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In Search of Hyperglycaemia – Tracing the Path that Leads to the New Diagnostic Criteria for Diabetes Mellitus

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ABSTRACT

The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus announced the new diagnostic criteria for diabetes mellitus on 23 July 1997. The most notable change in the new criteria is a reduction in the cut-off point for fasting plasma glucose to that of 7.0 mmol/L (126 mg/dL). The present criteria have evolved through many years of intensive research and discussions. We intend to trace the path that leads to this latest recommendation so as to understand the evolution of the present criteria and its implications.

Keywords: fasting plasma glucose, 2-hour post-load glucose, diabetes complications

INTRODUCTION

In the recent Report of the American Diabetes Association (ADA) Expert Committee on the Diagnosis and Classification of Diabetes Mellitus[1], the diagnostic criteria for diabetes mellitus have been modified from those previously recommended by the National Diabetes Data Group (NDDG)[2] and World Health Organisation (WHO)[3] (Table I). The modification has been considered necessary for the following reasons: firstly, it has been shown that in large population studies, the incidence of diabetes-specific complications (eg. retinopathy) increases sharply among individuals with fasting blood glucose above the level of 7.0 mmol/L (126 mg/dl)[4] (Fig 1) ie. lower than the previous cut-off point for fasting blood glucose of 7.8 mmol/L. Therefore, there is a need to review the cut-off point for fasting blood glucose so as to give a better estimate of the risk of developing diabetes-related complications in a population. Secondly, a discrepancy in the diagnostic.conclusions derived from the fasting plasma glucose (FPG) and 2-hour post-load glucose (2hPG) is commonly encountered both in clinical practice and population survey, based on the previous criteria. In other words, during a standard 75 g oral glucose tolerance test (OGTT), an individual may have a fasting plasma glucose of less than 7.8 mmol/L (140 mg/dL) (ie. hitherto normal) but a 2-hour post-load glucose exceeding 11.1 mmol/L (200 mg/dL) (ie. consistent with diabetes). The Expert Committee feels that such a discrepancy is unwarranted and can only give rise to confusion. Thirdly, a simpler and equally accurate test ie.fasting plasma glucose rather than an OGTT, should be advocated for the diagnosis of diabetes. The recent modification did not come as a surprise since the NDDG acknowledged and anticipated that criteria might need revision as research and knowledge advanced[2].

Definition of hyperglycaemia – past and present

Past

Defining exactly what constitutes hyperglycaemia has not been easy. Similar to parameters like height and weight, our average blood glucose levels span a wide range as a continuous variable. Therefore, any segregation between euglycaemia and hyperglycaemia is largely arbitrary and considerable overlap exists. A possible resolution to this issue was provided by two elegantly designed systematic surveys on the Pima Indian[5] and Nauruan populations[6] whose plasma glucose exhibited a bimodal distribution (Figs 2a & b). In these two populations with extremely high prevalence of diabetes, there was a distinction between non-diabetics whose 2hPG levels were below 11.1 mmol/L (200 mg/dL) and diabetics whose 2hPG levels were above 13.3 mmol/L (240 mg/dL). The same bimodal distribution occurred for FPG where the value of about 7.8 mmol/L (140 mg/dL) divided the non-diabetic from the diabetic population. In a separate study, it was demonstrated that diabetic retinopathy was more prevalent in Caucasian subjects with a 2-hour capillary glucose of 11.1 mmol/L (200 mg/dL or more)[7]. Therefore, it was proposed that if the diagnosis of diabetes was to be based on the premise of subjects who had substantial glucose intolerance and an appreciable risk of specific diabetic complications, then a 2hPG of 11.1 mmol/L (200 mg/dL) would seem to be a reasonable value for diagnosis in at least the Caucasian population[6]. The notion was endorsed

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Table I – Comparison between diagnostic criteria for diabetes mellitus previously recommend by the World Health Organisation (WHO) in 1980 with the present recommendation by Report of the Expert Committee on the Diagnosis and Classification of Diabetes from the American Diabetes Association (ADA) and WHO

