Diagnosing diabetes mellitus in the Asian population

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Western guidelines have been used to diagnose diabetes mellitus in Asia. The increased availability of data from Asian populations, however, has made it apparent that modifications to western guidelines are needed when they are used in Asia. Both the American Diabetes Association and the World Health Organization have recently modified their diagnostic criteria for diabetes mellitus. The implications of these new criteria in Asia are discussed in this paper. The significance of using fasting plasma glucose measurements and/or oral glucose tolerance tests in the diagnosis of diabetes mellitus is analysed. A simple approach to diagnose diabetes mellitus in the Hong Kong Chinese population is also suggested.

HKMJ 2000;6:53-9

Key words: Blood glucose/analysis, Diabetes mellitus; Ethnic groups; Predictive value of tests

Introduction

Diabetes mellitus is a heterogeneous metabolic syndrome that is characterised by chronic hyperglycaemia due to insulin resistance, insulin insufficiency, or both. With a better understanding of the pathophysiology and regulation of glucose metabolism, new classifications of diabetes based on aetiologies (Box 1) and clinical staging (Fig) have been recommended by the World Health Organization (WHO) and the American Diabetes Association (ADA).[1,2] In particular, the previous classification of insulin-dependent diabetes mellitus and non–insulin-dependent diabetes mellitus have now been replaced by type 1 and type 2 diabetes mellitus, respectively, because of the considerable overlap in the clinical stages between the two types of diabetes. In clinical practice, the diagnosis of diabetes mellitus remains largely a clinical one and relies mainly on the measurement of plasma glucose (PG) levels with or without the presence of hyperglycaemic symptoms.

The gold standard

In 1985, the WHO recommended the use of either a fasting PG concentration of ≥7.8 mmol/L (140 mg/dL) and/or a 2-hour post–glucose loading PG (or random PG) concentration of ≥11.1 mmol/L (200 mg/dL) as diagnostic criteria.[3] In asymptomatic subjects, the test is repeated to confirm the diagnosis. Up to 1996, the ADA adopted similar diagnostic criteria.[4]

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Box 1. Aetiological classification of disorders of glycaemia[2]

(1) Type 1 diabetes mellitus
Consists of β-cell destruction, usually leading to absolute insulin deficiency. Can be:
(a) Autoimmune
(b) Idiopathic

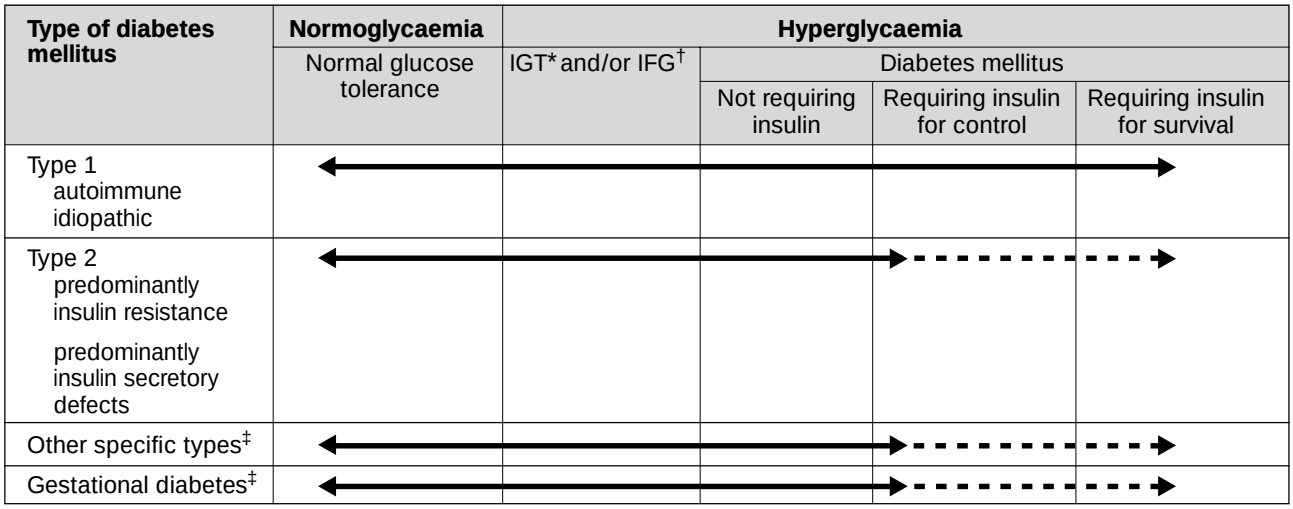
(2) Type 2 diabetes mellitus
May range from predominantly insulin-resistant type with relative insulin deficiency, to a predominantly secretory type with or without insulin resistance

