million people living with diabetes by 2045

(8). High blood glucose causes almost 4 million deaths each year *(7)*, and the IDF estimates that the annual global health care spending on diabetes among adults was US$ 850 billion in 2017 *(8)*.

The effects of diabetes extend beyond the individual to affect their families and whole societies. It has broad socio-economic consequences and threatens national productivity and economies, especially in low- and middle-income countries where diabetes is often accompanied by other diseases.

1.2 Aetio-pathology of diabetes

It is now generally agreed that the underlying characteristic common to all forms of diabetes is the dysfunction or destruction of pancreatic β-cells *(9–12)*. Many mechanisms can lead to a decline in function or the complete destruction of β-cells (these cells are not replaced, as the human pancreas seems incapable of renewing β-cells after the age of 30 years *(13)*). These mechanisms include genetic predisposition and abnormalities, epigenetic processes, insulin resistance, auto-immunity, concurrent illnesses, inflammation, and environmental factors. Differentiating β-cell dysfunction and decreased β-cell mass could have important implications for therapeutic approaches to maintaining or improving glucose tolerance *(11)*. Understanding β-cell status can help define subtypes of diabetes, and guide treatment *(12)*

2. Classification systems for diabetes

2.1 Purpose of a classification system for diabetes

Hyperglycaemia is the defining common feature of all types of diabetes, but aetiology, underlying pathogenic mechanisms, natural history and treatment for the different types of diabetes differ. Ideally, all types of diabetes would be defined by defining features that are specific and exclusive to that type of diabetes *(3)*. However, some types of diabetes are difficult to classify.

Classification systems can broadly be used for three primary aims:

- Guide clinical care decisions
- Stimulate research into aetio-pathology
- Provide a basis for epidemiological studies

Any classification system should be able to help with all three of these key activities, but at present there are so many gaps in understanding the causes of diabetes that the current classification cannot fulfil this triple role.

Clinical care decisions

Subtyping diabetes is important in clinical care for diagnosis, to guide treatment choices, and when making treatment decisions for a person whose glycaemic control is unsatisfactory. An incorrect treatment decision could risk a person developing diabetic ketoacidosis (DKA) or lead to unnecessary insulin therapy in the case of some forms of monogenic diabetes. The phenotype of both T1DM (overweight or obese) and T2DM (younger, normal weight) have changed over time and contributes to clinicians' increasing difficulty classifying types of diabetes.

Aetio-pathology

The aetiology and pathogenesis of diabetes can be described simplistically as problems with insulin sensitivity and insulin secretion, but the underlying specific defects are complex and not well understood. While some specific defects have been identified (e.g. genetic abnormalities resulting in insulin secretory problems), defining the mechanisms underlying common forms of diabetes remains challenging as they are increasingly recognized to involve a complex interplay of genetic, epigenetic, proteomic and metabolomic processes. Identifying these abnormalities will improve our understanding of the underlying mechanisms of diabetes and its treatment, but at present, our limited knowledge of these complex abnormalities hinders the development of a practical and clinically useful classification system for diabetes.

This problem also currently applies to the field of pharmacogenomics. A systematic review commissioned by WHO has examined the association between specific genetic variants and response to blood glucose lowering therapies *(14)*. While it is well known in clinical practice that some people respond better than others to a specific blood glucose-lowering treatment, studies of genetic variants and drug response in a person with diabetes have to date demonstrated only small and inconsistent effects

across studies. While pharmacogenomics holds promise to more precisely target therapy for T2DM, it is not currently clinically helpful.

Epidemiological studies

Most epidemiological studies report overall prevalence of diabetes without distinguishing between subtypes, despite the value of subtyping for such studies. Subtyping T1DM and T2DM in population studies is feasible using frequently available clinical information *(15, 16)*. Some studies have reported the population prevalence of other forms of diabetes, e.g. monogenic diabetes *(17, 18)* and diabetes due to pancreatic disease *(19)*. Classification of diabetes type is particularly important for incidence studies and studies on diabetes-related complications.

2.2 Previous WHO classifications of diabetes

Diabetes has been known about for many centuries. The 5th century physician Aretaeus first used the term "diabetes" (meaning "a siphon" in Greek) to describe the disease as a "melting down of flesh and limbs into urine". Indian physicians during the 5th century BC described the sweet, honey-like taste of urine in polyuric patients (*madhu meha,* meaning "honey urine") that attracted ants and other insects, but the word "mellitus" (Latin for "honey") was added in the 17th century. As early as the 5th century AD descriptions of diabetes mentioned two forms, one in older, fatter people and the other in thinner people with short survival *(20)*.

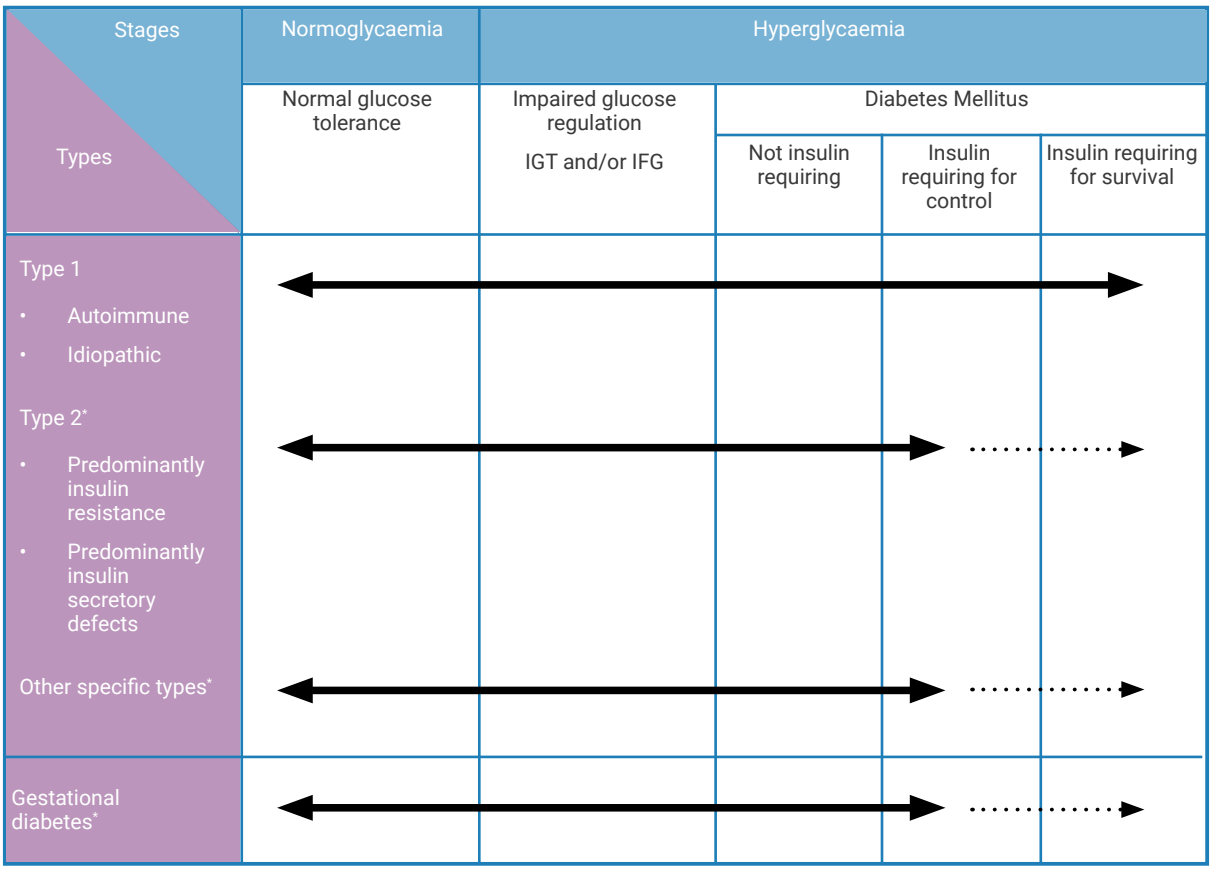
WHO published its first classification system for diabetes in 1965 using four age of diagnosis categories: infantile or childhood (with onset between the ages of 0–14); young (with onset between the ages of 15–24 years); adult (with onset between the ages of 25–64 years); and elderly (with onset at the age of 65 years or older). In addition to classifying diabetes by age, WHO recognized other forms of diabetes: juvenile-type; brittle; insulin-resistant; gestational; pancreatic; endocrine and iatrogenic *(1)*.

WHO published its first widely accepted and globally adopted classification of diabetes in 1980 *(21)* and an updated version of this in 1985 *(22)*. These classifications included two major classes of diabetes: insulin dependent diabetes mellitus (IDDM), or type 1; and non-insulin dependent diabetes mellitus (NIDDM), or type 2 *(21)*. The 1985 report omitted the terms "type 1" and "type 2", but retained the classes IDDM and NIDDM, and introduced a class of malnutrition-related diabetes mellitus (MRDM) *(22)*. Both the 1980 and 1985 reports included two other classes of diabetes: "other types" and "gestational diabetes mellitus" (GDM). These were reflected in the *International nomenclature of diseases (IND)* in 1991, and the tenth revision of the *International Classification of Diseases (ICD–10)* in 1992. These reports represented a compromise between clinical and aetiological classification and allowed clinicians to classify individual subjects even when the specific cause or aetiology was unknown.

In 1999 WHO recommended that the classification should encompass not only the different aetiological types of diabetes, but also the clinical stages of the disease *(2)* (see Figure 1). The clinical staging reflects that people with diabetes, regardless of type, can progress through several stages, from normoglycaemia to severe hyperglycaemia with ketosis. However, not everyone will go through all stages. Moreover, individuals with T2DM may move from stage to stage in either direction. People who have, or who

are developing, diabetes can be categorized by stage according to clinical characteristics, in the absence of information concerning the underlying aetiology. In 1999, WHO reintroduced the terms type 1 and type 2 diabetes and dropped MRDM because of lack of evidence to support its existence as a distinct type.

