Review Article

The diagnosis of Diabetes Mellitus

A contest between 3 points!

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ABSTRACT

A major debate is currently taking place on the world diabetes scene on the merits of fasting versus 2-hour postprandial glucose concentrations as a reference point for the diagnosis of diabetes. Other time points of the oral glucose tolerance test on the other hand, seem to attract little attention. In Saudi Arabia however, we have been intrigued by the scale and severity of hyperglycemia observed at one-hour following glucose load. Plasma glucose concentration one-hour postprandially is strikingly abnormal amongst native Saudis and interestingly, is associated with insulin resistance and features of syndrome X. Such observations have prompted us to call into question the wisdom of current practices, namely of excluding the one-hour plasma glucose concentration in the diagnosis of diabetes. In the proceeding article therefore, we describe in detail our local observations and debate the wider scientific and historical issues surrounding the place of one-hour glucose concentration as a potentially useful diagnostic point in the detection and classification of glucose intolerance.

Keywords: Diabetes Mellitus, diagnosis, oral glucose tolerance test, postprandial glucose, macrovascular complications.

Saudi Med J 2001; Vol. 22 (10): 839-842

When the American Diabetes Association (ADA) first published its proposals on the new definition and classification of diabetes in 1997,[1] many in the medical community welcomed the new guidelines and nearly everyone saw the good reasons behind it. To completely abandon the oral glucose tolerance test (OGTT), hitherto a test of immense value and sentiment, in favor of using fasting plasma glucose concentration alone was seen as a practical attempt to simplify and facilitate the diagnosis of diabetes. After all, who would want to use the OGTT, a test renowned for its poor reproducibility and inconvenience if the measurement of fasting glucose concentration alone could actually suffice? The ADA subsequently declared that a fasting plasma glucose concentration of 7.0 mmol/L, a level shown to coincide with a reference value of 11.1 mmol/L at 2 hours of OGTT and to predict diabetic complications such as retinopathy, was to be the new and preferred measurement necessary to establish the diagnosis of diabetes (no place for the OGTT). It was not long however, before the ADA's new guidelines ran into problems:[2] it soon emerged for example, that the concordance rate between fasting and 2-hour glucose concentrations was significantly lower than expected as a substantial proportion of subjects defined to be diabetic on the basis of elevated 2-hour glucose concentrations actually had fasting glucose concentration that was below the diabetic range and vice versa;[3,4] moreover, the 2-hour glucose concentration has shown itself to be a strong marker of mortality independent of fasting glucose concentration level[5-7] and to be indeed, better than fasting glucose as a predictor of macrovascular

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disease,[8-10] the latter being of course the main cause of death in diabetic patients. Whereas the ADA has so far stuck to its guidelines (relying solely on measurement of fasting glucose), the European and the World Health Organization (WHO) groups[11-13] continue to reserve a place for the OGTT (2-hour) in the screening and classification of glucose tolerance.

In the meantime, and while the rest of the world decides to await the outcome of the current debate, we, for our part would like to bring something else into the fray. We have been interested in the value of plasma glucose concentration measured at one-hour post-glucose load as a point of potential diagnostic value for the detection and classification of diabetes. We have been intrigued by observations that we had made in Saudi Arabians which we believe, may call into question the wisdom of current practices, namely of excluding the one-hour plasma glucose concentration as a screening test for glucose intolerance. In the proceeding discussion, we describe those observations and debate the reasons why we believe interest in the one-hour glucose concentration should be revived.

Characteristics of oral glucose tolerance test profile in Saudi Arabians. Almost everything about diabetes such as, its underlying nature, prevalence rate and type and severity of complications is influenced by ethnic and genetic factors. Is it possible therefore that the diagnostic criteria of diabetes should also be set in a way so as to take into account the ethnic background of the population in question? A number of observations in Saudi Arabians prompted us to ask precisely this question in relation to the one-hour glucose concentration:

A. During the course of an investigation into the etiology of type 2 diabetes in the local population we screened 97 young healthy Saudi Arabians not known to have diabetes, using the OGTT.[14] Apart from 10 people discovered to have unrecognized diabetes, we noted that a large proportion of the volunteers screened (27/97 subjects, 28%) had a very interesting glucose profile, in that while the fasting (< 7.0 mmol/L) and 2-hour plasma (< 11.1 mmol/L) glucose concentrations were below the diabetic threshold, the one-hour glucose concentration was by contrast strikingly abnormal (> 11.1 mmol/L), as highlighted by the following examples: 1. Fasting 5.4, one-hour 12.6, 2-hour 7.5 mmol/L . 2. Fasting 6.0, one-hour 14.8, 2-hour 6.9 mmol/L 3. Fasting 5.1, one-hour 12.4, 2-hour 8.4 mmol/L. Based on current WHO/ADA criteria, interpretation of the above examples would be as follows: both first and 2nd cases would be considered as being normal, while the 3rd as having only impaired glucose tolerance (IGT). Since neither the current WHO nor ADA criteria make allowance for what happens to blood sugar at one hour, the glucose profile of the 2nd case would be considered as being entirely "normal" in spite of having a blood sugar reading of 14.8 mmol/L. This could raise a clinical dilemma for the treating physician: is it clinically justifiable for example, to disregard postprandial hyperglycemia (in some cases we have seen glucose concentration as high as 17 mmol/L at one-hour) just because it did not fall on the "official" 2-hour time point of the OGTT?

