Diagnostic Criteria and Classification

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Abstract

Diabetes is an important contributor to global burden of disease. The number of people with diabetes has increased substantially since the first global estimates were published in 2000. Nevertheless, diabetes prevalence estimates are highly

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dependent on factors such as data sources and quality, method used to diagnose diabetes, diagnostic criteria, and modelling assumptions. This chapter includes a review of the development of the current diagnostic criteria for diabetes and considers classification systems for diabetes.

Keywords
Diabetes · Intermediate hyperglycemia · Fasting plasma glucose · Glycated hemoglobin

Diabetes is recognized as an important contributor to global burden of disease and consequently the 2025 global goals arising from the 2011 United Nations High-Level Meeting on Noncommunicable Diseases (NCDs) include halting the rise in age-standardized adult prevalence of diabetes at 2010 levels (World Health Organization 2013b).

The number of people with diabetes has almost tripled since the first global estimates were published by the International Diabetes Federation in 2000 (International Diabetes Federation 2000). The latest figures suggest that 415 million people aged 20–79 years had diabetes in 2015 with almost half of these having undiagnosed diabetes (International Diabetes Federation 2015). This figure is remarkably similar to the NCD Risk Factor Collaboration (NCD-RisC) estimate of 422 million adults with diabetes in the world in 2014 (NCD Risk Factor Collaboration (NCD-RisC) 2016).

Diabetes prevalence estimates are highly dependent on a number of factors including data sources and quality, method used to diagnose diabetes, diagnostic criteria, and modeling assumptions. Studies used to estimate global diabetes prevalence and numbers have used a variety of methods to diagnose diabetes including diabetes biomarkers (fasting glucose, post-load glucose, and glycated hemoglobin (HbA1c)), self-reported diabetes, medical records, use of blood glucose-lowering therapies, and occasionally urine glucose. The International Diabetes Federation method preferentially selects data sources according to a prespecified set of criteria and on quality judged by an expert panel. The NCD-RisC estimate included a modeled conversion to a consistent definition of diabetes based on fasting plasma glucose to adjust for differences in diabetes biomarker data. Given these differences in methodologies, it is remarkable that both of these studies produced very similar and consistent results.

Over the years there have been a series of consensus expert meetings to consider the diagnosis and classification of diabetes in order to achieve international harmonization not only to compare epidemiological information but also to provide uniformity in diagnosing an individual with diabetes and the considerable impact of such a diagnosis. The World Health Organization published its first report on the diagnosis and classification of diabetes in 1965 (World Health Organization 1965). Since then, several modifications have been made to both the diagnostic criteria and classification by the World Health Organization (1980, 1985, 1999; World Health Organization & International Diabetes Federation 2006; Report of a World Health Organization Consultation 2011) and the American

Diabetes Association (National Diabetes Data Group 1979; The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 1997 and 2003; American Diabetes Association 2010).

In addition to diagnosing people with diabetes, different forms of diabetes have been recognized and described for many years. This chapter reviews the development of the current diagnostic criteria for diabetes and considers classification systems for diabetes.

Diagnostic Criteria for Diabetes

Uniform and agreed diagnostic criteria for diabetes are essential for individual health and clinical care and epidemiological studies and monitoring population changes over time such as progress against the United Nations' targets. A diagnosis of diabetes has important implications for the individual not only for health but also as a result of labeling including employment, health and life insurance, driving, and social opportunities and has potential cultural, ethical, and human rights consequences. While we focus on biomedical criteria for establishing the presence of diabetes, diagnosing and labeling an individual with diabetes has far broader implications.

Drawing the line between normal and abnormal is difficult when a population biomarker such as glucose is a continuum without a self-evident cut point. The evolution of glucose based on the World Health Organization diagnostic criteria is summarized in Table 1. It is interesting to note that the 1965 World Health Organization technical report stated that the "committee recognized the difficulties posed by attempting to make world-wide recommendations on laboratory tests, particularly with respect to the glucose tolerance test blood-sugar values," a situation which has remained largely unchanged for the past 50 years. Consequently while the many expert consultations over a long period have produced the current universally accepted diagnostic criteria for diabetes, some aspects continue to be debated and may well be revised in the future.