Figure 1 : Disorders of glycaemia: aetiological types and clinical stages (WHO, 1999)



*In rare instances patients in these categories (e.g. Vacor Toxicity, Type 1 presenting in pregnancy, etc.) may require insulin for survival.

Source: reproduced from the World Health Organization's 1999 classification *(2)*.

2.3 Recent calls to update the WHO classification of diabetes

There have been recent calls to review and update the classification system for diabetes. This is because many people with diabetes do not fit into any single category; there have been recent advances in knowledge of pathophysiological pathways and emerging technologies to examine pathology and treatments that act on specific pathways; and there is a trend towards individualized treatment.

There is well-established acceptance of the overlap of diabetes subtypes, especially in relation to T1DM, T2DM and so-called latent autoimmune diabetes of adults (LADA) *(3)*. Laboratory tests could in some instances improve disease classification and potentially improve the efficacy of treatment for diabetes, but many of these tests are beyond the reach or affordability of most clinical settings throughout the world.

A recent proposal suggested a classification system centred on the β-cell *(10)*. Proponents for this model note that all forms of diabetes have abnormal pancreatic β–cell function and that individually or in concert, 11 distinct pathways contribute to β–cell stress, dysfunction, or loss. In this way treatments could be targeted to specific mediating pathways of hyperglycaemia in a given patient. This proposal expands on an earlier model which described eight core defects of diabetes *(23)*. While the β–cell-centric model is a conceptual framework to help optimize diabetes care and precision treatment, it is predicated on additional diagnostic tests that are either not standardized or not routinely available in most clinical settings, e.g. measurement of C-peptide, β-cell-specific autoantibodies, markers of low-grade inflammation, measures of insulin resistance, and assays for β-cell mass.

2.4 WHO classification of diabetes 2019

Ideally a single classification system for diabetes would facilitate three primary purposes: clinical care, aetio-pathology and epidemiology. However, this is not possible with our current state of knowledge and the resources available in most countries throughout the world.

With this in mind, the Expert group considered it best to define a classification system that prioritizes clinical care and helps health professionals choose appropriate treatments, and whether or not to start treatment with insulin, particularly at the time of diagnosis.

The group considered that the prerequisites of a clinically based classification system include being internationally applicable and using easy and readily available clinical parameters and resources; being reliable and equitable; and feasible to implement.

The only classification system which could currently go some way towards achieving this is one based on clinical parameters to identify diabetes subtypes. Some countries and clinical or research centres can supplement this approach with specific additional investigations, but these are not universally available and a classification system which relied on these measures would have limited global applicability.

Clinically, genotyping is relevant to monogenic diabetes but not T1DM or T2DM which are polygenic (genome-wide association studies have identified over 100 associated genetic markers *(9)*). At this time,

genotyping for diabetes subtyping is only relevant to patients in whom clinicians suspect monogenic diabetes and may be useful in a research setting in relation to other types of diabetes.

Autoantibodies against a variety of β-cell components including glutamic acid decarboxylase (GAD65), islet antigen-2 (IA-2), zinc transporter 8 (ZnT8) and insulin are commonly found in people with classical T1DM but can also be found in some people with T2DM.

Endogenous insulin production can be assessed by measuring blood C-peptide either in the fasting state or after a stimulus, most commonly intravenously administered glucagon. C-peptide can also be measured in urine. In the early stages of diabetes, measuring C-peptide provides information which may help to distinguish T1DM from T2DM, but is not routinely done clinically.

Table 2: Types of diabetes

Type 1 diabetes
Type 2 diabetes
Hybrid forms of diabetes
Slowly evolving immune-mediated diabetes of adults
Ketosis prone type 2 diabetes
Other specific types (see Tables)
Monogenic diabetes
- Monogenic defects of β-cell function
- Monogenic defects in insulin action
Diseases of the exocrine pancreas
Endocrine disorders
Drug- or chemical-induced
Infections
Uncommon specific forms of immune-mediated diabetes
Other genetic syndromes sometimes associated with diabetes
Unclassified diabetes
This category should be used temporarily when there is not a clear diagnostic category especially close to the time of diagnosis of diabetes
Hyperglyacemia first detected during pregnancy
Diabetes mellitus in pregnancy
Gestational diabetes mellitus

2.4.1 Type 1 diabetes

Data on global trends in T1DM prevalence and incidence are not available, but data from many high-income countries indicate an annual increase of between 3% and 4% in the incidence of T1DM in childhood *(24)*.

Males and females are equally affected *(25)*. Despite T1DM occurring frequently in childhood, onset can occur in adults and 84% of people living with T1DM are adults *(26)*. T1DM decreases life expectancy by around 13 years in high-income countries *(27)*. The prognosis is far worse in countries with limited access to insulin. Distinguishing T1DM and T2DM in adults can be challenging, and misclassifying T1DM as T2DM and vice versa may impact estimates of prevalence and incidence *(28)*. A recent study applied a T1DM genetic risk score to individuals of European descent taking part in the UK's Biobank research project and concluded that 42% of T1DM occurred after the age of 30 years, and accounted for 4% of all cases of diabetes diagnosed between the ages of 31 and 60 years. The clinical characteristics of these individuals included a lower body mass index, use of insulin within 12 months of diagnosis, and increased risk of diabetic ketoacidosis *(29)*.

The rate of β-cell destruction is rapid in some individuals and slow in others *(30)*. The rapidly progressive form of T1DM is commonly observed in children but may also occur in adults. Some patients, particularly children and adolescents, may present with ketoacidosis as the first manifestation of the disease *(31)*. Others may have modest hyperglycaemia that can rapidly change to severe hyperglycaemia and/or ketoacidosis in the presence of infection or other stress. Still others, particularly adults, may retain residual β-cell function sufficient to prevent ketoacidosis for many years. At the time of classical clinical presentation with T1DM, there is little or no insulin secretion as manifested by low or undetectable levels of C-peptide in blood or urine *(32)*. The presence of obesity in people with T1DM parallels the increase of obesity in the general population.

Between 70% and 90% of people with T1DM at diagnosis have evidence of an immune-mediated process with β-cell autoantibodies against glutamic acid decarboxylase (GAD65), islet antigen-2 (IA-2), ZnT8 transporter or insulin, and associations with genes controlling immune responses *(33)*. In populations of European descent, most of the genetic associations are with HLA DQ8 and DQ2. The specific pathogenesis in those without immune features is unclear *(34)*, although some may have monogenic forms of diabetes. These two groups of T1DM have previously been referred to as type 1A (autoimmune) and type 1B (non-immune) diabetes but this terminology is not frequently used nor is it clinically helpful (28). Consequently, this report refers only to T1DM without the subtypes used in the WHO 1999 classification *(2)*.

Fulminant type 1 diabetes is a form of acute onset T1DM in adults mainly reported in East Asia *(35, 36)*. It accounts for approximately 20% of acute-onset T1DM in Japan *(37)* and 7% in Korea *(38)*. It is also common in China *(39)* but rare in people of European descent. The major clinical characteristics of fulminant type 1 diabetes include abrupt onset; very short duration (usually less than 1 week) of hyperglycaemic symptoms; virtually no C-peptide secretion at the time of diagnosis; ketoacidosis at the time of diagnosis; mostly negative for islet-related autoantibodies; increased serum pancreatic enzyme levels; frequent flu-like and gastrointestinal symptoms just before the disease onset. Cellular infiltration of macrophages and T cells into islets suggests an accelerated immune response to virus-infected islet cells and rapid destruction of β-cells.

Measuring islet autoantibodies remains important to research as it can help shed light on the aetiology and pathogenesis of T1DM *(40)*. While measuring islet autoantibodies has limited value in clinical practice, in classical T1DM it may have a role when there is uncertainty as to whether a person has T1DM or T2DM. However, the decision to use insulin should not rely on the presence of such markers, but rather on the clinical need.

2.4.2 Type 2 diabetes

T2DM accounts for between 90% and 95% of diabetes, with highest proportions in low- and middle-income countries. It is a common and serious global health problem that has evolved in association with rapid cultural, economic and social changes, ageing populations, increasing and unplanned urbanization, dietary changes such as increased consumption of highly processed foods and sugar-sweetened beverages, obesity, reduced physical activity, unhealthy lifestyle and behavioural patterns, fetal malnutrition, and increasing fetal exposure to hyperglycaemia during pregnancy. T2DM is most common in adults, but an increasing number of children and adolescents are also affected *(7)*.

β-cell dysfunction is required to develop T2DM. Many with T2DM have relative insulin deficiency and early in the disease absolute insulin levels increase with resistance to the action of insulin *(11)*. Most people with T2DM are overweight or obese, which either causes or aggravates insulin resistance *(41, 42)*. Many of those who are not obese by BMI criteria have a higher proportion of body fat distributed predominantly in the abdominal region, indicating visceral adiposity compared to people without diabetes *(43)*. However, in some populations, such as Asians, β-cell dysfunction appears to be a more notable prominent than in populations of European descent *(44)*. This is also observed in thinner people from low- and middle-income countries such as India *(45)*, and among people of Indian descent living in high-income countries *(46, 47)*.

For most people with T2DM, insulin treatment is not required for survival but may be required to lower blood glucose to avert chronic complications. T2DM often remains undiagnosed for many years because the hyperglycaemia is not severe enough to provoke noticeable symptoms of diabetes *(48)*. Nevertheless, these people are at increased risk of developing macrovascular and microvascular complications *(49)*. Complications are a particular problem in young-onset T2DM – increasingly recognized as a severe phenotype of diabetes and associated with greater mortality rates, more complications, and unfavorable cardiovascular disease risk factors when compared to T1DM of similar duration *(50, 51)*. In addition, the response to oral blood glucose medications is often poor among young people with diabetes *(52)*.