	WHO (1980)	Present Recommendation (ADA, 1997)	(WHO, 1998)	
Normal				
FPG	–	< 6.0 mmol/L (110 mg/dL)	< 6.0 mmol/L (110 mg/dL)	
2hPG	< 7.8 mmol/L (140 mg/dL)	< 7.8 mmol/L (140 mg/dL)	< 7.8 mmol/L (140 mg/dL)	
Borderline glucose tolerance	**IGT**	**IFG**	**IGT**	**IFG**
FPG	< 7.8 mmol/L (140 mg/dL)	⩾ 6.0 to < 7.0 mmol/L (110 – 126 mg/dL)	< 7.0 mmol/L (126 mg/dL)	⩾ 6.0 to < 7.0 mmol/L (110 – 126 mg/dL)
2hPG	⩾ 7.8 to < 11.1 mmol/L (140 – 200 mg/dL)	–	⩾ 7.8 to < 11.1 mmol/L (140 – 200 mg/dL)	< 7.8 mmol/L (140 mg/dL)
Diabetes				
FPG	⩾ 7.8 mmol/L (140 mg/dL) *or*	⩾ 7.0 mmol/L (126 mg/dL) *or*	⩾ 7.0 mmol/L (126 mg/dL) *or*	
2hPG	⩾ 11.1 mmol/L (200 mg/dL)	⩾ 11.1 mmol/L (200 mg/dL)	⩾ 11.1 mmol/L (200 mg/dL)	

IGT : Impaired glucose tolerance
IFG : Impaired fasting glucose
FPG : Fasting plasma glucose
2hPG : 2-hour post-load glucose

* In the absence of unequivocal hyperglycaemia with acute metabolic decompensation, these criteria should be confirmed by repeat testing on a different day.

The experts recommend that in the presence of classical symptoms of diabetes (polyuria, polydipsia and unexplained weight loss), a diagnosis of diabetes is accepted with a random plasma glucose concentration ⩾ 11.1 mmol/L (200 mg/dL)

successively by the NDDG in 1979 and WHO in 1980 when the cut-off for normality for FPG and 2hPG stood at 7.8 mmol/L (140 mg/dL) and 11.1 mmol/L (200 mg/dL) respectively.

At the same setting, WHO also defined a condition of impaired glucose tolerance (IGT) in which FPG is less than 7.8 mmol/L (140 mg/dL) but rises to between 7.8 (140 mg/dL) and 11.1 mmol/L (200 mg/dL) two hours after an OGTT. Individuals with IGT were characterised by decompensation into overt diabetes at a rate of 1% – 5 % per year. On the other hand, a substantial proportion of individuals showed spontaneous reversion to normal glucose tolerance and the remainder stayed as IGT[2]. Retinopathy and nephropathy characteristic of diabetes generally do not develop. However, there is evidence that individuals with IGT are at an increased risk of morbidity and mortality from atherosclerotic disease.

Present

Subsequently, it was found that a FPG of ⩾ 7.8 mmol/L (140 mg/dL) and 2hPG glucose of 11.1 mmol/L (200 mg/dL) probably defined different aspects of hyperglycaemia[8] ie. it is easier for one to exceed the 2hPG cut off of 11.1 mmol/L (200 mg/dL) than to fulfill a FPG of ⩾ 7.8 mmol/L (140 mg/dL). In the study by Harris et al[9], almost all individuals with FPG ⩾ 7.8 mmol/L (140 mg/dL) had 2hPG ⩾ 11.1 mmol/L (200 mg/dL) if given an OGTT, whereas only about one fourth of those with 2hPG ⩾ 11.1 mmol/L (200 mg/dL) and without previously known diabetes had FPG ⩾ 7.8 mmol/L (140 mg/dL). In other words, the cut-point of FPG ⩾ 7.8 mmol/L (140 mg/dL) probably defined a greater degree of glucose intolerance than did the cut point of 2hPG ⩾ 11.1 mmol/L (200 mg/dL).The present Expert Committee considers it necessary to modify that diagnostic criteria so that the values for both tests (ie. FPG and 2hPG) should reflect a similar degree of hyperglycaemia and risk of adverse outcome.

It is felt that the 2hPG of 11.1 mmol/L (200 mg/dL) should remain because observations based upon large population survey done amongst the Pima Indians[4] and the Egyptians[10] revealed that at approximately this point, the prevalence of the microvascular complications specific for diabetes eg. retinopathy and nephropathy increased dramatically (Fig 1).