Current Diagnostic Criteria

Diabetes

Diabetes can be associated with classical symptoms of hyperglycemia which include polyuria, polydipsia, polyphagia, and weight loss. The presence of these symptoms and an unequivocally elevated random plasma glucose are sufficient to make a diagnosis of diabetes. However many people with diabetes can remain asymptomatic for many years and blood tests are required for diagnosis. Diagnostic tests currently accepted by the World Health Organization and the American Diabetes Association include the measure of fasting plasma glucose, 2-h post-load plasma glucose during an oral glucose tolerance test (OGTT), and HbA1c. Asymptomatic people with

Table 1 Summary of WHO glucose-based diagnostic criteria for diabetes and intermediate hyperglycemia

	1965	1980	1985	1999	2006
Normal		Not defined	Not defined		Not defined
FPG	Not specified			<6.1 mmol/L (110 mg/dl)	
2hPG	<6.1 mmol/L (110 mg/dl)			Not specified but <7.8 mmol/L (140 mg/dl) implied	
Diabetes					
FPG	Not specified	≥8.0 mmol/L (144 mg/dl)	≥7.8 mmol/L (140 mg/dl)	≥7.0 mmol/L (126 mg/dl)	≥7.0 mmol/L (126 mg/dl)
		AND/OR	OR	OR	OR
2hPG	≥7.2 mmol/L (130 mg/dl)	≥11.0 mmol/L (199 mg/dl)	≥11.1 mmol/L (200 mg/dl)	≥11.1 mmol/L (200 mg/dl)	≥11.1 mmol/L (200 mg/dl)
IGT	Referred to as borderline state				
FPG		<8.0 mmol/L (144 mg/dl)	<7.8 mmol/L (140 mg/dl)	<6.1 mmol/L (110 mg/dl)	<6.1 mmol/L (110 mg/dl)
		AND	AND	AND	AND
2hPG	6.1–7.1 mmol/L (110–128 mg/dl)	≥8.0 and <11.0 mmol/L (145–199 mg/dl)	≥7.8 and <11.1 mmol/L (140–199 mg/dl)	≥7.8 and <11.1 mmol/L (140–199 mg/dl)	≥7.8 and <11.1 mmol/L (140–199 mg/dl)
IFG	Not defined	Not defined	Not defined		
FPG				≥6.1 and <7.0 mmol/L (110–125 mg/dl)	≥6.1 and <7.0 mmol/L (110–125 mg/dl)
				AND	AND
2hPG				<7.8 mmol/L (140 mg/dl) (if measured)	<7.8 mmol/L (140 mg/dl) (if measured)

FPG fasting plasma glucose, *2hPG* 2-h plasma glucose during an oral glucose tolerance test, *IGT* impaired glucose tolerance, *IFG* impaired fasting glucose

fasting plasma glucose ≥7.0 mmol/L (126 mg/dl), 2-h post-load plasma glucose ≥11.1 mmol/L (200 mg/dl), and/or HbA1c ≥6.5% (48 mmol/mol) are considered to have diabetes (Table 2). For asymptomatic people, repeat testing, preferably with the same test, is recommended to confirm the diagnosis.

Over the years there have been four major changes related to diagnostic criteria for diabetes:

Standardization of the Glucose Load Used in the OGTT

Since 1979/1980 the accepted glucose dose for an OGTT to diagnose diabetes in nonpregnant adults has been standardized to 75 g. This decision basically represented a compromise between the 50 g dose used in Europe and the 100 g used in the USA at that time.

Table 2 Current diagnostic criteria for diabetes and intermediate hyperglycemia

	World Health Organization (2006, 2011)			American Diabetes Association (2015)	
		Intermediate hyperglycemia			
	Diabetes	Impaired glucose tolerance	Impaired fasting glucose	Diabetes	Intermediate hyperglycemia (prediabetes)
Fasting plasma glucose	≥7.0 mmol/L (126 mg/d)	<7.0 mmol/L (126 mg/dl)	6.1–6.9 mmol/L (110–125 mg/dl)	≥7.0 mmol/L (126 mg/dl)	5.6–6.9 mmol/L (100–125 mg/dl)
	AND/OR	AND	AND	OR	OR
2-hr plasma glucose during an oral glucose tolerance test	≥11.1 mmol/L (200 mg/dl)	7.8–11.0 mmol/L (140–199 mg/dl)	<7.8 mmol/L (140 mg/dl) (if measured)	≥11.1 mmol/L (200 mg/dl)	7.8–11.0 mmol/L (140–199 mg/dl)
	AND/OR			OR	OR
Glycated hemoglobin	≥6.5% (48 mmol/mol)			≥6.5% (48 mmol/mol)	5.7–6.4% (39–47 mmol/mol)
				OR	
Random plasma glucose				≥11.1 mmol/L in patients with classic symptoms of hyperglycemia	

2-h Post-Load Glucose Levels

The original World Health Organization criterion for diagnosing diabetes was based solely on a 2-h post-load plasma glucose ≥7.2 mmol/L (130 mg/dl) (World Health Organization 1965). This was changed in 1979/1980 with the diagnostic cut point set at ≥11.1 mmol/L (200 mg/dl). Despite the evidence on which this is based not being particularly strong, this level has remained unchanged because no convincing new evidence has emerged to indicate that this should be changed.