(3) Other specific types
(a) Genetic defects of β-cell function (eg maturity-onset diabetes of youth types 1-4)
(b) Genetic defects in insulin action (eg type A insulin resistance)
(c) Diseases of the exocrine pancreas (eg pancreatitis, haemochromatosis)
(d) Endocrinopathies (eg acromegaly, Cushing's syndrome)
(e) Drug or chemical induced (eg thiazides, glucocorticoids)
(f) Infections (eg congenital rubella)
(g) Uncommon forms of immune-mediated diabetes (eg 'stiff man' syndrome)
(h) Other genetic syndromes sometimes associated with diabetes (eg Down's syndrome, Lawrence-Moon-Biedel syndrome)

(4) Gestational diabetes
Includes the former categories of gestational impaired glucose tolerance and gestational diabetes

The 2-hour PG cut-off value of 11.1 mmol/L remains the gold standard because of its pathophysiological significance. In prospective studies, diabetic retinopathy was found in patients whose 2-hour PG level was ≥11.1 mmol/L.[5,6] There is also evidence that 11.1 mmol/L is the 2-hour PG level at which insulin secretion from pancreatic β cells starts to decline.[7,8] On the other hand, the fasting PG cut-off value of

Fig. Disorders of glycaemia: aetiological types and clinical stages[1,2]



* IGT impaired glucose tolerance
† IFG impaired fasting glycaemia
‡ In rare instances, patients in these categories (eg type 1 diabetes mellitus during pregnancy) may require insulin for survival

7.8 mmol/L has been more arbitrarily defined. The threshold was based mainly on the finding that more than 90% of subjects who had a fasting PG level of ≥7.8 mmol/L would be classified as having diabetes mellitus according to the 2-hour PG level if a subsequent oral glucose tolerance test (OGTT) were performed.[9] However, subjects who have a fasting PG level of <7.8 mmol/L would not necessarily have a 2-hour PG level of <11.1 mmol/L. In fact, there is now abundant evidence that confirms the poor sensitivity of using a fasting PG cut-off value of 7.8 mmol/L to diagnose diabetes, as based on a 2-hour PG cut-off value of 11.1 mmol/L.[10,11] To achieve an optimal balance between the sensitivity and specificity of this method of diagnosing diabetes, a lower fasting PG value, ranging from 5.3 to 7.1 mmol/L, has been suggested for use in different ethnic groups.[12-14] In the Hong Kong Chinese population, the fasting PG cut-off value that corresponds to a 2-hour PG level of 11.1 mmol/L is between 5.5 and 5.8 mmol/L.[15,16]

New diagnostic criteria

In 1997, the ADA modified their diagnostic criteria by reducing the fasting PG cut-off value from 7.8 to 7.0 mmol/L (126 mg/dL), while keeping the 2-hour (or random) PG cut-off value the same (ie 11.1 mmol/L).[1] The diagnosis needs to be confirmed by repeating the test on a different day; however, the OGTT is discouraged for routine clinical use. In epidemiological studies, one fasting PG measurement will suffice.[1] In 1998, the WHO proposed similar modifications to the diagnostic cut-off levels.[2] The WHO reserved the use of fasting PG or 2-hour PG measurements for epidemiological purposes and suggested that ideally, both values should be used. The revised criteria are summarised in Table 1.

