Review

Diagnosing diabetes mellitus – do we need new criteria?

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Summary The current classification and diagnostic criteria for diabetes mellitus were introduced by the United States National Data Group in 1979 and endorsed by the World Health Organization in 1980, with modifications in 1985 and 1994. The criteria, chosen to reflect the risk of complications, were the synthesis of considerable thought and expertise and represented a consensus which, it was hoped, would prove helpful to all those involved with diabetes – practising clinician, research scientist and epidemiologist alike. The inconvenience, variability and non-physiological nature of the oral glucose tolerance test (OGTT) are well-recognised. In spite of these limitations the 2-h post-load plasma glucose has remained the standard against which all other tests have been evaluated. This article reviews the original justification for the OGTT, and in the light of more recent epidemiological research seeks to place the current diagnostic criteria for diabetes into a pathophysiological, diagnostic and prognostic perspective. [Diabetologia (1997) 40: 247–255]

Keywords Diabetes mellitus, diagnosis, oral glucose tolerance test, fasting plasma glucose, 2-h plasma glucose, haemoglobin A_{1c}, retinopathy, nephropathy, complications.

The current classification and diagnostic criteria for diabetes mellitus were introduced by the United States National Diabetes Data Group in 1979 [1] and with some modification endorsed by the World Health Organization (WHO) in 1980 [2] with further refinement in 1985 [3] and 1994 [4]. They were the synthesis of considerable thought and expertise and represented a consensus which, it was hoped, would prove helpful to all those involved with diabetes – practising clinician, research scientist and epidemiologist alike. The diagnosis of diabetes, in the absence of symptoms, depends on observing a high glucose concentration in blood obtained when the patient is fasting or during an oral glucose tolerance test (OGTT). Since insulin-dependent diabetes mellitus (IDDM) generally presents with symptoms or acute metabolic complications, these criteria, in practice, are usually applied to non-insulin-dependent diabetes mellitus (NIDDM) for which they were justified by the identification of persons at high risk of complications. By reviewing the original justification for the diagnostic criteria including the OGTT, and in the light of more recent epidemiological research, this article seeks to place the current diagnostic criteria for diabetes into pathophysiological, diagnostic and prognostic perspective. It is suggested that a reappraisal of the diagnostic criteria is now indicated.

Historical background

The history of our understanding of diabetes provides an illuminating backdrop to the development of the

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Abbreviations: WHO, World Health Organization; OGTT, oral glucose tolerance test; IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus; IRI, immunoreactive insulin.

current diagnostic criteria. This disease, recognised since antiquity [5], continues to excite, perplex and frustrate modern medicine and to impose a heavy financial burden.

Until the first quarter of the 20th century, classical symptoms and the presence of reducing substances in the urine were the hallmarks of diagnosis. With the advent of blood glucose measurement, fasting hyperglycaemia was the *sine qua non* of diagnosis [6]. The OGTT was introduced as a research tool in the 1920s [7] and later was widely adopted as a diagnostic method [8, 9]. In the intervening years many attempts have been made to refine both the test and the criteria for its interpretation. It was subsequently realised that the original diagnostic criteria for diabetes (the mean plus 2SD of glucose levels after an oral glucose load in healthy subjects) [9, 10], while defining a statistical abnormality, were not necessarily associated with any clinical abnormality at that time [11].

The question of which level of hyperglycaemia was diagnostic of diabetes became more than an intellectual curiosity when over the years following the discovery of insulin the full impact of the morbidity and mortality resulting from the microvascular complications and other less specific forms of vascular disease became clear. In the 1950s and 1960s emphasis on earlier recognition of the disease, with the hope that earlier treatment would prevent the development of complications, led to the widespread adoption of the OGTT to detect the condition at an early stage. The publication by West [12] of the widely differing blood glucose concentrations accepted as normal provided a stimulus to reach an international consensus.

Dichotomising continuous variables

Why are diagnostic criteria based on an artificial dichotomisation of a continuous variable? All diagnostic criteria for diabetes have been based on some mesurement of blood or urine glucose. Hyperglycaemia is the defining sign of diabetes, but the disease results from one or more of several underlying defects, such as islet cell autoimmunity or insulin resistance. These abnormalities, however, are not always accompanied by hyperglycaemia or symptoms or signs typical of diabetes. The diagnosis of diabetes should continue to be made by some measure of hyperglycaemia, but there will not be a perfect correlation between the underlying defects and any particular level of glycaemia. Thus, the choice of a diagnostic level is problematic, and can be based on many factors, including associations of various levels of hyperglycaemia with signs or symptoms and risk of long-term complications of diabetes.