Fasting Plasma Glucose

There have been a number of changes in relation to fasting plasma glucose levels. Initially no diagnostic level was set for fasting glucose. In 1979 the National Diabetes Data Group set a diagnostic level for fasting plasma glucose ≥7.8 mmol/L (140 mg/dl) on the basis of a bimodal distribution in some populations (National Diabetes Data Group 1979). In 1980, the World Health Organization recommended a fasting plasma glucose ≥8.0 mmol/L (145 mg/dl) (World Health Organization 1980) and revised this to ≥7.8 mmol/L (140 mg/dl) in 1985 (World Health Organization 1985). In 1997/1998 the diagnostic fasting plasma glucose was lowered to ≥7.0 mmol/L (126 mg/dl) (the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 1997; World Health Organization 1999). This was based on achieving a better alignment of fasting and 2-h post-load glucose and was largely

based on the point where prevalence of diabetes-specific microvascular complications increases.

HbA1c Included as a Diagnostic Criterion

HbA1c was adopted as a diagnostic criterion for diabetes by the American Diabetes Association in 2010 (American Diabetes Association 2010) and the World Health Organization in 2011 (Report of a World Health Organization Consultation 2011). This was also based on the point where prevalence of diabetes-specific microvascular complications increases (see below).

Intermediate Hyperglycemia

It has long been recognized that lesser degrees of hyperglycemia below diabetes levels are associated with an increased risk of progression to diabetes and with increased risk of cardiovascular events. There is also an increased focus on identifying these people in order to implement interventions to reduce this risk, particularly to decrease risk of developing diabetes. Intermediate hyperglycemia is often referred to as "prediabetes," a somewhat controversial term since the development of diabetes is not invariable and can only accurately be applied retrospectively. Nevertheless, the term remains popular and commonly used in clinical practice and the literature.

Two states of intermediate hyperglycemia are recognized – impaired fasting glucose and impaired glucose tolerance. In 1979 the National Diabetes Data Group (1979) introduced the category of impaired glucose tolerance to denote a state of increased risk of progressing to diabetes, although it was also noted that many would revert to normal. This term was introduced to remove the stigma of diabetes from the other terms in use at the time to denote the range between "normal" and diabetes. This category and definition was included in the 1980 World Health Organization report (World Health Organization 1980). Impaired glucose tolerance is not a clinical entity but is a risk factor for future diabetes and/or adverse outcomes. The universally accepted definition of impaired glucose tolerance includes a fasting plasma glucose <7.0 mmol/L (126 mg/dl) and 2-h post-load plasma glucose of 7.8–11.0 mmol/L (140–199 mg/dl) (Table 2) (World Health Organization & International Diabetes Federation 2006).

In 1997 an expert committee (the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 1997) introduced impaired fasting glucose to describe a range of fasting plasma glucose equivalent to impaired glucose tolerance, and this was included in the 1999 World Health Organization technical report (World Health Organization 1999). As with impaired glucose tolerance, impaired fasting glucose is a not clinical entity but rather a risk factor for future diabetes and adverse outcomes.

When this category was initially introduced and adopted, the World Health Organization and American Diabetes Association used the same definition, namely,

a fasting plasma glucose of 6.1–6.9 mmol/L (110–125 mg/dl). However the definition of impaired fasting glucose is currently not universally agreed. The World Health Organization continues to recommend diagnosis of impaired fasting glucose based on a fasting plasma glucose 6.1–6.9 mmol/L (110–125 mg/dl) and 2-h postload plasma glucose <7.8 mmol/L (140 mg/dl) (if measured) (Table 2; World Health Organization & International Diabetes Federation 2006). However in 2003 the American Diabetes Association changed its diagnostic criteria and lowered the fasting plasma glucose range to 5.6–6.9 mmol/L (100–125 mg/dl) to define impaired fasting glucose (Table 2; the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 2003). The World Health Organization decision to continue with the original impaired fasting glucose criteria was based on concerns about the implications of the significant global increase in impaired fasting glucose prevalence with the lower cut point and the impact on individuals and health systems and in particular the lack of evidence of any benefit in terms of reducing adverse outcomes or progression to diabetes with the lower cut point (World Health Organization and International Diabetes Federation 2006).