New intermediate group

The fasting PG cut-off level of 7.0 mmol/L was chosen because of its strong association with the

Table 1. Previous and revised criteria according to the American Diabetes Association (ADA) and the World Health Organization (WHO)

Diagnosis	Previous criteria		Revised criteria*	
	Fasting PG† (mmol/L)	2-hour PG (random PG) [mmol/L]	Fasting PG (mmol/L)	2-hour PG‡ (random PG) [mmol/L]
Diabetes mellitus	≥7.8 and/or	≥11.1	≥7.0 and/or	≥11.1
IGT§	<7.8 and	≥7.8 to 11.1	<7.0 and	≥7.8 to 11.1
IFG‖	na	na	≥6.1 to 7.0	-
NFG¶	na	na	<6.1	-

* Diagnosis has to be confirmed by repeating the test on a separate day
† PG plasma glucose
‡ The oral glucose tolerance test (2-hour PG) has been discouraged by the ADA for routine clinical use
§ IGT impaired glucose tolerance
‖ IFG impaired fasting glucose (ADA); impaired fasting glycaemia (WHO)
¶ NFG normal fasting glucose
na not applicable

development of retinopathy, coronary artery disease, and its correspondence to a 2-hour PG measurement of 11.1 mmol/L.[1] The PG level, however, should be viewed as a continuum regarding its relationships with cardiovascular risks. In non-diabetic Hong Kong Chinese subjects (based on the 1985 WHO diagnostic criteria of a fasting PG, <7.8 mmol/L and 2-hour PG, <11.1 mmol/L), we have previously found that subjects with a fasting PG level of 5.7 to 7.8 mmol/L, when compared with those with a fasting PG level of less than 5.7 mmol/L, have significantly higher systolic blood pressures, body mass indices, waist to hip ratios, glycated haemoglobin (HbA_{1c}) levels, insulin levels, and adverse lipid profiles.[16] Similarly, in Chinese people with normal glucose tolerance (based on the 1985 WHO criteria of both fasting PG and 2-hour PG, <7.8 mmol/L), increasing HbA_{1c} tertiles have been shown to be associated with increasing blood pressures, waist to hip ratios, PG, insulin levels, and adverse lipid profiles.[17]

Three major population-based studies have shown that there is a clear relationship between the degree of glycaemia and the mortality rate, even among subjects with normal glucose tolerance, as analysed by tertiles or quartiles of fasting blood glucose.[18-20] In accordance with the idea that the relationship between the PG and increased morbidity and mortality is continuous, both the ADA and WHO have suggested a new intermediate group based on the fasting PG level.[1,2] People who have a fasting PG level of 6.1 to 7.0 mmol/L (110-126 mg/dL) are considered to have impaired fasting glucose (IFG) by the ADA or impaired fasting glycaemia by the WHO. In contrast, people whose fasting PG level is <6.1 mmol/L are considered to have normal fasting glucose (NFG) [Table 1].

Oral glucose tolerance tests

The OGTT is usually performed for those who have borderline PG levels (either fasting or random). It has also been suggested as the screening test for high-risk subjects such as those with impaired glucose tolerance (IGT), a family history of diabetes, obesity, or hypertension.[21] However, the OGTT has long been criticised because of its inconvenience to patients, high cost, and poor reproducibility.[22] In Hong Kong Chinese patients, we have previously found that the reproducibility of the OGTT is only 66%.[23] This result did not improve even among subjects with risk factors for glucose intolerance such as those having a high level of HbA_{1c} or obesity. The ADA has discouraged the use of the OGTT in its revised diagnostic criteria.[1] If the OGTT is indicated, however, the previous 2-hour PG cut-off levels are still applicable, such that subjects with a fasting PG level of <7.0 mmol/L and a 2-hour PG level of 7.8 to 11.1 mmol/L are considered to have IGT.[1,2]