Many factors increase the risk of developing T2DM including age, obesity, unhealthy lifestyles and prior gestational diabetes (GDM). The frequency of T2DM also varies between different racial and ethnic subgroups, especially in young and middle-aged people. There are particular populations that have a higher occurrence of type 2 diabetes, for example Native Americans, Pacific Islanders, and populations in the Middle East and South Asia *(4, 53)*. It is also often associated with strong familial, likely genetic or epigenetic predisposition *(4, 41)*. However, the genetics of T2DM are complex and not clearly defined, though studies suggest that some common genetic variants of T2DM occur among many ethnic groups and populations *(54)*.

Ketoacidosis is infrequent in T2DM but when seen it usually arises in association with the stress of another illness such as infection *(55, 56)*. Hyperosmolar coma may occur, particularly in elderly people *(57)*.

The specific aetiologies of T2DM are still unclear, and likely reflect several different mechanisms. It is likely that in future, subtypes will be created that may be classified under "other types" (see "Other specific types of diabetes").

2.4.3 Hybrid forms of diabetes

Attempts to distinguish T1DM from T2DM among adults have resulted in proposed new disease categories and nomenclatures, including slowly evolving immune-mediated diabetes and ketosis-prone T2DM *(28)*.

Slowly evolving immune-mediated diabetes

A slowly evolving form of immune-mediated diabetes has been described for many years, most frequently in adults who present clinically with what is initially thought to be T2DM, but who have evidence

of pancreatic autoantibodies that can react with non-specific cytoplasmic antigens in islet cells, glutamic acid decarboxylase (GAD), protein tyrosine phosphatase IA-2, insulin, or ZnT8. This form of diabetes has often been referred to as "latent autoimmune diabetes in adults" (LADA). The rationale for using the word "latent" was to distinguish these slow-onset cases from classical adult T1DM *(58)*. However, the appropriateness of this name has been questioned *(59)*. This group of people does not require insulin therapy at diagnosis, are initially controlled with lifestyle modification and oral agents, but progress to requiring insulin more rapidly than people with typical T2DM *(60)*. In some regions of the world this form of diabetes is more common than classic, rapid-onset T1DM *(9)*. A similar subtype has also been reported in children and adolescents with clinical T2DM and pancreatic autoantibodies and has been referred to as latent autoimmune diabetes in youth *(61, 62)*.

There are no universally agreed criteria for this subtype of diabetes, but three criteria are often used: positivity for GAD autoantibodies, age older than 35 years at diagnosis, and no need for insulin therapy in the first 6–12 months after diagnosis. Among individuals with clinically diagnosed T2DM, the prevalence of autoantibodies to GAD differs between regions and ethnic groups, with 5–14% in Europe, North America, and Asia having autoantibodies, with some variation with younger age at diagnosis and by ethnicity. Of these autoantibody-positive individuals, 90% have GAD autoantibodies and 18–24% have autoantibodies to protein tyrosine phosphatase IA-2 or ZnT8. GAD autoantibodies in people with apparent T2DM persist, with one study reporting 41% seroconverting to autoantibody-negative status during a 10-year follow-up *(63)*. However even in T1DM, GAD autoantibodies may still be detected 10 years after diagnosis *(64)*.

Whether slowly evolving immune-mediated diabetes represents a separate clinical subtype or is merely a stage in the process leading to T1DM has provoked considerable discussion *(28)*. Some have argued that the basis for designating this as a distinct subtype are insubstantial, that the epidemiology is plagued by methodological problems, and that the clinical value of diagnosing it has not been demonstrated *(59)*, while others have called for a new definition, one that includes the double component of β-cell autoimmunity and insulin resistance *(65)*. Relative differences between slowly evolving immune-mediated diabetes and T1DM include obesity, features of the metabolic syndrome, retaining greater β-cell function, expressing a single autoantibody (particularly GAD65), and carrying the transcription factor 7-like 2 (TCF7L2) gene polymorphism *(66)*.

Ketosis-prone type 2 diabetes

Over the past 15 years, a ketosis-prone form of diabetes initially identified in young African-Americans *(67)* has emerged as a new clinical entity *(68)*. This subtype has variously been described as a variant of T1DM or T2DM. Some have suggested that people classified with idiopathic or type 1B diabetes should be reclassified as having ketosis-prone type 2 diabetes *(69, 70)*.

Ketosis-prone type 2 diabetes is an unusual form of non-immune ketosis-prone diabetes first reported in young African-Americans in Flatbush, New York, USA *(67, 71)*. Subsequently similar phenotypes were described in populations in sub-Saharan African *(68)*. Typically, those affected present with ketosis and evidence of severe insulin deficiency but later go into remission and do not require insulin treatment. Reports suggest that further ketotic episodes occur in 90% of these people within 10 years. In high-income countries, obese males seem to be most susceptible to this form of diabetes but a similar

pattern of presentation has been observed in lean individuals in populations in low-income countries. Ketosis-prone type 2 diabetes is observed in all populations, but it is least common in populations of European origin. While it presents with diabetic ketoacidosis, the subsequent clinical course more closely resembled T2DM (72). The underlying pathogenesis is unclear. There is a transient secretory defect of β-cells at the time of presentation with remarkable recovery of insulin-secretory capacity during the period(s) of remission *(68)*. No genetic markers or evidence of auto-immunity have been identified.

Ketosis-prone T2DM can be differentiated from T1DM and classical T2DM by specific epidemiologic, clinical, and metabolic features of diabetes onset and by the natural history of impairment in insulin secretion and action. Glucose toxicity may play a role in the acute and phasic β-cell failure in ketosis-prone type 2 diabetes. Restoration of normoglycaemia after insulin therapy is accompanied by a dramatic and prolonged improvement in β-cell insulin secretory function *(68)*.

2.4.4 Other specific types of diabetes

Table 3 contains a list of other specific types of diabetes

Table 3: Other specific types of diabetes*

Monogenic diabetes Monogenic defects of β-cell function (mutated gene followed by clinical syndrome)	**Monogenic defects in insulin action (mutated gene followed by clinical syndrome)**
GCK MODY	INSR Type A insulin resistance
HNF1A MODY	INSR Leprechaunism
HNF4A MODY	INSR Rabson-Mendenhall syndrome
HNF1B RCAD	LMNA FPLD
mtDNA 3243 MIDD	PPARG FPLD
KCNJ11 PNDM	AGPAT2 CGL
KCNJ11 DEND	BSCL2 CGL
6q24 TNDM ABCC8 MODY INS PNDM WFS1 Wolfram syndrome FOXP3 IPEX syndrome EIF2AK3 Wolcott-Rallison syndrome	**Other generic syndromes sometimes associated with diabetes** (see Table 5)
Abbreviations: MODY = maturity-onset diabetes of the young; RCAD = renal cysts and diabetes; MIDD = maternally inherited diabetes and deafness; PNDM = permanent neonatal diabetes; TNDM = transient neonatal diabetes; DEND = developmental delay epilepsy and neonatal diabetes.	Abbreviations: FPLD = familial partial lipodystrophy; CGL = congenital generalized lipodystrophy
Diseases of the exocrine pancreas	**Endocrine disorders**
Fibrocalculous pancreatopathy	Cushing's syndrome
Pancreatitis	Acromegaly
Trauma/pancreatectomy	Phaeochromocytoma
Neoplasia	Glucagonoma
Cystic fibrosis	Hyperthyroidism
Haemochromatosis	Somatostatinoma
Others	Others
Drug- or chemical-induced diabetes (see Table 4)	**Uncommon forms of immune-mediated diabetes**
Infections	Insulin autoimmune syndrome (autoantibodies to insulin)
Congenital rubella	Anti-insulin receptor antibodies
Cytomegalovirus	«Stiff man» syndrome
Others	Others
Other clinically defined subgroups	
Diabetes associated with massive hypertriglyceridaemia	

*This is a list of the most common types in each category but is not exhaustive

Monogenic diabetes

Since the last WHO classification of diabetes *(2)* there have been considerable advances in defining the underlying molecular genetics that can help identify specific subtypes of diabetes. These advances have revealed clinical subgroups that are genetically heterogeneous and have resulted in the recognition of new genetic syndromes. The most important advance has been that genetic diagnosis can result in improved treatment outcomes for some people, albeit a small proportion of the total number of people with diabetes. As a consequence, genetic testing has been adopted for selected subgroups of people as an aid to clinical management in some countries.

A simple approach to classification of monogenic subtypes of diabetes uses the gene symbol of the mutated gene followed by the clinical syndrome *(73)*. For example, a child diagnosed with permanent neonatal diabetes (PNDM) due to a mutation in KCNJ11 is labeled as having KCNJ11 PNDM. If there is a clinical diagnosis of PNDM but a gene mutation had neither been looked for nor found, then the person would be categorized as PNDM only.

Monogenic defects of β-cell function

Clinical manifestations of monogenic defects in β-cell function include maturity-onset diabetes of the young (MODY), permanent neonatal diabetes (PNDM), transient neonatal diabetes (TNDM), and genetic syndromes where insulin-deficient diabetes is associated with specific clinical features *(74)*.