Measures of hyperglycaemia as diagnostic criteria for diabetes

Two-hour post-load plasma glucose. Population frequency distributions of blood glucose provided an approach to diagnosing diabetes. In Pima Indians 2-h post-load glucose concentrations are bimodally distributed [13, 14] (Fig. 1). Epidemiological surveys of other populations with a high prevalence of NIDDM including Mexican-Americans [15], Micronesians [16], Polynesians [17], and non-diabetic relatives of Caucasian subjects with NIDDM [18], have also demonstrated bimodality of 2-h post-load plasma glucose concentrations. In each of these populations the distribution was fitted better by a model of two overlapping normal distributions than by a single distribution. This suggested the presence of two subgroups differentiated by the degree of hyperglycaemia with the upper component of the frequency distribution representing diabetes. Longitudinal population studies indicated that at young ages most subjects were in the lower component of the distribution, but with advancing age some moved to the upper component, that is, developed diabetes.

Further support for equating diabetes with the upper component of the bimodal frequency distribution as defined by 2-h plasma glucose came from cross-sectional and longitudinal observations in Pima Indians and in the Whitehall and Bedford studies in the United Kingdom which showed that both retinopathy and nephropathy occurred almost exclusively among subjects with plasma glucose levels in the upper component [19–22] (Fig. 1). During a follow-up of 5–8 years, all three studies indicated that retinopathy developed almost exclusively in subjects with initial plasma glucose levels greater than 11.1 mmol/l. As a result of these findings, criteria based on the OGTT were adopted by the National Diabetes Data Group [1] and the WHO [2–4] (Table 1). Implicit in the OGTT criteria was the inference that a diagnostic level of blood glucose indicated an increased risk for the development of microvascular complications [23].

The relationship between glucose-stimulated insulin concentrations and the 2-h plasma glucose concentration shows an inverted U-shape [24–31]. The point of inflection of the insulin-glucose curve corresponds approximately with the antimode of the frequency distribution of 2-h post-load plasma glucose concentrations and with a threshold for the prevalence of complications. This correspondence may provide the physiologic basis for the bimodality of glucose concentrations in that glucose concentrations are not stable at this level due to failing insulin secretion. This observation provides further support for a cut off point dividing the population into those with and without diabetes.

Fasting plasma glucose. The simplicity of fasting plasma glucose measurement has resulted in it being
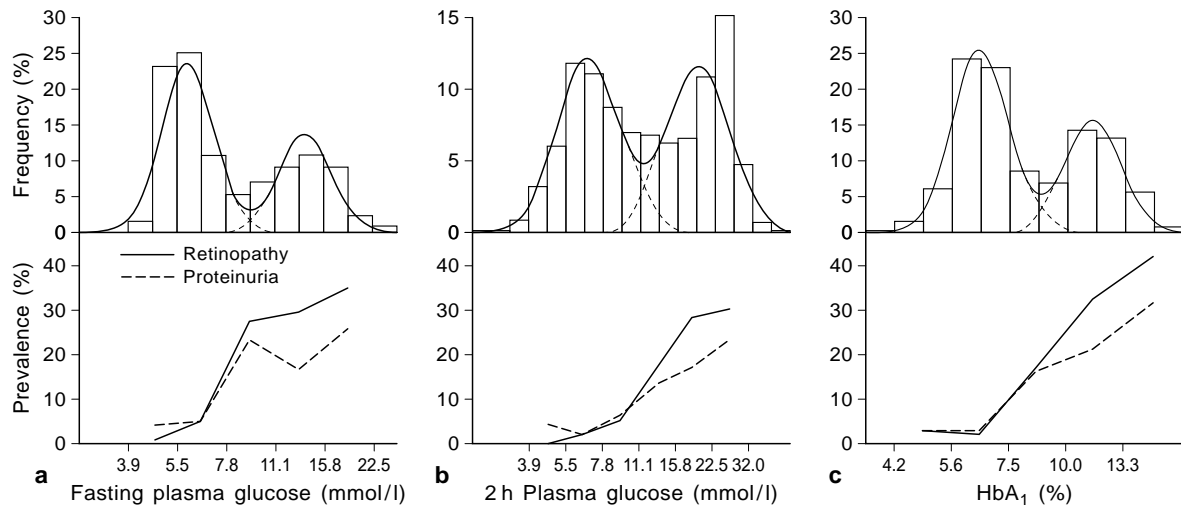
Fig. 1a–c. *Upper panel*: Frequency distributions of fasting plasma glucose (**a**), 2-h plasma glucose (**b**) and glycated haemoglobin (**c**) in subjects aged at least 35 years regardless of previously diagnosed diabetes or hypoglycaemic treatment. For each variable the bars show frequencies by intervals which are equally spaced on a logarithmic scale. The smooth curves represent a mathematical model of two overlapping normal distributions with a common variance which was fit by maximum likelihood. *Lower panel*: Prevalence of retinopathy and heavy proteinuria in the same subjects according to glucose concentrations or glycated haemoglobin [37]