There is also no universal agreement on HbA1c to diagnose intermediate hyperglycemia. Currently the World Health Organization does not specify HbA1c diagnostic criteria for intermediate hyperglycemia. The American Diabetes Association recommends an HbA1c 5.7–6.4% (39–47 mmol/mol) to diagnose intermittent hyperglycemia, which the American Diabetes Association terms prediabetes (Table 2; American Diabetes Association 2015). An International Expert Committee with members appointed by the American Diabetes Association, the European Association for the Study of Diabetes, and the International Diabetes Federation considered this issue in 2008. While not defining a specific cut point, the Committee suggested prevention interventions in very-high-risk individuals with HbA1c values close to the 6.5% (48 mmol/mol) HbA1c threshold of diabetes (i.e., ≥6.0%). However interventions would also be appropriate in individuals with lower HbA1c values with other established risk factors (The International Expert Committee 2009).

Hyperglycemia in Pregnancy

Women with hyperglycemia during pregnancy are at increased risk of adverse outcomes for both themselves and their baby, and treatment is effective in reducing this risk. However, there has been considerable controversy on what constitutes glucose intolerance in pregnancy, and consequently there have been a number of procedures and glucose cutoffs proposed.

The original criteria for gestational diabetes mellitus proposed by O'Sullivan and Mahan in the 1960s used a 3-h 100 g OGTT and was based on risk of the mother developing diabetes in the future (O'Sullivan and Mahan 1964), but it was also observed that treatment with a specific diet and insulin significantly reduced the risk of macrosomia compared with untreated women (O'Sullivan et al. 2003). When the 2-h 75 g OGTT was adopted as the standard procedure in 1979/1980 as

the diagnostic test for diabetes and glucose intolerance, the World Health Organization recommended the 75 g glucose load as the testing procedure for pregnant women and also recommended that the criteria for diabetes and impaired glucose tolerance be used to interpret the results of OGTT testing in pregnant women (World Health Organization 1980). This was subsequently modified by the World Health Organization in 1985 with the term gestational diabetes being used for any glucose intolerance first detected during pregnancy (World Health Organization 1985).

Following the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study (HAPO Study Cooperative Research Group 2008), revisions to the diagnostic criteria were suggested. This international multicenter study tested 25,505 pregnant women with a 2-h 75 g OGTT and followed them through pregnancy for adverse maternal and fetal outcomes. In 2013 the World Health Organization revised its diagnosis and classification of hyperglycemia first detected during pregnancy and recommended two categories of glucose intolerance based on a 2-h 75 g OGTT (World Health Organization 2013a):

- Diabetes mellitus in pregnancy
- Gestational diabetes mellitus

This move away from classifying pregnant women with either diabetes or impaired glucose tolerance/impaired fasting glucose in the one category of gestational diabetes mellitus represented a return to the 1980 World Health Organization recommendations (World Health Organization 1980).

The diagnosis of diabetes in pregnancy is based on the 2006 World Health Organization criteria for diabetes (World Health Organization 2006) when one or more of the following criteria are met:

- Fasting plasma glucose $\geq$7.0 mmol/L (126 mg/dl)
- 2-h plasma glucose $\geq$11.1 mmol/L (200 mg/dl) following a 75 g oral glucose load
- Random plasma glucose $\geq$11.1 mmol/L (200 mg/ dl) in the presence of diabetes symptoms

The World Health Organization does not recommend use of HbA1c for the diagnosis of diabetes during pregnancy, whereas the American Diabetes Association includes HbA1c as a diagnostic option (American Diabetes Association 2015).

The World Health Organization criteria for the diagnosis of gestational diabetes mellitus at any time in pregnancy include any one or more of the following (World Health Organization 2013a):

- Fasting plasma glucose 5.1–6.9 mmol/L (92–125 mg/dl)
- 1-h plasma glucose $\geq$10.0 mmol/L (180 mg/dl) following a 75 g oral glucose load
- 2-h plasma glucose 8.5–11.0 mmol/L (153–199 mg/dl) following a 75 g oral glucose load

Methods Used to Derive Diagnostic Cut Points

Two main methods have been used to derive diagnostic cut points for diabetes (World Health Organization 2006) – the population distribution of plasma glucose and plasma glucose levels associated with risk of diabetes-specific microvascular complications, particularly retinopathy.