Dominantly inherited early-onset familial diabetes (generally with onset before the age of 25 years) that is not dependent on insulin and results from β-cell dysfunction was recognized clinically as MODY *(75)*. The commonest genetic subtypes are due to mutations in the glucokinase gene (GCK MODY) and hepato-nuclear factor gene (HNF1A MODY and HNF4A MODY) *(76)*. Phenotype and treatment responses vary. GCK MODY results in life-long mild fasting hyperglycaemia that deteriorates little with age. These people rarely develop microvascular complications and typically do not require pharmacological treatment for hyperglycaemia *(77)*. HNF1A MODY, the commonest form of MODY, results in progressive and marked hyperglycaemia with a high risk of microvascular and macrovascular complications. These people are acutely sensitive to the hypoglycaemic effects of sulfonylureas *(77)*, allowing people with insulin-treated HNF1A to be successfully transferred to sulphonylureas *(74)*. People with HNF4A MODY are similar to those with HNF1A MODY except they have marked macrosomia and transient neonatal hypoglycaemia *(78)*.

Diabetes diagnosed before the age of 6 months is most likely monogenic neonatal diabetes rather than T1DM *(74)*. Approximately half have TNDM and the diabetes resolves; and the majority (~70%) with TNDM have abnormalities in the chromosome 6q24 region *(79)*. Approximately half of those with PNDM have mutations in KCNJ11 or ABCC8 genes which encode the Kir6.2 and SUR1 subunits of the ATP-sensitive potassium channel (K_{ATP} channel) *(80–82)*. Most of these individuals can eventually be treated with oral sulfonylureas and do not require insulin.

The other common causes of isolated PNDM are heterozygous insulin gene mutations *(83)*. There are a wide variety of other genetic subtypes of neonatal diabetes mainly associated with multisystem clinical syndromes *(84)*.

Maternally inherited diabetes and deafness (MIDD) results from a heteroplasmic mitochondrial gene mutation at position 3243 *(85)*. In addition to diabetes and sensori-neural deafness, those affected also have myopathy, pigmented retinopathy, cardiomyopathy, and focal glomerulosclerosis *(86, 87)*. Other mitochondrial defects may also result in diabetes *(88)*. Some multisystem monogenic syndromes have marked β-cell dysfunction. Wolfram's syndrome (WFS1 and WFS2) is an autosomal recessive disorder characterized by severe insulin-deficient diabetes associated with optic atrophy, diabetes insipidus, and neural deafness (DIDMOAD) *(89)*.

A study published in 2017 showed that up to 6.5% of Norwegian autoantibody-negative children with diabetes aged under 15 years have MODY, one-third of whom had not been recognized as such *(90)*. An Australian community-based study found 0.24% of participants with diabetes diagnosed under the age of 35 years had MODY, with one in four being previously unrecognized *(91)*.

Monogenic defects of insulin action

Monogenic causes of insulin resistance are less common than monogenic β-cell defects. They typically present with features of insulin resistance in the absence of obesity, including hyperinsulinaemia, acanthosis nigricans, polycystic ovarian disease and virilization *(92)*. Diabetes only develops when the β-cells fail to compensate for the insulin resistance (see Table 3).

Mutations in the insulin receptor result in a range of clinical presentations and degrees of hyperglycaemia *(93)*. Leprechaunism and Rabson-Mendenhall syndrome are two paediatric syndromes that have mutations in the insulin receptor gene with extreme insulin resistance, dysmorphism, severe intra-uterine retardation and early mortality *(94)*. Milder mutations produce what is known as Type A insulin resistance syndrome.

Insulin resistance is a feature of a group of disorders of lipid storage characterized by lipodystrophy *(94)*. Familial partial lipodystrophy is a dominant condition characterized by limb lipoatrophy in young adult life, accompanied by hyperlipidaemia and insulin-resistant diabetes. Mutations in the LMNA gene coding for nuclear lamin A/C are the commonest genetic risk factor *(95)*. PPARG mutations also result in a partial lipodystrophy which is usually associated with severe insulin resistance, early onset T2DM and hypertension *(96)*.

Diseases of the exocrine pancreas

Any process that diffusely damages the pancreas can cause diabetes. Acquired processes include pancreatitis, trauma, infection, pancreatic cancer and pancreatectomy *(97, 98)*. With the exception of cancer, damage to the pancreas must be extensive for diabetes to occur. However, adenocarcinomas that involve only a small portion of the pancreas have been associated with diabetes. This implies a mechanism other than simple reduction in β-cell mass *(99)*. In cystic fibrosis there is both exocrine pancreatic failure and reduced insulin secretion resulting in diabetes, but the relationship between these two defects is not clear *(100)*. Fibrocalculous pancreatopathy may be accompanied by abdominal

pain and pancreatic calcification on X-ray or ultrasound and ductal dilatation *(101)*. Pancreatic fibrosis and calcified stones in the exocrine ducts are found at autopsy.

Diabetes following pancreatic disease (incidence 2.59 per 100 000 person-years) has been reported to be more common than T1DM (incidence 1.64 per 100 000 person-years). The majority of diabetes following pancreatic disease is classified by clinicians as T2DM (87.8%) and uncommonly as diabetes of the exocrine pancreas (2.7%). Proportions of people using insulin within 5 years of diagnosis were 4.1% for T2DM, 20.9% for diabetes following acute pancreatitis, and 45.8% for diabetes following chronic pancreatic disease *(102)*.

Endocrine disorders

Several hormones (e.g. growth hormone, cortisol, glucagon, epinephrine) antagonize insulin action. Diseases associated with excess secretion of these hormones are also associated with diabetes (e.g. acromegaly, Cushing's syndrome, glucagonoma and phaeochromocytoma) *(103)*. These forms of hyperglycaemia typically resolve when the underlying condition causing hormone excess is successfully treated. Somatostatinoma can cause diabetes, at least in part by inhibiting insulin secretion *(104)*. Hyperglycaemia generally resolves following successful removal of the tumour.

Table 4: Drugs or chemicals that can induce diabetes

Glucocorticoids
Thyroid hormone
Thiazides
Alpha-adrenergic agonists
Beta-adrenergic agonists
Dilantin
Pentamidine
Nicotinic acid
Pyrinuron
Interferon-alpha
Others

Drug- or chemical-induced diabetes

Many drugs can impair insulin secretion or insulin action (see Table 4). These drugs may precipitate diabetes in persons with insulin resistance or moderate β-cell dysfunction *(105, 106)*. Certain toxins such as pyrinuron (a rat poison) and pentamidine can permanently destroy pancreatic β-cells *(107)*. Such drug reactions are fortunately rare.

Infection-related diabetes

Particular viruses have been associated with β-cell destruction and have been implicated in inducing or triggering T1DM, but their role in its aetiology has remained uncertain. Diabetes occurs in some people with congenital rubella *(108)*. In addition, Coxsackie B and viruses such as cytomegalovirus, adenovirus and mumps) have been implicated in inducing T1DM *(109–111)*.

Uncommon specific forms of immune-mediated diabetes

Some forms of diabetes that are associated with particular immunological diseases have a different pathogenesis or aetiology to those that lead to T1DM. Hyperglycaemia of a severity sufficient to fulfill the criteria for diabetes has been reported in rare instances in individuals who spontaneously develop insulin autoantibodies *(112)*. However, these individuals generally present with symptoms of hypoglycaemia rather than hyperglycaemia. The "stiff man syndrome" is an autoimmune disorder of the central nervous system, characterized by stiffness of the axial muscles with painful spasms (*113, 114)*. Affected people usually have high titres of GAD65 autoantibodies and approximately half will develop diabetes. People receiving interferon alpha have been reported to develop diabetes associated with islet cell autoantibodies and, in certain instances, severe insulin deficiency *(115)*.

Insulin receptor autoantibodies can cause diabetes by binding to the insulin receptor, thereby reducing the binding of insulin to target tissues *(116)*. However, these autoantibodies can also act as an insulin agonist after binding to the receptor and can thereby cause hypoglycaemia. Insulin receptor autoantibodies are occasionally found in patients with systemic lupus erythematosus and other autoimmune diseases *(117)*. As in other states of extreme insulin resistance, people with insulin receptor autoantibodies often have acanthosis nigricans. In the past, this syndrome was termed Type B insulin resistance.

Other genetic syndromes sometimes associated with diabetes

Many genetic syndromes are accompanied by an increased incidence of diabetes *(118)*. These include the genetic syndromes associated with severe early-onset obesity, including Prader–Willi syndrome, Alstrom syndrome and the many genetically defined subtypes of Bardet-Biedl syndrome. A second grouping is the chromosomal abnormalities of Down's syndrome, Klinefelter's syndrome and Turner's syndrome. A final group is that of the neurological disorders, particularly Friedreich's ataxia, Huntington's chorea, and myotonic dystrophy (see Table 5).

Table 5: Other genetic syndromes sometimes associated with diabetes

Down syndrome
Friedreich's ataxia
Huntington's chorea
Klinefelter's syndrome
Lawrence-Moon-Biedel syndrome
Myotonic dystrophy
Porphyria
Prader-Willi syndrome
Turner's syndrome
Others

2.4.5. Unclassified diabetes

Subtyping diabetes has become increasingly complex and it is not always possible to classify all newly diagnosed cases of diabetes as belonging to a specific category. Consequently, a category of "unclassified diabetes" has been introduced. For most individuals given this label at diagnosis, it is a temporary category as they can be classified into an appropriate type at some point after diagnosis.

The worldwide increase in the prevalence of obesity *(119)* has resulted in T2DM being diagnosed in children and young adults and at the same time children and young adults with T1DM are more commonly overweight or obese than in the past. In addition, ketosis or frank ketoacidosis are not confined to T1DM. These issues make the classification of diabetes difficult, particularly at diagnosis. While further investigation may help – including measurement of C-peptide and T1DM-associated autoantibodies, and the monitoring of the course of endogenous insulin secretion with time – these investigations are not widely available throughout the world. Until there is a definite diagnosis of the type of diabetes, a classification of "unclassified" should be used and attempts to classify the type of diabetes should continue to support appropriate management decisions.