The next step is to search for a reasonable cut-off point for the FPG that correlates well with the 2hPG of 11.1 mmol/L (200 mg/dL). The Expert Committee carefully examined data obtained from the Third National Health and Nutrition Examination Survey (NHANES III) in the US as well as epidemiological studies in Pima Indians[4], the Egyptians[10] and 13 other Pacific populations[8]. The FPG estimated from these studies which ranged between 120 to 126 mg/dL and the Committee decided upon the higher value of 7.0 mmol/L (126 mg/dL) so that slightly fewer people would be diagnosed with diabetes if the new FPG criterion was used alone than if either the FPG or the OGTT was used.

Further evidence substantiating the necessity to bring down the value of FPG comes from another long-term, large-scale study – the Paris Prospective Study[11]. In this study, the authors demonstrated convincingly that coronary heart disease (CHD) risk is almost doubled for a fasting blood glucose concentration above 6.9 mmol/L (124 mg/dL). Further elevation in fasting blood glucose level is associated with marked increase in risk for coronary heart disease. This increase in coronary risk appears to approach a plateau at a fasting blood glucose level of 7.8 mmol/L (140 mg/dL) beyond which any increase in fasting blood glucose is translated to only a relatively slight increase in the incidence of coronary heart disease[11,12]. One of the authors pointed out that the previous diagnostic criteria of FPG ⩾ 7.8 mmol/L (140 mg/dL) and 2hPG ⩾ 11.1 mmol/L (200 mg/dL) have been defined mainly in view of the risk of microangiopathy. However, the prognosis in non-insulin dependent diabetes is more related to macroangiopathy, which accounts for more than 50% of deaths. Hence, the

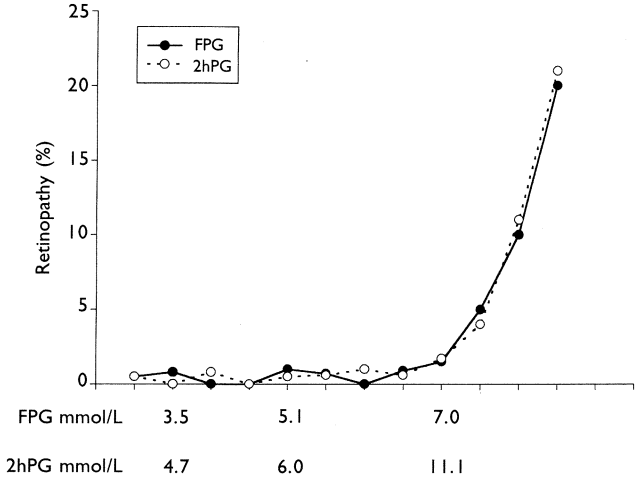

Fig 1 – Schematic diagram showing exponential rise in prevalence of retinopathy with increasing FPG and 2hPG.

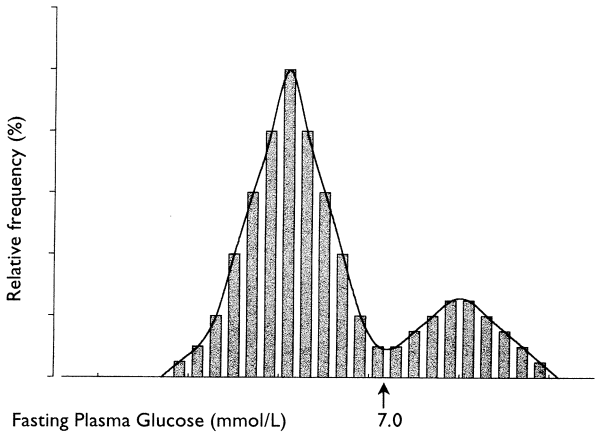

Fig 2a – Schematic diagram showing a bimodal distribution of FPG.