Table 1. World Health Organization criteria for the OGTT

Category	Venous plasma glucose (mmol/l)		
	Fasting		2-h
Normal glucose tolerance	< 7.8	and	< 7.8
Impaired glucose tolerance	< 7.8	and	7.8–11.0
Diabetes	≥ 7.8	or	≥ 11.1

While the terminology 'normal' is not used by WHO, it is used here to mean the absence of impaired glucose tolerance and diabetes. The two most widely used methods, venous plasma glucose (generally measured by a hospital laboratory on a venous specimen) and capillary whole blood glucose (measured by a self-monitoring enzyme-impregnated test strip), are equivalent at 2 h but not in the fasting state.
The criteria for impaired glucose tolerance defined by the NDDG [1] and the WHO [2, 3] differ – the latter are used in this paper.
Cut-off points for serum glucose or capillary whole blood glucose are slightly different and can be found elsewhere [3]

subjected to epidemiological scrutiny similar to that of the 2-h value [16, 19, 20]. It was soon realised that among the Pimas fasting glucose was also bimodally distributed and, as with 2-h glucose, there was a threshold for risk of complications (Fig. 1). On average, fasting insulin concentrations increase progressively with increasing glycaemia until the onset of NIDDM and then gradually decline. These latter two characteristics have been confirmed in longitudinal studies [30].

The above relationships were originally described with assays of total immunoreactive insulin (IRI), which do not distinguish insulin from proinsulin and other products of insulin secretion. A smaller proportion of IRI is true insulin at higher degrees of hyperglycaemia, yet the same pattern of a positive association of insulin with glucose over the glycaemic range was confirmed when the proinsulin concentration was subtracted from IRI [31].

The intravenous glucose tolerance test provides a supraphysiological short-term stimulus to insulin secretion and a 'first phase' insulin response can be precisely measured. That the acute insulin response is mostly absent when the fasting glucose level is greater than 6.4 mmol/l [32] supports an upper limit of normal fasting glucose similar to that proposed by the National Diabetes Data Group [1]. Reports on first-phase insulin secretion in impaired glucose tolerance are conflicting although in a recent study the first phase insulin response was absent in subjects with persistent impaired glucose tolerance [33].

Fasting plasma glucose concentrations considered consistent with a diagnosis of diabetes were defined by Fajans and Conn [9], by Mosenthal and Barry [10] and more recently by the WHO [2–4]. Although fasting plasma glucose may be used to diagnose diabetes (greater than 7.8 mmol/l, WHO criteria), and is currently being used as a major entrance criterion (greater than 6.0 mmol/l) in the United Kingdom Prospective Diabetes Study [34], its value as a diagnostic tool has largely been replaced by 2-h plasma glucose when the OGTT is performed in epidemiological studies. This is perhaps a result of misconceptions that have arisen regarding the inter-relation of the fasting and 2-h glucose concentrations. There is often a failure to realise that, although these two measures are highly correlated, the 2-h and fasting values defined as diagnostic of diabetes by the WHO criteria are not equivalent. In a survey of the United States adult population, approximately three quarters of subjects without previously known diabetes but with

diagnostic 2-h plasma glucose concentrations greater than 11.1 mmol/l had fasting glucose values below the level defined as diagnostic by the WHO (7.8 mmol/l) [35]. On the other hand, nearly all persons with fasting plasma glucose greater than 7.8 mmol/l had 2-h glucose concentrations 11.1 mmol/l or more. These diagnostic cut off points imply that if WHO criteria are to be applied, and it is considered necessary to diagnose all persons with unknown diabetes, measurement of fasting plasma glucose is inadequate and the OGTT must be used in all persons whose fasting glucose concentrations fall below the diagnostic level. This would not be necessary, however, if a lower diagnostic cut off point was adopted for fasting plasma glucose, as will be discussed. This would allow diagnosis and screening by the much simpler and more economical fasting plasma glucose measurement.