Some studies have reported a bimodal distribution of plasma glucose in which populations can be divided into two separate but overlapping groups. With a bimodal distribution, the point at which the two curves intersect has been used to separate abnormal from normal. A bimodal distribution of 2-h post-load plasma glucose was first described in a 1971 study in Pima Indians (Rushforth et al. 1971). Later studies on populations with high prevalence of diabetes reported a similar bimodal distribution of glucose (Zimmet and Whitehouse 1978; Raper et al. 1984; Rosenthal et al. 1985; Loo et al. 1993; Dowse et al. 1994; Omar et al. 1994; Engelgau et al. 1997; Lim et al. 2002; Fan et al. 2005). Plasma glucose levels in the higher glucose distribution are associated with symptoms of diabetes and diabetes retinal and renal complications. Data on bimodal distributions were used to set the diagnostic 2-h post-OGTT plasma glucose level which remains in current use (National Diabetes Data Group 1979).

However, an international data pooling study by the DETECT-2 collaboration on bimodal distribution of plasma glucose measured during an OGTT, which included 43 studies from 27 countries, questioned the use of bimodal distribution as a suitable method for identifying diagnostic cut points for diabetes (Vistisen et al. 2009). In studies where a bimodal distribution was observed, the cut point for fasting plasma glucose ranged from 5.7 mmol/L 9103 mg/dl) to 8.5 mmol/L (153 mg/dl) (median 7.1 mmol/L (128 mg/dl)) and for 2-h plasma glucose ranged from 9.1 mmol/L (164 mg/dl) to 17.9 mmol/L (323 mg/dl) (median 12.4 mmol/L (223 mg/dl)).

Since 1997, the occurrence of diabetes-specific complications has been used to derive diagnostic cut points for diabetes, particularly using data from epidemiological studies which have examined both prevalent and incident retinopathy across a range of plasma glucose levels. Typically deciles (ten equal sized groups) of the distribution of plasma glucose are plotted against prevalence of retinopathy. The distribution graphs show that the prevalence of retinopathy remains low but then increases substantially and the diagnostic cut point is determined as the level at which the risk of retinopathy increases significantly. Few studies have been ideal for this purpose and most have limited statistical power. Studies have also differed in methodologies to diagnose retinopathy and whether or not people with previously diagnosed diabetes are included in the analysis. Some of these differences are highlighted in the three studies which have been used to set diagnostic levels. In the Egyptian study retinopathy prevalence increased from the eighth decile (fasting plasma glucose 7.2 mmol/L [130 mg/dl]; 2-h post-load plasma glucose 12.1 mmol/L [218 mg/dl]; HbA1c 6.9% [52 mmol/mol]), the ninth decile (fasting plasma glucose 7.5 mmol/L [135 mg/dl]; 2-h post-load plasma glucose 13.5 mmol/L [243 mg/dl]; HbA1c 6.7% [50 mmol/mol]), in the Pima Indian population, and the tenth decile (fasting plasma glucose 6.7 mmol/L [121 mg/dl]; 2-h post-load plasma glucose

10.8 mmol/L [195 mg/dl]; HbA1c 6.2% [44 mmol/mol]) in a US population (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 1997).

In order to address the limited statistical power of individual studies, the DECTECT-2 collaboration pooled data on over 45,000 participants from 9 studies which enabled a more detailed analysis of this relationship. The distribution of glycemic measures was plotted in vigintiles (20 equally sized groups) and by 0.5 unit intervals of glycemic measures against the occurrence of retinopathy cases which were unequivocally specific to diabetes (Fig. 1) (Colagiuri et al. 2011). The