The implications of using the new diagnostic criteria in the Asian population

In 1993, Cockram et al[24] reported the crude prevalence of diabetes mellitus in the Hong Kong Chinese population to be 4.6%, based on a survey of 1513 adults of working age. Of the cases of diabetes mellitus, 61.8% had been undiagnosed previously. After excluding known cases, the prevalence of diabetes mellitus was calculated to be 2.83%, using the 1985 WHO criteria.[25] If the 1997 ADA criteria (fasting PG, ≥7.0 mmol/L; no 2-hour PG measurement) were applied to the same group of adults, the prevalence of diabetes was calculated to be 1.41%: a net reduction of 1.42%.[25] This difference was accounted for by the 'loss' of 1.95% of people with a fasting PG level of <7.0 mmol/L, but with a 2-hour PG level of ≥11.1 mmol/L. However, the loss was partially compensated by an increase of 0.54% of people whose fasting PG level was 7 to 7.8 mmol/L and 2-hour PG was less than 11.1 mmol/L. This group had diabetes mellitus according to the new criteria but not the old ones.[25] If the 2-hour PG measurement were also taken into account (using the 1998 WHO criteria), the 'new' prevalence of diabetes would then be 3.37%: a net increase of 0.54%. Similarly, in Japan, the prevalence of type 2 diabetes mellitus of 13.3% consists of only 7.8% of people in whom the disease was diagnosed, based on a fasting PG cut-off level of ≥7.0 mmol/L. The remaining 5.5% of subjects had a fasting PG level of <7.0 mmol/L and the diagnosis was based on the 2-hour PG level of ≥11.1 mmol/L (Sasaki A, unpublished data, 1999).

A reanalysis of European epidemiological data from 26 190 subjects showed that the difference in prevalence of diabetes mellitus using the ADA criteria (fasting PG, ≥7 mmol/L) and WHO criteria (2-hour PG, ≥11.1 mmol/L) ranged from -4.0% to +13.2% and that the overall difference was +0.5%.[26] Only 28% of the 1517 diabetic patients were classified as having diabetes mellitus according to both criteria. Interestingly, the WHO and ADA criteria were more likely to diagnose diabetes in lean individuals, and middle-aged obese individuals, respectively.[26]

Despite its low sensitivity of diagnosing diabetes mellitus, using a fasting PG measurement is a more reproducible test when used in the Hong Kong Chinese population. Based on the measurements of

the fasting PG level on two occasions within 6 weeks, the diagnoses (diabetes, IFG, or NFG) were highly consistent, with an overall reproducibility of 90.8%.[25] In addition, patients who were classified as having diabetes mellitus according to the new criteria had higher HbA_{1c} and fructosamine levels than did diabetic patients whose disease was diagnosed by using the old criteria.[25]

Missed glucose intolerance

Based on the available epidemiological data, it is essential to reduce the fasting PG cut-off value. Using the fasting PG level alone to diagnose diabetes mellitus is more convenient and the result is more reproducible. The omission of the 2-hour PG measurement, however, will fail to identify subjects who would have glucose intolerance (ie IGT) or diabetes mellitus as defined by the 2-hour PG measurement. Furthermore, if the OGTT is subsequently performed in individuals who have a fasting PG level below 7.0 mmol/L, a proportion of them will be found to have IGT or diabetes mellitus. This group is referred to as having 'missed glucose intolerance' (MGI).