Glycated haemoglobin. Glycated haemoglobin is now established as the preferred method of monitoring long-term glycaemic control. In Pima Indians, glycated haemoglobin has the same desirable properties as the fasting and 2-h post-load plasma glucose concentrations, namely bimodality and a threshold for association with microvascular disease, especially retinopathy [36, 37] (Fig. 1). Its utility as a diagnostic test has been examined in many studies but, unfortunately, with few exceptions, these have been with reference to the OGTT [38–43]. Thus, while most writers have concluded that glycated haemoglobin is an inadequate diagnostic test, this conclusion is based on the assumption that the OGTT represents the 'gold standard'.

Comparison of measures of hyperglycaemia

The specific complications of diabetes represent an alternative standard by which to compare diagnostic tests. Although the microvascular complications of diabetes cannot be equated with diabetes, they do represent a specific and relevant clinical endpoint by which to judge alternative tests. We have recently compared the three measures, plasma glucose, fasting and 2 hours after a 75 g load and glycated haemoglobin to diagnose diabetes in this perspective [44]. Cross-sectional and longitudinal studies were performed among 960 Pima Indian subjects aged 25 years and over who were not receiving insulin or oral hypoglycaemic treatment at the baseline examination. All three variables were associated with retinopathy with evidence of a threshold below which retinopathy was absent or rare and above which the prevalence and incidence of retinopathy were high (Fig. 2). All three measures of glycaemia were also associated with nephropathy but not as strongly as with retinopathy. The 2-h plasma glucose was superior to
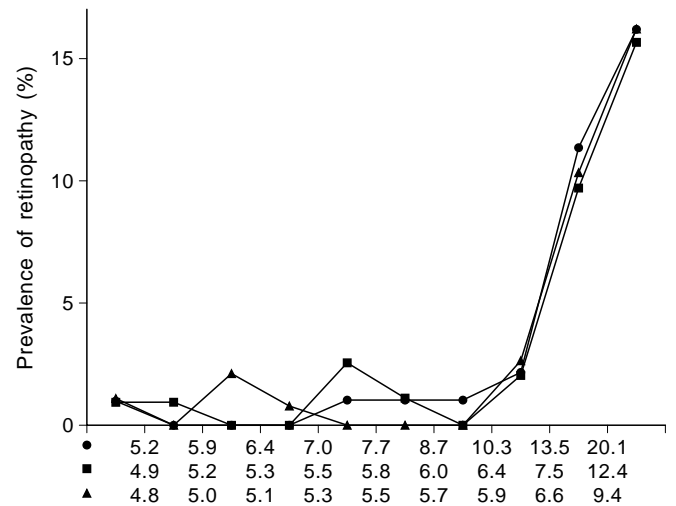

Fig. 2. Prevalence of retinopathy in relation to tenths of 2-h plasma glucose, fasting plasma glucose, and haemoglobin A_{1c} [44]

fasting glucose for predicting the presence of retinopathy but otherwise no variable was significantly more strongly associated with prevalent or incident cases of either complication [44]. In another study of Pima Indians previously diagnosed by WHO criteria, the three measures of glycaemia were also found to be equivalent as predictors of retinopathy [45].

The relationships of fasting and 2-h plasma glucose and glycated haemoglobin with macrovascular complications were examined in Islington, UK [46] and in Hoorn, the Netherlands [47]. In both studies all three measures had similar associations with peripheral vascular disease [46, 47]. In Islington however, the 2-h glucose was most strongly associated with major coronary heart disease [46]. In the Paris Prospective Study, the incidence of fatal cardiovascular disease was related to the fasting and 2-h plasma glucose concentrations at a baseline examination. There was a marked increase in incidence of disease at a fasting plasma glucose greater than 6.9 mmol/l, similar to the increased incidence at 2-h plasma glucose greater than 11.1 mmol/l [47 a]. Data from the Pima Indians and those cited above which have pointed to the equivalence of fasting and 2-h plasma glucose require confirmation in other populations and for various complications.