2.4.6. Hyperglycaemia first detected during pregnancy

In 2013 WHO updated its 1999 definition and diagnostic criteria for hyperglycaemia first detected in pregnancy. The new classification includes two categories of hyperglycaemia when first recognized in pregnancy. One is diabetes mellitus, defined by the same criteria as in non-pregnant persons. The other is gestational diabetes, defined by newly recommended glucose cut-off points that are lower than those for diabetes *(120)*. This classification of hyperglycaemia in pregnancy has not been revisited for this document.

3. Assigning diabetes type in clinical settings

The Expert group decided to focus on providing a practical clinical guide for clinicians faced with the challenge of assigning a type of diabetes to individuals at the time of presentation with hyperglycaemia to help choose an appropriate treatment, particularly whether insulin treatment should be started. With the limited access in most countries throughout the world to laboratory investigations which might assist with the classification of an individual, the Expert group opted for providing guidance on identifying clinical subtypes, while recognizing the limitations of this approach.

Countries and centres able to test for genes, for islet autoimmunity and for endogenous insulin production can use these to increase the accuracy of clinical subtyping of diabetes.

Steps in clinical subtyping an individual first diagnosed with diabetes:

1. Confirm diagnosis of diabetes in an asymptomatic individual
1. Exclude secondary causes of diabetes
1. Consider the following which may assist in differentiating subtypes:
   - » age at diagnosis
   - » family history
   - » physical findings, especially presence of obesity
   - » presence of features of metabolic syndrome
1. Note presence or absence of ketosis or ketoacidosis
1. Perform diagnostic tests if available (β-cell autoantibodies, C-peptide)

It may not be possible to definitively subtype an individual at the time of presentation and classification may only become possible over time when, for example, the longer term insulin requirement to manage glycaemia has been established. Consequently, the individual should be monitored and the appropriateness of the assigned diabetes classification should be regularly reviewed, especially in individuals without the classical features of diabetes subtypes.

3.1 Age at diagnosis as a guide to subtyping diabetes

The following presents the major diagnostic diabetes subtypes according to usual age at diagnosis. The group with highest heterogeneity and risk of misclassification is that of young adults aged 20 to 40 years *(9)*.

3.1.1. Age < 6 months

Types of diabetes:

- » Monogenic neonatal diabetes – transient or permanent
- » Type 1 diabetes – extremely rare

The majority presenting in this age group will have monogenic neonatal diabetes – either transient or permanent. This can only be definitely diagnosed by genetic testing, but where this is not possible,

careful assessment of the clinical course should establish either the transient nature of the diabetes or that insulin therapy is not required. While mostly occurring before 6 months of age, neonatal diabetes may present up to 12 months of age. T1DM is extremely rare in the first year of life *(121, 122)*.

3.1.2. Age 6 months to < 10 years

- Types of diabetes:
- Type 1 diabetes
- Monogenic neonatal diabetes – transient or permanent
- Type 2 diabetes – rare before puberty

T1DM is the most common type of diabetes in this age group. The diagnosis of T1DM is relatively straightforward in normal-weight individuals who present with ketoacidosis aged 10 years or younger and who are autoantibody-positive. Both T2DM (even if the individual is obese) and monogenic diabetes (except for neonatal diabetes and GCK) are rare before puberty.

3.1.3. Age 10 to < 25 years

Types of diabetes:

- Type 1 diabetes
- Type 2 diabetes
- Monogenic diabetes

The relative proportions of different types of diabetes in this age group differ by ethnic group. T2DM with onset in youth occurs most often during the second decade of life and there is usually a strong family history of T2DM in first- and second-degree relatives. While all ethnic groups can be affected, prevalence is much lower in populations of European descent. It is the predominant form of youth-onset diabetes in some countries – 90% in Hong Kong, 60% in Japan and 50% in Taiwan. The presence of obesity varies with ethnicity and is found in virtually all people with youth-onset T2DM in the USA and Europe; by contrast, half of Asian children with T2DM have a normal weight. The presentation of youth-onset T2DM can vary from asymptomatic hyperglycaemia detected through screening or during routine physical examination, to ketoacidosis in up to 25% of patients *(123)* or hyperglycaemic hyperosmolar state *(124)*.

Features favouring a diagnosis of T2DM rather than T1DM at diagnosis include:

- Overweight or obesity
- Age above 10 years
- Strong family history of T2DM
- Acanthosis nigricans
- Undetectable islet autoantibodies (if measured)
- Elevated or normal C-peptide (if assessed)

The peak age at diagnosis of people with monogenic diabetes is around 15–20 years of age (derived from UK referrals data) *(125)* and this subtype of diabetes should be considered in this age group.

Clinical prediction models have been developed that can be used to discriminate between monogenic diabetes and T1DM and T2DM in individuals diagnosed between the ages of 1 and 35 years (126). The models are available online at www.diabetesgenes.org.

3.1.4. Age 25 to 50 years

Types of diabetes:

- Type 2 diabetes
- Slowly evolving immune-mediated diabetes
- Type 1 diabetes

Slowly evolving immune-mediated diabetes in adults usually presents after the age of 25 years and mostly after the age of 35 years. It is found in around 10% of people presenting as T2DM in Europe, North America, and Asia. Pancreatic autoantibodies (especially GAD autoantibodies) are a feature. Subtypes of diabetes other than T2DM should be considered in adults who have a normal weight and are without other metabolic syndrome features. These features are present in 33% of adults with slowly evolving immune-mediated diabetes, compared to 83% in people with T2DM *(9)*.

T1DM accounts for an estimated 5% of diabetes diagnosed between the ages of 31 and 60 years *(29)*. T1DM should be especially considered on clinical grounds in adults presenting with one or more of the following: ketosis, rapid weight loss, age of onset below 50 years, BMI below 25kg/m2, or personal and/or family history of autoimmune disease *(127)*.

3.1.5. Age > 50 years

Types of diabetes:

- Type 2 diabetes
- Slowly evolving immune-mediated diabetes in adults
- Type 1 diabetes

The same considerations apply in this age group as those that apply to individuals aged 20–50 years, although T1DM presenting in this age group is less common (see section “Age 25 to < 50 years”).

3.2 Differential diagnosis of individuals presenting with ketosis or ketoacidosis

Types of diabetes:

- Type 1 diabetes
- Ketosis-prone type 2 diabetes
- Type 2 diabetes with onset in youth
- Type 2 diabetes with onset in adults

In people with diabetes diagnosis before the age of 20 years, diabetic ketoacidosis at the time of diagnosis occurs in approximately 25% but varies within and across populations. The prevalence decreases with age from 37% in children aged 0 to 4 years to 15% among those aged 15 to 19 years. Diabetic ketoacidosis prevalence is significantly higher in people with T1DM (about 30%) compared with T2DM (about 10%). However, higher proportions (nearly 20%) have been reported in young-onset T2DM in the US *(128)*.

The possibility of ketosis-prone type 2 diabetes should be considered in adults of all ethnicities (except caucasian populations) who present with ketosis, but otherwise have most features of T2DM. However, diagnosis can only be established over time *(69, 70)*.

The increasing popularity of ketogenic diets may also influence the clinical presentation and should be considered.

Various schemes have been proposed for classifying patients with ketosis-prone diabetes *(129–132)*. A comparison of these systems reported that the AB system (130) based on the presence of autoimmunity (A +/−) or preserved β-cell function (β +/−) performed best with regard to accuracy and value in predicting long-term insulin dependence and clinical phenotype *(133)*. However, this scheme is not widely used and requires assessments not generally available in most clinical care settings.

4. Future classification systems

Advances in understanding of the various aetio-pathological pathways and mechanisms leading to hyperglycaemia and diabetes are needed in order to develop newer classification systems. While classical T1DM and T2DM can usually be distinguished clinically, many people with diabetes present with features that make it difficult to distinguish the two. Determining whether hybrid subtypes represent distinct entities or are part of a continuous spectrum will also require new knowledge.

A research imperative is to elucidate the aetio-pathological pathways to β-cell destruction or diminished function. Since this is a common feature of all diabetes, it is possible that future classification systems will focus on this, provided distinctive pathways linked with unique clinical subtypes can be identified that may be relevant to personalizing treatment. Biomarkers and imaging tools are needed to assess β-cell mass and loss of functional mass and to monitor progression and response to therapeutic interventions *(12)*.

New algorithms, similar to those developed for identifying people who have monogenic diabetes and who should be considered for genetic testing, are likely to assist in clinical decision-making. A recent study reported five distinct subtypes of T2DM on the basis of clustering of clinical, blood-based, and genetic information in newly diagnosed people with diabetes in Sweden *(134)*. These subgroups differed in disease progression and risk of diabetic complications. The subgroups included very insulin-resistant patients with significantly higher risk of diabetic kidney disease, a subgroup of younger and insulin-deficient patients with poorly controlled diabetes, and a large subgroup of elderly patients with the most benign disease course. The results were replicated in three independent cohorts in Sweden and Finland and this grouping may be relevant to more diverse populations but requires

further studies. However, implementing such a classification system would be challenging in many settings as the measurement of some of the variables used in defining the subgroups in the Swedish context (autoantibodies, C-peptide, genetic typing) is not routinely done and is often not available in most of the world.