In a previous survey, 10% to 30% of 1513 Hong Kong Chinese individuals were found to have MGI (ie a normal fasting PG but an abnormal 2-hour PG) depending on the presence or absence of risk factors for glucose intolerance (unpublished data, 1999). The diagnosis of IGT cannot be made without performing an OGTT. Studies have confirmed the adverse relationship between IGT and cardiovascular diseases.[27] In addition, we have previously shown that 11.5% of cases of IGT progress to diabetes mellitus each year in the Hong Kong Chinese population.[28] This conversion rate is one of the highest reported among different ethnic populations and is lower than the rate of 15.7% per year reported by Pan et al in the Da Qing Study, which involved the Chinese population in northern China.[29]

To minimise missing the diagnosis of diabetes or IGT, we have attempted to identify the characteristics of individuals with MGI. In a local study of Chinese individuals with no history of diabetes,[25] OGTTs were performed in those with IFG and those with risk factors for glucose intolerance such as hypertension and obesity. In this way, more than half of those tested were found to have MGI.[25] Hence, if the OGTT were performed in high-risk individuals (approximately 20% of the population), approximately 70% of the MGI cases would be identified (unpublished data, 1999).

Guidelines for diagnosing and classifying glucose intolerance in Asia

The Japanese Diabetes Association (JDA) has recently recommended a set of criteria to definite glucose intolerance and to diagnose diabetes mellitus (Box 2).[30] Most of the recommendations from the JDA are applicable to Hong Kong. However, using an optimal HbA_{1c} cut-off level to screen or diagnose diabetes is still controversial and the measurement of the HbA_{1c} level in Hong Kong has not been standardised. On the other hand, the creation of additional terms such as 'borderline' glucose intolerance may create further confusion, because this group includes subjects with IFG and/or IGT.

Recently, the Asian-Pacific Type 2 Diabetes Group recommended the use of the new WHO and ADA diagnostic criteria to diagnose diabetes mellitus and emphasised that a casual glucose measurement cannot be used to diagnose IGT or IFG.[31] The diagnosis of diabetes should always be confirmed by repeating the test on another day, unless there is unequivocal hyperglycaemia with acute metabolic decompensation or other obvious symptoms. To reduce the number of cases of missed diagnosis owing to the omission of 2-hour PG measurements, performing an OGTT is recommended for people who have high normal fasting or random glucose levels. These values are arbitrarily taken as a fasting PG level of 5.6 to 6.9 mmol/L or a random PG level of 6.5 to 11.0 mmol/L.[31]

Glycated haemoglobin levels

In the Hong Kong Chinese population, using paired values of the fasting PG level and HbA_{1c} level allows

Box 2. Japanese Diabetes Association diagnostic criteria for glucose intolerance and diabetes mellitus[30]

(1) Criteria for glucose intolerance
(a) Normal type: fasting PG* <6.1 mmol/L and 2-hour PG (after OGTT†) <7.8 mmol/L
(b) Diabetic type: fasting PG, 7 mmol/L or 2-hour PG (after OGTT) ≥11.1 mmol/L or a casual PG ≥11.1 mmol/L
(c) Borderline type: neither normal nor diabetic type

(2) Criteria for diabetes mellitus
(a) PG of the 'diabetic type' and confirmed on two or more occasions examined on separate days
(b) A single PG of the 'diabetic type' when any one of the following conditions exists:
- Typical symptoms of diabetes (eg thirst, polyuria, polydipsia, or weight loss)
- Glycated haemoglobin HbA_{1c} ≥6.5% (based on the Japanese Diabetes Society Committee for Standardisation of Glycohaemoglobin)
- Unequivocal evidence of diabetic retinopathy

* PG plasma glucose
† OGTT oral glucose tolerance test

the identification of people in whom diabetes mellitus has a high likelihood of developing.[32-34] The likelihood ratio of having diabetes in people whose fasting PG level is ≥5.6 mmol/L and HbA_{1c} level is ≥5.5% has been shown to be 5.36, compared with a value of only 0.10 in people with a fasting PG level of <5.6 mmol/L and HbA_{1c} level of <5.5%.[32] If these paired values were increased to 6.1 mmol/L and 6.1%, the likelihood ratio of having diabetes increases further, to 17.2.[33] If fasting PG and HbA_{1c} measurements are used as initial screening tests and if an OGTT is performed only in those with a high likelihood ratio to confirm their glycaemic status, more than 80% of OGTTs will be unnecessary. In a Japanese study, the HbA_{1c} measurement was available in 54% of a random sample of 10 865 adults older than 20 years. Using fasting PG and 2-hour post–glucose loading PG measurements as reference tests, 13.6% of men in their 50s and 17.3% of women in their 60s were considered to have a very high likelihood of having diabetes if the HbA_{1c} level was 6.1% or higher.[35]