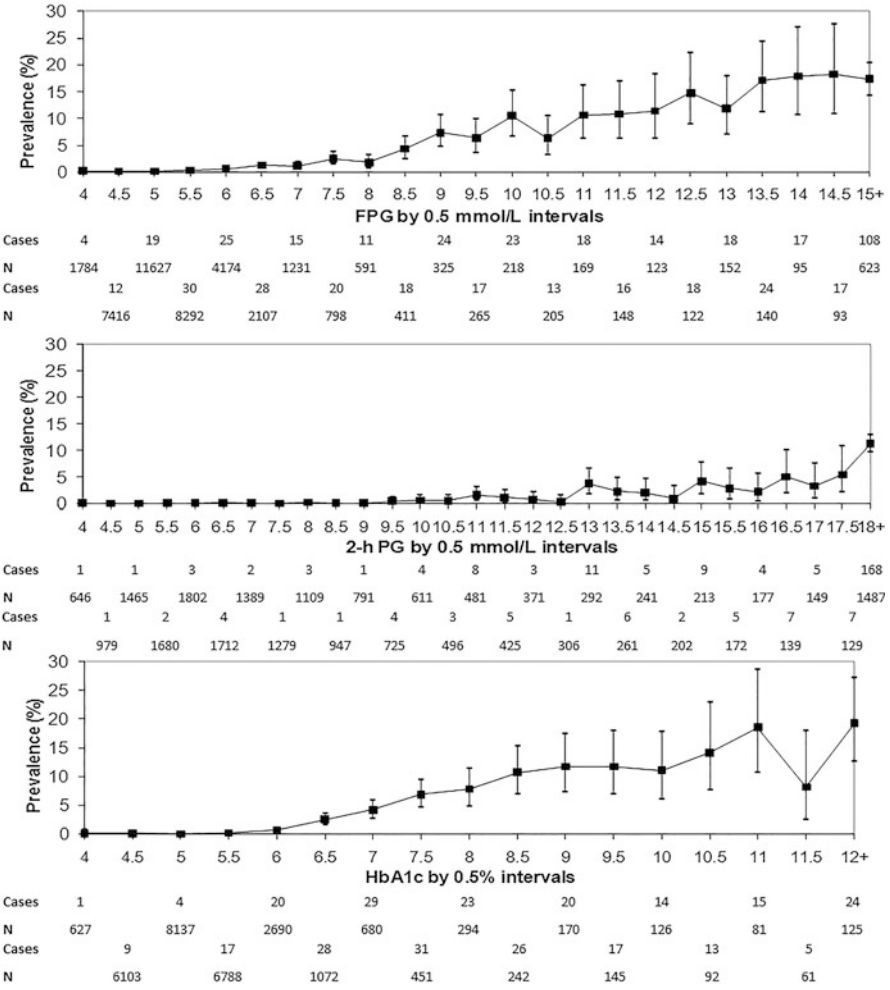

Fig. 1 Prevalence of diabetes-specific retinopathy (moderate or more severe retinopathy) with 95% confidence intervals, number of retinopathy cases, and participants within each interval by 0.5 unit intervals for fasting plasma glucose (FPG), 2-h post-load plasma glucose (2-h PG), and glycated hemoglobin (HbA1c) (Reproduced with permission; Colagiuri et al. 2011)

various analyses performed in that study indicated that HbA1c of 6.5% (48 mmol/mol) was an appropriate alternative diagnostic criterion for diabetes. This study was used by set the HbA1c diagnostic criterion which has now been universally adopted (The International Expert Committee 2009; World Health Organization 2011).

Performance of the Different Criteria on Diabetes Prevalence

Although three measures of glycemia are currently accepted for the diagnosis of diabetes, the results from each of these glycemic biomarkers will not necessarily provide a similar diagnostic result on diabetes status for an individual or for population prevalence. The implications are particularly significant for an individual, but there has been little research on the actual impact, both in terms of societal and health implications. This is one reason why all guidelines recommend repeat confirmatory testing in an asymptomatic individual with an elevated glycemic measure.

Most studies which have compared the various diagnostic criteria have focused on the population impact. The DETECT-2 study on glycemic measures and diabetes-specific retinopathy showed that for the 16,000 participants without known diabetes who had all three glycemic measures, the proportion with newly diagnosed diabetes were 7.7% for fasting plasma glucose $\geq$7.0 mmol/L (126 mg/dl), 13.9% for 2-h post-load plasma glucose $\geq$11.1 mmol/L (200 mg/dl), and 5.7% for HbA1c $\geq$6.5% (48 mmol/mol) (Colagiuri et al. 2011).

A recent study by the NCD Risk Factor Collaboration (NCD-RisC 2015) compared fasting plasma glucose, 2-h plasma glucose in an OGTT, and HbA1c on both the population prevalence of diabetes and previously undiagnosed diabetes. Population prevalence of diabetes based on fasting plasma glucose or 2-h plasma glucose was higher by 2–6% than prevalence based on fasting plasma glucose alone. Overall prevalence based on HbA1c was similar to prevalence based on fasting plasma glucose but was lower than prevalence based on fasting plasma glucose in 42.8% of studies, higher in another 41.6%, and similar in the other 15.6%. Diabetes defined as HbA1c 6.5% (48 mmol/mol) or more had a pooled sensitivity of 52.8% and a pooled specificity of 99.7% compared with fasting plasma glucose 7.0 mmol/L (126 mg/dl) or more for diagnosing previously undiagnosed participants, and sensitivity compared with diabetes defined based on fasting plasma glucose or 2-h plasma glucose was 30.5%. This finding suggests that 47.2% of participants without a previous diagnosis of diabetes who would have diabetes based on their fasting plasma glucose concentration would not have diabetes based on an HbA1c test.