References

1. Diabetes mellitus. Report of a WHO Expert Committee. Geneva: World Health Organization; 1965.
2. World Health Organization: Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and Classification of Diabetes Mellitus. Geneva: World Health Organization; 1999.
3. Leslie RD, Palmer J, Schloot NC, Lernmark A. Diabetes at the crossroads: relevance of disease classification to pathophysiology and treatment. Diabetologia. 2016;59:13–20.
4. Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. Nature. 2001;414:782–787.
5. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia. Geneva: World Health Organization; 2006.
6. Report of a World Health Organization consultation. Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus. Diabetes Res Clin Pract. 2011;93: 299–309.
7. Global report on diabetes. Geneva: World Health Organization; 2016.
8. IDF Diabetes Atlas. 8th Edition. Brussels: International Diabetes Federation, 2017.
9. Tuomi T, Santoro N, Caprio S, Cai M, Weng J, Groop L. The many faces of diabetes: a disease with increasing heterogeneity. Lancet 2014; 383:1084–1094.
10. Schwartz SS, Epstein S, Corkey BE, Grant SF, Gavin JR 3rd, Aguilar RB. The time is right for a new classification system for diabetes: rationale and implications of the β-cell-centric classification schema. Diabetes Care. 2016;39:179–86.
11. Kahn SE, Cooper ME, del Prato S. Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. Lancet. 2014;383:1068–1083.
12. Skyler JS, Bakris GL, Bonifacio E, Darsow T, Eckel RH, Groop L, et al. Differentiation of diabetes by pathophysiology, natural history, and prognosis. Diabetes. 2017;66: 241–255.
13. Perl S, Kushner JA, Buchholz BA, Meeker AK, Stein GM, Hsieh M et al. Significant human β cell turnover is limited to the first three decades of life as determined by in vivo thymidine analog incorporation and radiocarbon dating. J Clin Endocrinol Metab. 2010;95: E234–39.
14. Hocking S. Systematic review of the association between inherited genetic variants and response to blood glucose lowering therapies. 2017 (https://sydney.edu.au/content/dam/corporate/documents/faculty-of-medicine-and-health/research/centres-institutes-groups/boden/2018-Hocking-S-Systematic-review-association-between-inherited-genetic-variants-and-response-to-blood-glucose-lowering-therapies.pdf, accessed 1 March 2019).
15. Ng E, Vanderloo SE, Geiss L, Johnson JA. Concordance between self-report and a survey-based algorithm for classification of type 1 and type 2 diabetes using the 2011 population-based Survey on Living with Chronic Diseases in Canada (SLCDC)-Diabetes component. Can. J. Diabetes. 2013;37:249–53.
16. Bellatorre A, Jackson SH, Choi K. Development of the diabetes typology model for discerning Type 2 diabetes mellitus with national survey data. PloS One. 2017;12:e0173103.
17. Johansson BB, Irgens HU, Molnes J, Sztromwasser P, Aukrust I, Juliusson PB, et al. Targeted next-generation sequencing reveals MODY in up to 6.5% of antibody-negative diabetes cases listed in the Norwegian Childhood Diabetes Registry. Diabetologia. 2017;60:625–635.

18. Davis TME, Makepeace AE, Ellard S, Colclough K, Peters K, Hattersley A, et al. The prevalence of monogenic diabetes in Australia: the Fremantle Diabetes Study Phase II. MJA. 2017;207:344–347.

19. Woodmansey C, McGovern AP, McCullough KA, Whyte MB, Munro NM, Correa AC, et al. Incidence, demographics, and clinical characteristics of diabetes of the exocrine pancreas (Type 3c): a retrospective cohort study. Diabetes Care. 2017;40:1486–1493.

20. Karamanou M, Protogerou A, Tsoucalas G, Androutsos G, Poulakou-Rebelakou E. Milestones in the history of diabetes mellitus: the main contributors. World J Diabetes. 2016;7:1–7.

21. WHO Expert Committee on Diabetes Mellitus. Second Report. Technical report Series 646. Geneva, World Health Organization; 1980.

22. Diabetes mellitus: report of a WHO Study Group. Technical Report Series 727. Geneva: World Health Organization; 1985.

23. Defronzo RA. Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes 2009;58:773–795.

24. Patterson CC, Dahlquist GG, Gyürüs E, Green A, Soltesz G. EURODIAB study group incidence trends for childhood type 1 diabetes in Europe during 1989–2003 and predicted new cases 2005–20: a multicentre prospective registration study. Lancet. 2009;373:2027–2033.

25. Maahs DM, West NA, Lawrence JM, Mayer-Davis EJ. Epidemiology of type 1 diabetes. Endocrinol Metab Clin North Am. 2010;39:481–497.

26. Centers for Disease Control and Prevention. National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014. Atlanta: U.S. Department of Health and Human Services; 2014.

27. Livingstone SJ, Levin D, Looker HC, Lindsay RS, Wild SH, Joss N et al. Scottish Diabetes Research Network epidemiology group; Scottish Renal Registry. Estimated life expectancy in a Scottish cohort with type 1 diabetes, 2008-2010. JAMA. 2015;313:37–44.

28. Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. Lancet. 2014;383:69–82.

29. Thomas NJ, Jones SE, Weedon MN, Shields BM, Oram RA, Hattersley AT. Frequency and phenotype of type 1 diabetes in the first six decades of life: a cross-sectional, genetically stratified survival analysis from UK Biobank. Lancet Diabetes and Endocrinology. 2018;6:122–129.

30. Hagopian WA, Karlsen AE, Gottsater A, Landin-Olsson M, Grubin CE, Sundkvist G, et al. Quantitative assay using recombinant human islet glutamic acid decarboxylase (GAD65) shows that 64K autoantibody positivity at onset predicts diabetes type. J.Clin.Invest. 1993;91:368–374.

31. Jackson W, Hofman PL, Robinson EM, Elliot RB, Pilcher CC, Cutfield WS. The changing presentation of children with newly diagnosed type 1 diabetes mellitus. Pediatr.Diabetes. 2001;2:154–159.

32. Madsbad S, Krarup T, Regeur L, Faber OK, Binder C. Insulin secretory reserve in insulin dependent patients at time of diagnosis and the first 180 days of insulin treatment. Acta Endocrinol (Copenh). 1980;95:359–363.

33. Eisenbarth GS. Update in type 1 diabetes. J Clin Endocrinol Metab. 2007;92:2403–7.

34. Gianani R, Campbell-Thompson M, Sarkar SA, et al. Dimorphic histopathology of long-standing childhood-onset diabetes. Diabetologia. 2010;53:690–98.

35. Hanafusa T, Imagawa A. Fulminant type 1 diabetes: a novel clinical entity requiring special attention by all medical practitioners. Nat Clin Pract Endocrinol Metab. 2007;3:36–45.

36. Imagawa, A, Hanafusa, T, Miyagawa, J, Matsuzawa, Y for the Osaka IDDM Study Group. A novel subtype of type 1 diabetes mellitus characterized by a rapid onset and an absence of diabetes-related antibodies. NEJM. 2000;342:301–7.

37. Imagawa A, Hanafusa T, Awata T, Ikegami H, Uchigata Y, Kobayashi T et al. Report of the Committee of the Japan Diabetes Society on the research of fulminant and acute-onset type 1 diabetes mellitus: new diagnostic criteria of fulminant type 1 diabetes mellitus. J Diabetes Investig. 2012;3:536–9.

38. Cho YM, Kim JT, Ko KS, Koo BK, Yang SW, Park MH et al. Fulminant type 1 diabetes in Korea: high prevalence among patients with adult onset type 1 diabetes. Diabetologia. 2007;50:2276–227.

39. Luo S, Zhang Z, Li X, Yang L, Lin J, Yan X et al. Fulminant type 1 diabetes: a collaborative clinical cases investigation in China. Acta Diabetol. 2013;50:53–9.

40. Sosenko JM, Krischer JP, Palmer JP, Mahon J, Cowie C, Greenbaum CJ. A risk score for type 1 diabetes derived from autoantibody-positive participants in the diabetes prevention trial-type 1. Diabetes Care. 2008;31:528–533.

41. Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. Lancet. 2005;365:1333–1346.

42. Bogardus C, Lillioja S, Mott DM, Hollenbeck C, Reaven G. Relationship between degree of obesity and in vivo insulin action in man. Am.J.Physiol. 1985;248:E286–E291.

43. Mooy JM, Grootenhuis PA, de Vries H, Valkenburg HA, Bouter LM, Kostense PJ, et al. Prevalence and determinants of glucose intolerance in a Dutch caucasian population. The Hoorn Study. Diabetes Care. 1995;18:1270–1273.

44. Ma RCW, Chan JCN. Type 2 diabetes in East Asians: similarities and differences with populations in Europe and the United States. Ann N Y Acad Sci. 2013;1281:64–91.

45. Narayan KM. Type 2 diabetes: Why we are winning the battle but losing the war. 2015 Kelly West Award Lecture. Diabetes Care. 2016;39:653–663.

46. Kanaya AM, Herrington D, Vittinghoff E, Ewing SK, Liu K, Blaha MJ, et al. Understanding the high prevalence of diabetes in U.S. south Asians compared with four racial/ethnic groups: the MASALA and MESA studies. Diabetes Care. 2014;37:1621–8.

47. Gujral UP, Narayan KM, Kahn SE, Kanaya AM. The relative associations of β-cell function and insulin sensitivity with glycemic status and incident glycemic progression in migrant Asian Indians in the United States: the MASALA study. J Diabetes Complications. 2014; 28:45–50.

48. U.K. Prospective Diabetes Study Group. U.K. prospective diabetes study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. Diabetes. 1995;44:1249–58.

49. Yoon KH, Lee JH, Kim JW, Cho JH, Choi YH, Ko SH, et al. Epidemic obesity and type 2 diabetes in Asia. Lancet. 2006;368:1681–1688.

50. Constantino MI, Molyneaux L, Limacher-Gisler F, Al-Saeed A, Luo C, Wu T et al. Long-term complications and mortality in young-onset diabetes. Type 2 diabetes is more hazardous and lethal than type 1 diabetes. Diabetes Care. 2013;36:3863–3869.

51. Hamman RF, Bell RA, Dabelea D, D'Agostino Jr RB, Dolan L, Imperatore G, et al for the SEARCH for Diabetes in Youth Study Group. The SEARCH for diabetes in youth study: rationale, findings, and future directions. Diabetes Care. 2014;37:3336–3344.