Although there is enough evidence to support the use of the HbA_{1c} measurement as an alternative or adjunct investigation to the PG measurement, it should be used only as a screening test for diabetes.[36] Measuring the HbA_{1c} level is insufficiently sensitive as a direct substitute for the OGTT. In addition, the high cost and lack of laboratory standardisation of HbA_{1c} measurement have so far limited its use in the diagnosis of glucose intolerance.

Diagnosing diabetes mellitus in the Hong Kong Chinese population

Based on the current literature, we propose that in symptomatic patients, a fasting PG or random PG measurement can be used to diagnose diabetes mellitus using the new ADA and WHO criteria. A second measurement on a separate day is required to confirm the diagnosis before clinical management is started. In epidemiological surveys, either a fasting PG or 2-hour PG measurement after a 75-g OGTT can be used. To screen individuals without risk factors for glucose intolerance, a fasting PG measurement will be the first choice of test. In those with risk factors for glucose intolerance, such as a family history of diabetes, history of gestational diabetes, obesity, or hypertension, an OGTT or a single blood test to determine fasting PG and HbA_{1c} levels should be performed. The choice between the use of an OGTT or measuring the fasting PG and HbA_{1c} levels will depend on the patient's preference and the resources available in the clinic. In addition, in some selected high-risk groups, which include those with a history of IGT or IFG, or those with fasting PG and HbA_{1c} levels above certain cut-off levels, an OGTT is the preferred choice of test (Table 2).

Conclusion

Blood glucose has a continuum of relationships with health risks, including both microangiopathic and cardiovascular complications, and can interact with other risk factors such as blood pressure and blood lipids to cause tissue damage. Furthermore, microangiopathic complications such as retinopathy and albuminuria have been reported in patients with impaired glucose tolerance, including Chinese patients.[37,38] There is now a consensus that the fasting PG cut-off value should be reduced to 7.0 mmol/L, although there is still controversy regarding the use of OGTT and the definitions of IFG. Data from Asia suggest that the omission of the OGTT (hence the 2-hour PG measurement) can lead to—at least in the Japanese and Hong Kong Chinese populations—the missed diagnosis of glucose intolerance in a substantial proportion of

Table 2. Recommended approach to make a diagnosis of diabetes mellitus in Hong Kong

Category	Choice of test
Symptomatic patients	Fasting or random PG* (on two separate occasions)
Epidemiological survey	Fasting or 2-hour PG after OGTT† (one value only)
Diabetes screening	
no risk factor	Fasting PG
risk factor present	OGTT or paired test of fasting PG + HbA_{1c}‡
Selected subjects	
history of IGT§	OGTT
known IFG‖	
fasting PG ≥5.6 mmol/L and HbA_{1c} ≥5.5%	

* PG plasma glucose
† OGTT oral glucose tolerance test
‡ HbA_{1c} glycated haemoglobin
§ IGT impaired glucose tolerance
‖ IFG impaired fasting glucose (ADA); impaired fasting glycaemia (WHO)

cases, if only the fasting PG measurement is used. Hence, the 2-hour PG measurement is indicated in selected individuals with a high risk for glucose intolerance. Well-designed population-based studies that aim to assess the long-term significance of these new recommendations to diagnose categories of glucose intolerance in Asian populations are now needed.

Acknowledgements

I would like to thank Prof JCN Chan, Department of Medicine and Therapeutics, Chinese University of Hong Kong, and Prof T Kuzuya, Department of Medicine, Jichi Medical School, Japan, for their valuable opinions during the preparation of this manuscript.

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