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Editorial

Diabetes Mellitus: A New Look at Diagnostic Criteria

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The diagnosis of diabetes is usually straightforward, based on characteristic symptoms and signs together with an unequivocally raised blood glucose concentration. Similarly, there are levels of blood glucose which would universally be considered normal. However, in between there is a range of considerable diagnostic uncertainty. This uncertainty has been emphasized by the large scale population surveys of the last thirty years, which have failed to show any natural cut-off point between normal and abnormal glycaemia.

It could be argued that undue diagnostic emphasis has been placed on blood glucose, in that many other aspects of metabolism are also deranged in diabetes, but no useful alternative diagnostic measure has yet emerged. The glucose tolerance test has become widely accepted as a diagnostic aid when the clinical picture or degree of hyperglycaemia was equivocal. The hope that clear, standard diagnostic criteria could be universally applied has not been realised despite the adoption and trial of a wide variety of oral and intravenous loads. The distinction between diabetic and non-diabetic responses has remained blurred. There appears indeed to be a continuum from the clearly normal to the clearly abnormal, as with so many biological variates, such as blood pressure and body weight.

How then is the diagnosis to be made from the glucose tolerance test? This must depend on what the purpose is of making the diagnosis. Persons in whom the test is used are most frequently free of diabetic symptoms so that its purpose rests largely upon the presumption (one yet to be decisively confirmed) that diagnosis and subsequent treatment will slow progression and aid prevention of the long-term sequelae of the disease. A minimum requirement of a diagnostic test therefore is early identification of people who are at risk of developing the microangiopathic, the neuropathic and the macroangiopathic complications, as well as those likely to be specially at risk during pregnancy. Only planned prospective observations can determine at what point in the spectrum of glucose tolerance/intolerance the risk increases.

In the past there were few such data on which to base any rational diagnostic levels. There was a tendency to set the distinction between normal and abnormal at low levels, based on oral glucose tolerance tests performed on young and healthy volunteers, although the validity of this was questioned by one or two notable authorities [1]. It did have the effect of ensuring that few, if any, genuine diabetics escaped diagnosis, but at the expense of including large numbers of people with lesser degrees of glucose intolerance, usually older, fatter and with other diseases associated with mild degrees of carbohydrate intolerance. Including these as diabetics seemed justified by the widely accepted opinion that minor degrees of glucose intolerance worsened to unquestionable diabetes and that this deterioration would be arrested and its complications averted by treatment. Mildly impaired glucose tolerance was equated with 'early diabetes'. Evidence has now accumulated throwing considerable doubt on this notion [2, 3, 4].

Dissatisfaction also arises from the poor reproducibility of any procedure such as the glucose tolerance test. The known causes of its variability are legion, including previous diet, emotion, trauma, posture, drugs, other diseases, and time of day; some variation remains unexplained. In addition, there has been wide diversity in the load used, the blood sampled and the diagnostic values recommended by different national groups. The extent of the uncertainty existing even in the minds of physicians specialising in diabetes was documented by West [5], who

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Table 1. Crude mortality at ten years – all causes and from deaths ascribed to cardiovascular disease – in diabetics and "borderline" diabetics identified in the Bedford Survey. The control group was derived from a random sample of the cooperating population with a 2 hour blood sugar level < 120 mg/dl. When differences in age and baseline blood pressure are taken into account, there is significant excess mortality amongst diabetics of both sexes and the female borderline diabetics over the controls both for all causes and cardiovascular causes. The excess in male borderline diabetics did not reach the 5% level of significance

	Men			Women		
	n	All deaths	Cardiovascular deaths	n	All deaths	Cardiovascular deaths
Diabetics	51	19 (37.2%)	15 (29.4%)	63	25 (39.7%)	18 (28.5%)
Borderline "diabetics"	130	29 (22.3%)	19 (14.6%)	119	35 (29.4%)	25 (21.0%)
Controls	104	20 (19.2%)	12 (11.5%)	85	9 (10.6%)	4 (4.7%)

Table 2. Suggested criteria presented for discussion at the EASD meeting in Zagreb. Diagnostic values for oral glucose tolerance test, under standard conditions. Load 75 g glucose in 200–500 ml or 1.75 g/kg for children. Specific enzymatic glucose assay. Two classes of response are identified namely Diabetes Mellitus (DM) and Impaired Glucose Tolerance (IGT)

	Glucose concentration[a]		
	Venous whole blood	Capillary whole blood	Venous plasma
1. Diabetes Mellitus (DM)			
Fasting	> 7.0 mmol/l (120 mg/dl)	> 7.0 mmol/l (120 mg/dl)	> 8.0 mmol/l (140 mg/dl)
AND			
Two hours after glucose	> 10.0 mmol/l (180 mg/dl)	>11.0 mmol/l (200 mg/dl)	>11.0 mmol/l (200 mg/dl)
With at least one intervening value at or above the two hour value			
2. Impaired glucose tolerance (IGT)			
Fasting	< 7.0 mmol/l (120 mg/dl	< 7.0 mmol/l (120 mg/dl)	< 8.0 mmol/l (140 mg/dl)
AND			
Two hours after glucose	> 7.0 mmol/l (120 mg/dl)	> 8.0 mmol/l (140 mg/dl)	> 8.0 mmol/l (140 mg/dl)
BUT	< 10.0 mmol/l (180 mg/dl)	< 11.0 mmol/l (200 mg/dl)	< 11.0 mmol/l (200 mg/dl)