Guideline Recommendations for Procedures for Diagnosing Individual with Diabetes

The American Diabetes Association recommends type 2 diabetes testing be performed on individuals aged $\geq$45 years, and testing should be considered at any age for overweight or obese adults who have at least one risk factor for diabetes and

for children and adolescents who are overweight or obese who have at least two risk factors for diabetes (American Diabetes Association 2015). Repeat testing should be carried out at least every 3 years for those who test normal. In the UK, a two-step approach in identifying type 2 diabetes has been recommended by the National Institute for Health and Care Excellence. The first step is to conduct an assessment with a risk assessment tool or questionnaire on individuals aged ≥40 years or people aged 25–39 years who are of South Asian, Chinese, African-Caribbean, black African, and other black or ethnic minority backgrounds. The second step involves testing with a fasting plasma glucose or HbA1c in those people assessed as high risk according to the risk assessment (National Institute for Health and Care Excellence 2012). Individuals with fasting plasma glucose <5.5 mmol/L (100 mg/dl) or HbA1c <6.0% (42 mmol/mol) should be reassessed at least every 3 years, and those with fasting plasma glucose 5.5–6.9 mmol/L (100–125 mg/dl) or HbA1c 6.0–6.4% (42–47 mmol/mol) should be reassessed at least once a year. In Australia, guideline recommends that risk assessment should be performed on individuals aged ≥40 years or on indigenous people aged ≥18 years. The testing procedure for detecting type 2 diabetes depends on the diagnostic test. A three-step approach is recommended when glucose testing is used and a two-step approach when HbA1c testing is used. The initial step is risk assessment with the AUSDRISK tool (Chen et al. 2010) or risk factors associated with diabetes. If measurement of fasting plasma glucose is used as a second step in high-risk individuals, a third step of an OGTT is recommended for those with fasting plasma glucose 5.5–6.9 mmol/L (100–125 mg/dl) (Colagiuri et al. 2009). Since the introduction of HbA1c as a diagnostic test for diabetes, the Australian Diabetes Society recommends HbA1c for testing as an option in high-risk individuals obviating the need for an OGTT (d'Emden et al. 2015).

Classification of Diabetes

It has long been recognized that diabetes is a heterogeneous group of conditions with many different types, and since the 1965 World Health Organization expert meeting, there have been attempts to develop a standardized classification system. With the advancement of knowledge about the etiology and pathogenesis of diabetes over the past 50 years, classification systems have evolved and further changes are likely.

Having a uniform terminology and functional working classification of diabetes serves a number of purposes including as a basis for research into its causes, treatment, development of complications, and prevention; a framework for the collection of epidemiological data on etiology, natural history, and impact of diabetes and its complications; and an aid to the clinician in selecting appropriate treatment. Ideally classification systems should include classes which are mutually exclusive and homogeneous, require only simple clinical measurement or descriptive observations that are readily obtainable and have biological significance, and be based on knowledge of etiopathology.

History of Classification of Diabetes

The 1965 World Health Organization expert committee recommended classes of diabetes based on age of recognized onset as this was considered the only reliable means of classification (World Health Organization 1965). That committee recommended four classes – "infantile or childhood diabetes" with onset between ages 0 and 14 years, "young diabetes" with age of onset between 15 and 24 years, "adult diabetes" with onset between ages 25 and 64 years, and "elderly diabetes" with onset at age 65 and older. Other clinical types of diabetes were also recognized including "juvenile-onset diabetes" which could occur at any age in which the person required insulin and was ketosis prone, "brittle diabetes" in people with juvenile-onset diabetes which was difficult to control because of episodes of hyperglycemia and ketosis and episodes of hypoglycemia, "insulin-resistant diabetes" in people who required more than 200 units of insulin daily, "gestational diabetes," "pancreatic diabetes," "endocrine diabetes," and "iatrogenic diabetes."

The 1979 National Diabetes Data Group classification moved away from age-based classification and described four classes of diabetes: "insulin-dependent diabetes mellitus (IDDM or type 1 diabetes)"; "non-insulin-dependent diabetes mellitus (NIDDM or type 2 diabetes)" with two subtypes, obese NIDDM and non-obese NIDDM; "other types of diabetes" including the following subtypes – pancreatic, hormonal, drug, or chemical induced, insulin receptor abnormalities, genetic syndromes, and others; and gestational diabetes. This report also acknowledged that it may be difficult to definitively assign an individual to one specific class because of a lack of all the information required or because there are discrete stages in the natural history of each type of diabetes that may resemble other classes and that it might be necessary to delay a definitive classification until more clinical and diagnostic information becomes available (National Diabetes Data Group 1979). The 1980 World Health Organization expert committee adopted the National Diabetes Data Group classification as an interim measure (World Health Organization 1980). The 1985 World Health Organization report recommended one major change to the classification system for diabetes and added "malnutrition-related diabetes mellitus (MRDM)" as a fifth and separate class of diabetes (World Health Organization 1985).