An alternative approach to the selection of diagnostic criteria is to determine a threshold that best separates those at high and low risk of specific complications for diabetes. In fact, the risk for retinopathy, as demonstrated in epidemiological studies, was an implicit rationale behind the derivation of the 2-h 11.1 mmol/l criterion. In Pima Indians, values of fasting glucose and glycated haemoglobin equivalent to the 11.1 mmol/l WHO 2-h criterion have been derived from those points with similar ratios of sensitivity to specificity for retinopathy; points which give the

Table 2. Cut-off points based on three different methods

	2-h plasma glucose (mmol/l)	Fasting plasma glucose (mmol/l)	HbA$_{1c}$ (%)
Antimodal[a]	12.6	9.3	7.8
Equivalent to WHO[b]	(11.1)[c]	6.8	6.1
Equivalent to WHO prevalence[d]	(11.1)[c]	6.7	6.1

[a] Antimode of the frequency distribution fit by two overlapping normal curves [44]
[b] Defined as the point with the same ratio of sensitivity to 1-specificity for retinopathy as the WHO 2-h criterion of 11.1 mmol/l [44]
[c] 11.1 mmol/l by definition
[d] Defined as the point which gives the same prevalence of diabetes as the WHO 2-h criterion of 11.1 mmol/l [48]

same prevalence of diabetes as the WHO 2-h criterion can also be obtained [48] and these points are nearly identical to these defined by the relationship with retinopathy (Table 2). Other possibilities include the point of maximum separation of frequency distributions of these values or that which maximises the sum of sensitivity and specificity for retinopathy [44]. Ultimately, the costs and benefits of a diagnosis and its consequences should be considered in choosing a diagnostic cut off point.

All three tests have disadvantages in some situations. The OGTT is subject to considerable intra-individual variation [18, 49–51] and fasting plasma glucose appears preferable to 2-h plasma glucose in this respect. In a recent study of Dutch adults, in which the OGTT was repeated during a 2–6-week interval, the intra-individual coefficients of variation were 6.4 % for fasting glucose and 16.7 % for the 2-h plasma glucose [51]. Glycated haemoglobin has proven difficult to standardize [52] and is not as widely available as a measurement of glucose concentrations. Published studies which have compared the utility of this test with fasting and 2-h plasma glucose used different assays, thus making it difficult to assign an appropriate cut off point. These problems with glycated haemoglobin need to be solved before any criteria based on this measure can be universally applied. The fasting plasma glucose is probably the best single test for diagnosing diabetes because of its simplicity, low cost, reproducibility and worldwide availability.

Diagnosis of diabetes in pregnancy

Diagnostic criteria for diabetes have evolved somewhat differently in pregnant and non-pregnant adults. This has resulted in much confusion and a lack of comparability between studies [53–63] and even between different tests in the same person, if, as recommended by the National Diabetes Data Group and

practised in the United States, different test procedures are used during and after pregnancy. Several diagnostic methods, with their attendant cut off points, have been used, including the two-step OGTT procedure of O'Sullivan and Mahan [64] (endorsed by the United States National Diabetes Data Group, and, with modified cut off points by Carpenter and Coustan [65]), the single 75-g OGTT interpreted by a variety of criteria (e.g. WHO [1, 2], Diabetic Pregnancy Study Group of the European Association for the Study of Diabetes [DPSG-EASD] [56]), and standardized meal tolerance tests [66, 67]. Data obtained using each of these methods has been associated with maternal-fetal outcome [64, 68–71], and in some cases, to long-term outcome in the child [72–75]. The differences between cut off points used in different schemes (e.g. WHO and DPSG-EASD) reflect the inherent arbitrariness of cut off points for classifications based on continuously distributed data in the absence of evidence for a threshold predicting adverse outcomes in the mother or child.

With few exceptions, these testing methods have not been compared with each other, so it is impossible to determine if any one of them is superior to another in predicting adverse maternal or fetal outcomes. In one small study in Pima Indians [76] that compared the WHO and O'Sullivan and Mahan criteria (adapted to a 75-g load screen) in the same women, the O'Sullivan procedure was much less sensitive than the WHO procedure in predicting adverse maternal or fetal outcome. A more recent larger study reached similar conclusions demonstrating that the WHO criteria detected abnormalities in a greater proportion of women with adverse outcomes than the NDDG criteria [77].

The essential question for the future is whether these tests differ in predicting pregnancy outcome both in terms of the immediate consequences on the maternal-fetal unit and the future health of mother and child. The 75-g OGTT performed and interpreted by WHO criteria offers comparability with the non-pregnant state, which is another argument for its universal adoption for the diagnosis of diabetes in pregnancy.