The OGTT definitions above are not exhaustive. For example, the fasting blood sugar (FBS) concentration may meet the criteria for DM when subsequent post-load values fall short of them; or the FBS may fall short of the diagnostic values for DM while subsequent levels exceed them. We recommend that such cases should be assigned to IGT on the argument that a final diagnosis of DM should be unequivocal. This view differs from current proposals of the NIH working group which suggests that the diagnosis of DM can be made when FBS alone meets the stated criteria on more than one occasion

[a] S.I. Units 'rounded off'

enquired of a panel of U. S. and international experts what levels of blood glucose they considered diagnostic of diabetes 2 hours after a 75 g oral glucose load in a hypothetical 50 year old woman. Both within the U. S. and among national groups answers ranged from 120 to 200 mg/100 ml (6.7 to 11.1 mmol/l). The hard data now becoming available should help to resolve some of the diagnostic uncertainties and allow the adoption of more logically based and universally agreed procedures and blood glucose criteria. It is apparent that different degrees of glucose intolerance are associated with different long-term risks.

The long-term results of the Bedford study, where 249 so-called borderline diabetics (capillary blood glucose, measured with ferricyanide, of 120 to 200 mg/100 ml (6.7 to 11.1 mmol/l) 2 hours after 50 g oral glucose) and 114 newly detected diabetics (2 h glucose > 200 mg/100 ml (11.1 mmol/l)) have been followed for up to 10 years, are now available Both "borderline" and new diabetics had an increased incidence of atherosclerotic disease and risk of cardiovascular death over the ten years (Table 1) but, interestingly, only the new diabetics carried an increased risk of developing ophthalmoscopically significant retinopathy [6]. Systematic follow-up of another comparable glucose intolerant British population sample, the Whitehall study [4], has shown a similar cut-off point for the development of retinopathy [7]. Studies of the Pima Indians, a tribe with very high diabetes incidence, also showed a sharp increase in the risk of retinopathy and proteinuria in those individuals with plasma glucose values in excess of 200 mg/100 ml (11.1 mmol/l) 2 hours after a 75 g oral glucose load [8]. The Pimas indeed showed a clear bimodal distribution of 2 hour plasma glucose values with the division occurring from 204–245 mg/100 ml (11.2 to 13.6 mmol/l). Both the Bedford and Whitehall "borderline" groups showed a relatively low rate (2 to 3% per year) of 'worsening to diabetes' which, under controlled trial conditions, was not significantly influenced by treatment with carbohydrate-restricted diet and/or oral hypoglycaemic agents. A large proportion of these mildly glucose intolerant subjects reverted, apparently spontaneously, to normal tolerance and the rest remained substantially unchanged in respect of carbohydrate metabolism.

On the basis of these and other findings, several national groups have set out to establish new guidelines for the interpretation of the glucose tolerance test in the diagnosis of diabetes. These include a working party of the National Institutes of Health in the United States, the British Diabetic Association, the Australian Diabetes Society and now the European Association for the Study of Diabetes. There is broad agreement that there is now a strong case for excluding the lesser degrees of glucose intolerance from the diagnostic boundaries of diabetes mellitus. There is little clinical justification or medical benefit in defining such people as diabetics and the mere diagnostic pronouncement can do considerable social and psychological damage. We suggest for this group the use of the term Impaired Glucose Tolerance (IGT), which avoids the stigma of the word diabetes but none-the-less maintains an indication of the 'at-risk' status of such people. IGT is obviously not so much a diagnosis as a description but it is also a signal that attention may be required – although more from a cardiovascular than a diabetic point of view. It also recognizes that although small there is a greater likelihood of metabolic deterioration than in normoglycaemic individuals. A strong footnote should be added with respect to pregnancy. Here impaired glucose tolerance (IGT) is an indication for therapeutic intervention involving special medical and obstetric care. The available evidence strongly suggests that fetal outcome is thereby improved.

What glucose load should be used? And where should the diagnostic dividing lines be drawn? A minority would vary the load in adults according to weight or surface area. In North America the 100 g oral glucose load is widely used and the 50 g load in Europe, particularly the UK. A substantial number of workers throughout the world, however, use 75 g, which West in his encyclopaedic work [9] and several epidemiological study groups recommend. Each test load has its proponents and antagonists but there is, in fact, surprisingly little difference between the blood glucose values obtained. We recommend the 75 g load as a reasonable compromise which could be universally adopted.

What of the blood glucose values? Table 2 shows the values circulated at the EASD meeting at Zagreb and similar to those under consideration by the NIH study group, the British Diabetic Association and the Australian Diabetes Society. It can be seen that both fasting and 2-hour post-glucose load values are included. Some would prefer to base diagnostic decisions on the fasting or the 2-hour blood glucose concentration alone. The use of a fasting value is difficult to standardise experimentally and more readily misclassified after unsuspected dietary transgression. There is also less epidemiological data concerning its long-term predictive value compared with a response to oral glucose. The newly recommended values are also more in line with recent studies of normal populations covering a wide age range.

The numbers in Table 2 are neither sacrosanct nor eternal, but are for discussion. We have been asked to write this editorial by the Council of the EASD, in order to promote discussion and wide consultation. We would hope that readers interested in the topic, and indeed the subject is of interest and concern to all practising doctors, will correspond with us so that a wide consensus of views can be taken before details of the revised criteria are firmly recommended. Hopefully criticisms will be based on fact and logic. The W. H. O. Expert Committee on Diabetes will be reconvened shortly and undoubtedly will consider this subject. Perhaps a reasoned and united view can be presented to them.

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