The 1997 expert committee moved away from a classification system based largely on pharmacological treatment to one based on etiology. Changes made in 1997 included the following:

1. The terms insulin-dependent diabetes mellitus (IDDM) and non–insulin dependent diabetes mellitus (NIDDM) were eliminated because these terms often resulted in classifying individuals on treatment rather than etiology.
2. The terms type 1 and type 2 diabetes were retained but with Arabic rather than Roman numerals.
3. Type 1 diabetes included two subclasses – immune-related and idiopathic. In immune-related type 1 diabetes, there is a recognizable autoimmune process for the pancreatic islet cell destruction, and in the latter the etiology is unknown.

4. Malnutrition-related diabetes mellitus was removed because of lack of evidence that diabetes can be directly caused by protein deficiency.

Therefore, this system which was adopted by the World Health Organization in 1999 (World Health Organization 1999) proposed a return to four basic types of diabetes – type 1 diabetes, type 2 diabetes, other specific types, and gestational diabetes. Because of advances in knowledge, there was a more detailed classification of the other specific classes of diabetes which comprised genetic defects of β-cell function including maturity-onset diabetes of the young (MODY), genetic defects in insulin action, diseases of the exocrine pancreas (including fibrocalculous pancreatopathy), endocrinopathies, drug- or chemical-induced diabetes, infections (e.g., congenital rubella), uncommon forms of immune-mediated diabetes (e.g., anti-insulin receptor antibodies), and other genetic syndromes sometimes associated with diabetes (e.g., Wolfram's syndrome). In addition to types of diabetes, the classification system recognized different stages in the natural history of diabetes including normoglycemia, intermediate hyperglycemia (impaired glucose tolerance and impaired fasting glucose), and three stages of diabetes – not insulin requiring, insulin requiring for control, and insulin required for survival. It was recognized that the stages of hyperglycemia may change over time, and movement between these stages can be bi-directional. Also the underlying disease process may be identifiable at any stage in the development of diabetes, even at the stage of normoglycemia. For example, individuals with islet cell antibodies may be normoglycemic, and in people with type 2 diabetes, the severity of hyperglycemia may regress with weight loss or progress with weight gain (World Health Organization 1999).

Future Directions

While the application of the current classification system to individuals is at times straightforward, this is not always the case, especially with respect to etiology and severity of the defect resulting in hyperglycemia and treatment requirements. There are many examples of the clinical challenge in classifying individuals including obese adolescents where differentiating between type 1 and type 2 diabetes at diagnosis can be very difficult and in the case of latent autoimmune diabetes of adults (LADA) (Botero and Wolfsdorf 2005; Farsani et al. 2013).

All methods currently available to assist with the classification of individuals have limitations including phenotypic characteristics such as age of onset and weight, genotyping since most forms of diabetes are polygenic, humoral or cellular immune biomarkers, and assessment of β-cell function (C-peptide) and insulin resistance.

There have been recent calls to review the classification system (Leslie et al. 2016; Schwartz et al. 2016) in an attempt to better contribute to an understanding of etiology, natural history, pathophysiology, consequences, and treatment (Leslie et al. 2016).

Schwartz et al. (2016) have proposed a β-cell-centric classification system based on an abnormal β-cell being the final common denominator of all diabetes. This proposal suggests that the diabetes spectrum results from interactions between genetically predisposed β-cells with other factors, including insulin resistance, environmental influences, and immune dysregulation. This could lead the way to choice of therapy based on the particular pathway(s) which lead to hyperglycemia that could optimize processes of care and precision medicine in the treatment of diabetes.

While there is a move to align classification systems and precision medicine in the future, a range of challenges will need to be overcome including deficiencies in our current knowledge base and limited access to currently available diagnostic tests to classify individuals with hyperglycemia, especially on a global scale.

Conclusion

The classification and diagnostic criteria of diabetes have changed over time. With the continued advancement in diabetes research, the classification and diagnostic criteria will continue to evolve. Regardless of how diabetes is defined and detected, early detection, prevention, and treatment remain the most important steps in halting the increasing global burden of diabetes.

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