Diagnosing the undiagnosed

In the United States about half the people with diabetes according to WHO criteria are undiagnosed [35, 78]. This finding raises the obvious question of whether these undiagnosed diabetic persons should be detected and treated. This question is related to several key issues in screening for disease: 1) availability, accuracy, and acceptability of a screening test, 2) organizational and medical resources necessary for screening, referral and treatment, and 3) benefits and adverse effects of making a diagnosis. The

potential benefits of early diagnosis and treatment of diabetes might include a low incidence of symptoms or the acute or chronic complications of disease. Possible adverse effects include the psychological and economic damage caused by diagnosis and treatment which may be without medical benefit. These issues have been thoroughly discussed in relation to diabetes [79–83]. In many parts of the world, tests and resources for screening are readily available, but the question of benefits and costs of making a new diagnosis are difficult to answer. Screening procedures are clearly indicated for pregnant women and people with symptoms and signs suspected of being caused by diabetes and for those with diseases often associated with diabetes, for whom diagosis and treatment of diabetes would help in their management. Other than in pilot studies [84, 85], widespread screening for diabetes outside the context of regular medical care has not been instituted, and probably will not be, until better evidence of benefit is forthcoming. Screening could be carried out not only for diabetes, but also for lesser degrees of hyperglycaemia, such as impaired glucose tolerance, if clinical trials currently in progress demonstrate a benefit in treating this condition. In the future, screening for diabetes-susceptibility alleles [86–88] at specific genetic loci may further identify those individuals at increased risk of diabetes, but again, benefit of detecting persons with such genetic susceptibility should be demonstrated before such screening is widely advocated. Screening would become much easier to implement if the fasting plasma glucose became the standard diagnostic test and thus easy to apply on a large scale. This would eliminate the need for separate screening and diagnostic tests [79].

Unresolved issues

Data on bimodality and association with complications in Pima Indians and other populations [46, 47, 47a] suggest that the OGTT may not be necessary, as the same quality of information can be obtained by measurement of fasting plasma glucose or glycated haemoglobin. These findings need to be replicated or refuted in a wide variety of populations. The glycaemic thresholds for specific complications of diabetes and for other adverse health events are not yet precisely defined. Furthermore, measurements of serum insulin concentrations during the OGTT have been useful in pathophysiologic studies [29, 30, 89, 90]. Thus, while the currently available data suggest that the OGTT is not necessary for clinical purposes, it still may have a role in research. The optimal cut off point for diagnosis based on any of the quantitative variables cannot be determined solely from the types of data reviewed in this paper. Costs are considered in evaluating screening strategies, but they are

also critical in choosing a diagnostic level for diabetes. This is because the diagnosis of diabetes is not based on the presence of a discrete physiological abnormality, but by an imperfectly chosen point on a continuum of glycaemia. The choice of the cut off point depends on the medical, psychological, social and economic costs of making a diagnosis in someone who is not at substantial risk of diabetes-related symptoms or complications, or of not making a diagnosis in someone who is. The choice of exact cut off points should be made with consideration of costs, for which adequate data are, unfortunately, not available. Any dichotomous cut off point, however, will inevitably mask information regarding the severity of disease. The selection of glucose cut off points for making decisions about therapy is an additional question beyond that of diagnosing diabetes; therapeutic cut off points are not necessarily the same as diagnostic cut off points.

Each of the three tests of hyperglycaemia has disadvantages in some situations. The OGTT is subject to considerable intra-individual variation and glycated haemoglobin has proved difficult to standardise. None of these tests will be useful if it cannot be performed reliably. The choice of a diagnostic test may well be determined by local circumstances.

Conclusions

This review has discussed the definition of diabetes from pathophysiological, diagnostic and prognostic perspectives. In the last 10 years we have witnessed change both of horizon and perspective which has altered our conception and appreciation of the diagnosis of diabetes. The OGTT has remained the gold standard for over 60 years despite its biological and methodological limitations. A more fundamental or causal classification for the most common types of diabetes will undoubtedly be helpful. Nonetheless, glucose will presumably always be a major toxic factor whatever the aetiologic determinant; therefore hyperglycaemia is likely to remain the basis of the diagnosis of diabetes mellitus.

Are new diagnostic criteria needed? Epidemiologic data suggest that fasting and 2-h plasma glucose and glycated haemoglobin are equivalent for diagnostic purposes and this equivalence should be acknowledged in diagnostic criteria for diabetes. While the choice of cut off points depends on many considerations, those equivalent to the 11.1 mmol WHO criterion in terms of their relationship with retinopathy (e.g. fasting venous plasma glucose ~7 mmol/l) offer continuity with the past and compatibility with current clinical and epidemiological research. This diagnostic level was proposed by a Workgroup of the American Diabetes Association [91].

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