52. TODAY Study Group. A clinical trial to maintain glycemic control in youth with type 2 diabetes. N Engl J Med. 2012;366:2247–56.

53. Polonsky KS, Sturis J, Bell GI. Seminars in medicine of the Beth Israel Hospital, Boston. Non-insulin-dependent diabetes mellitus – a genetically programmed failure of the beta cell to compensate for insulin resistance. N Engl J Med. 1996;334:777–783.

54. Fuchsberger C, Flannick J, Teslovich TM, Mahajan A, Agarwala V, Gaulton KJ. The genetic architecture of type 2 diabetes. Nature. 2016; 536:41–47.

55. Newton CA, Raskin P. Diabetic ketoacidosis in type 1 and type 2 diabetes mellitus. Clinical and biochemical differences. Arch Intern Med. 2004;164:1925–1931.

56. Umpierrez GE, Casals MM, Gebhart SP, Mixon PS, Clark WS, Phillips LS. Diabetic ketoacidosis in obese African-Americans. Diabetes. 1995;44:790–795.

57. Pasquel FJ and Umpierrez GE. Hyperosmolar hyperglycemic state: a historic review of the clinical presentation, diagnosis, and treatment. Diabetes Care. 2014;37:3124–3131.

58. Tuomi T, Groop L, Zimmet P, Rowley M, Mackay I. Antibodies to glutamic acid decarboxylase (GAD) reveal latent autoimmune diabetes mellitus in adults with a non-insulin dependent onset of disease. Diabetes. 1993;42:359–362.

59. Gale EAM. Latent autoimmune diabetes in adults: a guide for the perplexed. Diabetologia. 2005;48:2195–2199.

60. Zimmet PZ, Tuomi T, Mackay IR, Rowley MJ, Knowles W, Cohen M, et al. Latent autoimmune diabetes mellitus in adults (LADA): the role of antibodies to glutamic acid decarboxylase in diagnosis and prediction of insulin dependency. Diabet Med. 1994;11:299–303.

61. Reinehr T, Schober E, Wiegand S, Thon A, Holl R, and the DPV-Wiss Study Group. β-cell autoantibodies in children with type 2 diabetes mellitus: subgroup or misclassification? Arch Dis Child. 2006;91: 473–77.

62. Klingensmith GJ, Pyle L, Arslanian S, et al, and the TODAY Study Group. The presence of GAD and IA-2 antibodies in youth with a type 2 diabetes phenotype: results from the TODAY study. Diabetes Care 2010;33: 1970–75.

63. Sorgjerd EP, Skorpen F, Kvaloy K, Midthjell K, Grill V. Time dynamics of autoantibodies are coupled to phenotypes and add to the heterogeneity of autoimmune diabetes in adults: the HUNT study, Norway. Diabetologia. 2012;55:1310–1851.

64. Williams GM, Long AE, Wilson IV, Aitken RJ, Wyatt RC, McDonald TJ, et al. Beta cell function and ongoing autoimmunity in long-standing, childhood onset type 1 diabetes. Diabetologia. 2016;59:2722–2726.

65. Redondo MJ. LADA: Time for a New Definition. Diabetes. 2013;62: 339–340.

66. Cervin C, Lyssenko V, Bakhtadze E, Lindholm E, Nilsson P, Tuomi T, et al. Genetic similarities between latent autoimmune diabetes in adults, type 1 diabetes, and type 2 diabetes. Diabetes. 2008;57:1433–1437.

67. Winter WE, Maclaren NK, Riley WJ, Clarke DW, Kappy MS, Spillar RP. Maturity-onset diabetes of youth in black Americans. N Engl J Med. 1987;316:285–291.

68. Mauvais-Jarvis F, Sobngwi E, Porcher R, Riveline J-P, Kevorkian J-P, Vaisse C, et al. Ketosis-prone type 2 diabetes in patients of Sub-Saharan African origin. Clinical pathophysiology and natural history of β-cell dysfunction and insulin resistance. Diabetes. 2004;53:645–653.

69. Sobngwi E, Gautier JF. Adult-onset idiopathic Type I or ketosis-prone type II diabetes: evidence to revisit diabetes classification. Diabetologia. 2002;45:283–285.

70. Sobngwi E, Mauvais-Jarvis F, Vexiau P, Mbanya JC, Gautier JF. Diabetes in Africans. Part 2: Ketosis-prone atypical diabetes mellitus. Diabetes Metab. 2002;28:5–12.

71. Banerji MA, Chaiken RL, Huey H, Tuomi T, Norin AJ, Mackay IR et al. GAD-antibody negative NIDDM in adult black subjects with diabetic ketoacidosis and increased frequency of human leukocyte antigen DR3 and DR4. Flatbush diabetes. Diabetes. 1994;43:741–45.

72. Thomas CC, Philipson LH. Update on Diabetes Classification. Med Clin N Am. 2015;99:1–16.

73. Hattersley A, Bruining J, Shield J, Njolstad P, Donaghue KC. The diagnosis and management of monogenic diabetes in children and adolescents. Pediatric Diabetes. 2009;10 (Suppl. 12):33–42.

74. Hattersley A, Bruining J, Shield J, Njolstad P, Donaghue K. ISPAD Clinical Practice Consensus Guidelines 2006–2007. The diagnosis and management of monogenic diabetes in children. Pediatric Diabetes. 2006;7:352–360.

75. Tattersall RB. Mild familial diabetes with dominant inheritance. Q J Med. 1974;43:339–357.

76. Shields BM, Hicks S, Shepherd MH, Colclough K, Hattersley AT, Ellard S. Maturity-onset diabetes of the young (MODY): how many cases are we missing? Diabetologia. 2010;53:2504–2508.

77. Hattersley AT, Pearson ER: Minireview: pharmacogenetics and beyond: the interaction of therapeutic response, beta-cell physiology, and genetics in diabetes. Endocrinology. 2006;147:2657–2663.

78. Spyer G, Macleod KM, Shepherd M, Ellard S, Hattersley AT. Pregnancy outcome in patients with raised blood glucose due to a heterozygous glucokinase gene mutation. Diabet Med. 2009;26:14–18.

79. Pearson ER, Boj SF, Steele AM, Barrett T, Stals K, Shield JP, et al. Macrosomia and hyperinsulinaemic hypoglycaemia in patients with heterozygous mutations in the HNF4A gene. PLoS.Med. 2007;4:e118.

80. Iafusco D, Stazi MA, Cotichini R, Cotellessa M, Martinucci ME, Mazzella M, et al. Permanent diabetes mellitus in the first year of life. Diabetologia. 2002;45:798–804.

81. Edghill EL, Dix RJ, Flanagan SE, Bingley PJ, Hattersley AT, Ellard S, et al. HLA genotyping supports a nonautoimmune etiology in patients diagnosed with diabetes under the age of 6 months. Diabetes. 2006;55:1895–1898.

82. Temple IK, Gardner RJ, Mackay DJ, Barber JC, Robinson DO, Shield JP. Transient neonatal diabetes: widening the understanding of the etiopathogenesis of diabetes. Diabetes. 2000;49:1359–1366.

83. Gloyn AL, Pearson ER, Antcliff JF, Proks P, Bruining GJ, Slingerland AS, et al. Activating mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir6.2 and permanent neonatal diabetes. N Engl J Med. 2004;350:1838–1849.

84. Ellard S, Flanagan SE, Girard CA, Patch AM, Harries LW, Parrish A, et al. Permanent neonatal diabetes caused by dominant, recessive, or compound heterozygous SUR1 mutations with opposite functional effects. Am J Hum Genet. 2007;81:375–382.

85. Babenko AP, Polak M, Cave H, Busiah K, Czernichow P, Scharfmann R, et al. Activating mutations in the ABCC8 gene in neonatal diabetes mellitus. N Engl J Med. 2006;355:456–466.

86. Stoy J, Edghill EL, Flanagan SE, Ye H, Paz VP, Pluzhnikov A, et al. Insulin gene mutations as a cause of permanent neonatal diabetes. Proc Natl Acad Sci USA. 2007;104:15040–15044.

87. Aguilar-Bryan L, Bryan J. Neonatal diabetes mellitus. Endocr Rev. 2008;29:265–291.

88. van den Ouweland JM, Lemkes HH, Ruitenbeek W, Sandkuijl LA, de Vijlder MF, Struyvenberg PA, et al. Mutation in mitochondrial tRNA(Leu)(UUR) gene in a large pedigree with maternally transmitted type II diabetes mellitus and deafness. Nat Genet. 1992;1:368–371.

89. Maassen JA, Kadowaki T. Maternally inherited diabetes and deafness: a new diabetes subtype. Diabetologia. 1996;39:375–382.

90. Johansson BB, Irgens HU, Molnes J, Sztromwasser P, Aukrust I, Juliusson PB, et al. Targeted next-generation sequencing reveals MODY in up to 6.5% of antibody-negative diabetes cases listed in the Norwegian Childhood Diabetes Registry. Diabetologia. 2017;60:625–635.

91. Davis TME, Makepeace AE, Ellard S, Colclough K, Peters K, Hattersley A, Davis WA. The prevalence of monogenic diabetes in Australia: the Fremantle Diabetes Study Phase II. MJA. 2017;207:344–347.

92. Kahn CR, Flier JS, Bar RS, Archer JA, Gorden P, Martin MM, et al. The syndromes of insulin resistance and acanthosis nigricans. Insulin-receptor disorders in man. N Engl J Med. 1976;294:739–745.

93. Taylor SI. Lilly Lecture: molecular mechanisms of insulin resistance. Lessons from patients with mutations in the insulin-receptor gene. Diabetes. 1992;41:1473–1490.

94. Taylor SI, Arioglu E. Genetically defined forms of diabetes in children. Journal of Clinical Endocrinology & Metabolism. 1999;84:4390–4396.