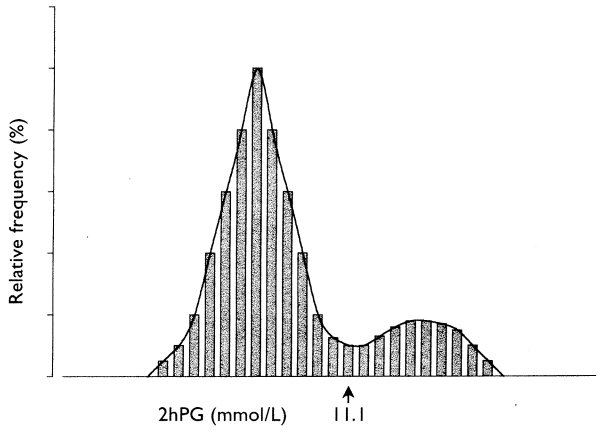

Fig 2b – Schmatic diagram showing a bimodal distribution of 2hPG.

present reduced cut-off point of FPG ≥ 7.0 mmol/L (126 mg/dL) (which is very close to the value of 6.9 mmol/L and will also take into consideration the risk for macroangiopathy such as coronary artery disease) appears to be justified in terms of CHD mortality[12].

In addition to the new cut-off point for FPG, the Expert Committee decided to introduce an intermediate group of subjects whose fasting glucose levels, although not meeting the criteria for diabetes, were nonetheless too high to be considered normal[1]. Known as impaired fasting glucose (IFG), this group is defined by a FPG ≤ 5.6 mmol/L (110 mg/dl) but ≤ 7.0 mmol/L (126 mg/dL).

The WHO Consultation Provisional Report in 1998 largely concurred with the recommendations made by the ADA Expert Committee except the followings[13]: firstly, the WHO experts felt that the diagnostic category IGT should remain since it is a stage in the natural history of disordered carbohydrate metabolism. However, the revised criteria for IGT would be FPG < 7.0 mmol/L (126 mg/dL) and 2hPG between 7.8 mmol/L (140 mg/dL) and 11.1 mmol/L (200 mg/dL) so as to reflect a lowered FPG cut-off point for the diagnosis of diabetes. In corollary, it was recommended not to abandon OGTT since it is necessary to identify subjects with IGT. Secondly, WHO experts agreed with the new category of IFG; however, they felt that it should be defined as individuals with a FPG ≥ 6.1 mmol/L (110 mg/dL) and < 7.0 mmol/L (126 mg/dL). Moreover, if the 2hPG was available, it should be < 7.8 mmol/L (140 mg/dL) so as to avoid having subjects with double diagnoses of IFG and IGT.

In conclusion, both the FPG and 2hPG should provide important information regarding risk of micro- and macrovascular disease. Therefore, the revised criteria for the diagnosis of diabetes are as shown in Table I[1].

Implication of new diagnostic criteria

The new criteria have important implications for clinicians, epidemiologists and health policy makers.

Firstly, the diagnosis of diabetes mellitus is now simplified. For all intents and purposes, only a random plasma glucose (if the patient is symptomatic) or a consistently elevated FPG is required for diagnosis. Although the OGTT is an acceptable diagnostic test and has been an invaluable tool in research, it is unnecessary and hence not recommended for routine use. In other words, clinicians are now encouraged to move away from performing OGTT routinely but to rely on either the FPG or random plasma glucose (in the presence of classical diabetes symptoms stated in Table I) for the reliable diagnosis of diabetes.

Secondly, although a FPG ≥ 7.0 mmol/L (126 mg/dL) and a 2hPG ≥ 11.1 mmol/L (200 mg/dL) have similar predictive values for adverse outcomes, the two tests are not perfectly correlated with each other[1]. In other words, simultaneous measurement of both FPG and 2hPG will inevitably lead to some diagnostic discrepancies and dilemmas. With this in mind, the Expert Committee recommends the

FPG alone for estimating the comparative prevalence of diabetes in different population since there is no basis to conclude that 2hPG is more reliable than FPG. Furthermore, it is easier to standardise the fasting state.

Thirdly, the revised criteria are for diagnosis and are not treatment criteria or goals of therapy. Hence, the American Diabetes Association's recommendation of FPG < 6.7 mmol/L (120 mg/dL) and HBA1c $< 7\%$ as treatment goals remains unchanged[1].

Last but not the least, with widespread adoption of the new criteria, a large impact on the number of people actually diagnosed to have diabetes is expected[1]. In the 1992 Singapore National Health Survey, 8.6% of the population was diabetic. With the present new recommendation which encourages the use of a simpler diagnostic procedure (ie. fasting blood glucose), the prevalence of diabetes is likely to increase in an affluent and rapidly aging society like ours. In response to the anticipated increasing prevalence of diabetes, it is time for those who are called to serve in health care to work closely together for the active prevention and management of diabetes and its consequences.

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