95. Owen KR, Groves CJ, Hanson RL, Knowler WC, Shuldiner AR, Elbein SC, et al. Common variation in the LMNA gene (encoding lamin A/C) and type 2 diabetes: association analyses in 9,518 subjects. Diabetes. 2007;56: 879–83.

96. Barroso I, Gurnell M, Crowley VE, Agostini M, Schwabe JW, Soos MA et al. Dominant negative mutations in human PPARgamma associated with severe insulin resistance, diabetes mellitus and hypertension. Nature. 1999;402:880–883.

97. Ewald N, Kaufmann C, Raspe A, Kloer HU, Bretzel RG, Hardt PD. Prevalence of diabetes mellitus secondary to pancreatic diseases (type 3c). Diabetes Metab Res Rev. 2012;28:338–342.

98. Hart PA, Bellin MD, Andersen DK, Bradley D, Cruz-Monserrate Z, Forsmark CE et al. Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC). Type 3c (pancreatogenic) diabetes mellitus secondary to chronic pancreatitis and pancreatic cancer. Lancet Gastroenterol Hepatol. 2016;1:226–237.

99. Permert J, Larsson J, Westermark GT, Herrington MK, Christmanson L, Pour PM et al. Islet amyloid polypeptide in patients with pancreatic cancer and diabetes. N Engl J Med. 1994;330:313–318.

100. Dobson L, Sheldon CD, Hattersley AT. Understanding cystic fibrosis-related diabetes: best thought of as insulin deficiency? J R Soc Med. 2004;97 Suppl 44:26–35.

101. Yajnik CS, Shelgikar KM, Naik SS, Kanitkar SV, Orskov H, Alberti KG, et al. The ketosis-resistance in fibro-calculous-pancreatic-diabetes. 1. Clinical observations and endocrine-metabolic measurements during oral glucose tolerance test. Diabetes. Res Clin Pract. 1992;15:149–156.

102. Woodmansey C, McGovern AP, McCullough KA, Whyte MB, Munro NM, Correa AC, et al. Incidence, demographics, and clinical characteristics of diabetes of the exocrine pancreas (Type 3c): a retrospective cohort study. Diabetes Care. 2017;40:1486–1493.

103. MacFarlane IA. Endocrine disease and diabetes mellitus. In: Textbook of diabetes. 2nd ed. Pickup JC, Williams G, Eds. Oxford: Blackwell; 1997; 64.10–64.20.

104. Krejs GJ, Orci L, Conlon JM, Ravazzola M, Davis GR, Raskin P, et al. Somatostatinoma syndrome. Biochemical, morphologic and clinical features. N Engl J Med. 1979;301:285–292.

105. Pandit MK, Burke J, Gustafson AB, Minocha A, Peiris AN. Drug-induced disorders of glucose tolerance. Ann Intern Med. 1993;118:529–539.

106. O'Byrne S, Feely J. Effects of drugs on glucose tolerance in non-insulin-dependent diabetics (Part II). Drugs. 1990;40:203–219.

107. Esposti MD, Ngo A, Myers MA. Inhibition of mitochondrial complex I may account for IDDM induced by intoxication with the rodenticide Vacor. Diabetes. 1996;45:1531–1534.

108. Forrest JM, Menser MA, Burgess JA. High frequency of diabetes mellitus in young adults with congenital rubella. Lancet. 1971;2:332–334.

109. King ML, Shaikh A, Bidwell D, Voller A, Banatvala JE: Coxsackie-B-virus-specific IgM responses in children with insulin-dependent (juvenile-onset; type I) diabetes mellitus. Lancet 1983;1:1397–1399.

110. Karjalainen J, Knip M, Hyoty H, Leinikki P, Ilonen J, Kaar ML, et al. Relationship between serum insulin autoantibodies, islet cell antibodies and Coxsackie-B4 and mumps virus-specific antibodies at the clinical manifestation of type 1 (insulin-dependent) diabetes. Diabetologia. 1988;31:146–152.

111. Pak CY, Eun HM, McArthur RG, Yoon JW. Association of cytomegalovirus infection with autoimmune type 1 diabetes. Lancet. 1988;2:1–4.

112. Hirata Y, Ishizu H. Elevated insulin-binding capacity of serum proteins in a case with spontaneous hypoglycemia and mild diabetes not treated with insulin. Tohoku J Exp Med. 1972;107:277–286.

113. Solimena M, Folli F, Aparisi R, Pozza G, De Camilli P. Autoantibodies to GABA-ergic neurons and pancreatic beta cells in stiff-man syndrome. N Engl J Med. 1990;322:1555–1560.

114. Levy LM, Dalakas MC, Floeter MK. The stiff-person syndrome: an autoimmune disorder affecting neurotransmission of gamma-aminobutyric acid. Ann Intern Med. 1999;131:522–530.

115. Fabris P, Betterle C, Greggio NA, Zanchetta R, Bosi E, Biasin MR, et al. Insulin-dependent diabetes mellitus during alpha-interferon therapy for chronic viral hepatitis. J Hepatol. 1998;28:514–517.

116. Kahn CR, Baird K, Filier JS, Jarrett DB. Effects of autoantibodies to the insulin receptor on isolated adipocytes. Studies of insulin binding and insulin action. J Clin Invest. 1997;60:1094–1106.

117. Rosenstein ED, Advani S, Reitz RE, Kramer N. The prevalence of insulin receptor antibodies in patients with systemic lupus erythematosus and related conditions. J Clin Rheumatol. 2001;7:371–373.

118. Robinson S, Kessling A. Diabetes secondary to genetic disorders. Baillieres Clin Endocrinol Metab. 1992;6:867–898.

119. Low S, Chin MC, Deurenberg-Yap M. Review on epidemic of obesity. Ann Acad Med Singapore. 2009;38:57–59.

120. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy: a World Health Organization Guideline. Diab Res Clin Pract. 2014;103:341–63.

121. Edghill EL, Dix RJ, Flanagan SE, Bingley PJ, Hattersley AT, Ellard S, et al. HLA genotyping supports a nonautoimmune etiology in patients diagnosed with diabetes under the age of 6 months. Diabetes 2006: 55: 1895–1898.

122. Iafusco D, Stazi MA, Cotichini R, Cotellessa M, Martinucci ME, Mazzella M, et al. Permanent diabetes mellitus in the first year of life. Diabetologia. 2002;45:798–804.

123. Rosenbloom AL. Obesity, insulin resistance, beta cell autoimmunity, and the changing clinical epidemiology of childhood diabetes. Diabetes Care. 2003;26:2954–2956.

124. eitler P, Haqq A, Rosenbloom A, Glaser N, for the Drugs and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society. Hyperglycemic hyperosmolar syndrome in children: pathophysiological considerations and suggested guidelines for treatment. J Pediatr. 2011;158:9–14.

125. Shields B, Colclough K. Towards a systematic nationwide screening strategy for MODY. Diabetologia. 2017;60:609–612.

126. Shields BM, McDonald TJ, Ellard S, Campbell MJ, Hyde C, Hattersley AT, et al. The development and validation of a clinical prediction model to determine the probability of MODY in patients with young-onset diabetes. Diabetologia, 2012;55: 1265–1272.

127. NICE guideline. Type 1 diabetes in adults: diagnosis and management. London: National Institute for Healthcare and Excellence; August 2015 (nice.org.uk/guidance/ng17, accessed 9 February 2019).

128. Rewers A, Klingensmith G, Davis C, Petitti DB, Pihoker C, Rodriguez B, et al. Presence of diabetic ketoacidosis at diagnosis of diabetes mellitus in youth: the Search for Diabetes in Youth Study. Pediatrics. 2008;121:e1258–66.

129. Umpierrez GE, Woo W, Hagopian WA, Isaacs SD, Palmer JP, Gaur LK, et al. Immunogenetic analysis suggests different pathogenesis for obese and lean African-Americans with diabetic ketoacidosis. Diabetes Care. 1999;22:1517–1523.

130. Maldonado M, Hampe CS, Gaur LK, D'Amico S, Iyer D, Hammerle LP, et al. Ketosis-prone diabetes: dissection of a heterogeneous syndrome using an immunogenetic and beta-cell functional classification, prospective analysis, and clinical outcomes. J Clin Endocrinol Metab. 2003;88:5090–5098.

131. Mauvais-Jarvis F, Sobngwi E, Porcher R, Riveline JP, Kevorkian JP, Vaisse C, et al. Ketosis-prone type 2 diabetes in patients of sub-Saharan African origin: clinical pathophysiology and natural history of β-cell dysfunction and insulin resistance. Diabetes. 2004;53:645– 653.

132. Pinero-Pilona A, Raskin P. Idiopathic type 1 diabetes. J Diabetes Complications. 2001;15:328–335.

133. Balasubramanyam A, Garza G, Rodriguez L, Hampe CS, Gaur L, Lernmark A, et al. Accuracy and predictive value of classification schemes for ketosis-prone diabetes. Diabetes Care. 2006;29:2575–9.

134. Ahlqvist E, Storm, P, Käräjämäki A, Martinell M, Dorkhan M, Carlsson A, et al. Novel sub-groups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. Lancet Diabetes Endocrinol. 2018;6(5):361–369.


LIMONADA
1 copo =
0g de carboidrato
ARROZ
2 colheres de sopa =
15g de carboidrato
BATATA
COZIDA
SALADA
crua à vontade =
0g de carboidrato
FARINHA
DE MANDIOCA
1 colher de sopa =
15g de carboidrato
FEIJÃO
2 conchas =
15g de carboidrato
UVA
15g de carboidrato
MELANCIA
MAÇÃ
AMEIXA

World Health Organization

Department for Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention

20 Avenue Appia
1211 Geneva 27
Switzerland
Téléphone: +41 22 791 3111

https://www.who.int/health-topics/diabetes