B. Upon reviewing all OGTT data for male patients referred to our hospital in 1997 to 1998, we again saw the same pattern of mid-test-abnormality: of 140 subjects screened, 40 (28%) turned out to have isolated hyperglycemia at one hour. Interestingly, the 2-hour glucose concentration was below 7.8 mmol/L in 35% of those with raised one-hour glucose concentration (such patients would not even qualify for IGT, despite the presence of excessive postprandial hyperglycemia).

C. Upon reviewing the local literature, we could find one published report whereby the investigators had performed OGTTs in Saudi Arabians with measurement of blood glucose at all 3 time points (fasting, 1 hour and 2 hour).[15] Out of 243 subjects tested in the study, 88 subjects (29%) were reported to have mid-test-abnormality, namely, "normal" glucose profile based on WHO criteria but with higher than normal (> 11 mmol/L) one hour glucose concentrations. Indeed, the authors of that report themselves questioned the validity of WHO criteria for the diagnosis of diabetes in the Arab population. We do not know however, whether such a pattern is seen in some ethnic groups more than others, or whether it only occurs in populations where diabetes is very common, such as Saudi Arabians.[16]

D. Obviously, one way to determine the significance of the one-hour glucose concentration would be to study subjects with elevated one-hour glucose concentration prospectively to determine the natural history of the abnormality in relation to the development of diabetic complications. Hopefully, this will be carried out in the near future. Meantime, in an effort to explore the notion that acute postprandial hyperglycemia at one hour might in itself be a risk factor, we examined the atherogenic profile of the 97 young Saudis mentioned above, comparing those with elevated (≥ 11.1 mmol/L) versus those with normal (< 11.1 mmol/L) one-hour glucose concentrations. As outlined in Table 1, hyperglycemia at one-hour (note: in the absence of diabetes as defined by ADA/WHO criteria) was associated with obesity, altered lipid profile, and a marked state of insulin resistance, the latter being in fact comparable in severity to that seen in patients with overt diabetes (data not shown). Although the number of subjects studied might be considered relatively small and the data preliminary, it might nevertheless indicate that acute postprandial hyperglycemia (elevated plasma glucose at one hour in the presence of an otherwise nondiabetic OGTT profile) is not without its potential hazards (Syndrome X).

Table 1 - Physical and metabolic characteristics of non-diabetic Saudi Arabian subjects with and without hyperglycemia at one-hour.

Characteristics	one-hour glu < 11.1 mmol/l (n=60)	one-hour glu ≥ 11.1 mmol/l (n=27)
Age (years)	29 ± 1	30 ± 1
BMI (kg/m^2)	24 ± 1	27 ± 1*
Waist/Hip Ratio	0.9 ± 0	0.9 ± 0
BP Sytolic (mmHg)	113 ± 2	114 ± 2
BP Diastolic (mmHg)	75 ± 1	78 ± 2
Cholesterol (mmol/l)	4.6 ± 0.1	5.4 ± 0.2**
Triglycerides (mmol/l)	1.3 ± 0.1	1.9 ± 0.2*
HDL (mmol/l)	1.2 ± 0	1.1 ± 0
LDL (mmol/l)	2.9 ± 0.1	3.5 ± 0.1*
Fasting Insulin (pmol/l)	56 ± 3	81 ± 7**
Insulin sensitivity (%)	96 ± 6	73 ± 9**

BMI=body mass index, BP=blood pressure, HDL=high density lipoprotein, LDL=low density lipoprotein, n=number
Comparisons were made using Student's t-test/Mann - Whitney (as appropriate), glu=glucose, Values are mean ± SEM (standard error of the mean.*=p<0.01, **=p<0.001)
Insulin sensitivity was measured using HOMA (homeostatic model assessment) (note: differences persist even after controlling for BMI and presence of family history of diabetes).

The one-hour glucose concentration: a case of unfair dismissal? As well as the local observations described above, there are several other reasons which we believe provide further evidence in support of the case of the one-hour glucose concentration as a useful screening test for glucose intolerance, as follows: 1. In the past, the one-hour glucose concentration played a complementary role and was indeed widely used as a standard point in the diagnosis and classification of diabetes. It is not clear to us however, the reasons why the one-hour glucose has fallen out of favor: was the decision to abandon the one-hour glucose, as a reference point for diabetes, made on the basis of scientific evidence or was it simply a matter of convenience? If the issue of poor reproducibility is ever advocated as the main drawback precluding use of the one-hour glucose concentration, then we should abandon the OGTT test as a whole, not just the one-hour time point since none of the points of the OGTT test (including the 2-hour glucose) are adequately reproducible. 2. While the one-hour glucose concentration may have been abandoned in the screening for the common types of diabetes, it has retained its place in the screening and diagnosis of gestational diabetes in the United States of America (USA) and elsewhere. Although gestational diabetes may be considered by many to represent a special case of carbohydrate intolerance, we should nonetheless, make up our minds whether hyperglycemia at one-hour is or is not detrimental to human metabolism. 3. The importance of postprandial hyperglycemia is being increasingly recognized. Indeed, such is the trend nowadays (albeit driven in part by the pharmaceutical industry) to treat and monitor diabetes for example, the success of antidiabetic agents being used to restore postprandial glucose homeostasis. What is not known however, is the actual time point postprandially (30 minutes, 60 minutes, 120 minutes, and so on) that is etiologically most sensitive and therefore, best placed to predict disturbances in postprandial glucose metabolism. To our knowledge, there is nothing to suggest for example, that the 2-hour glucose is superior to that of the one-hour time point as a marker of insulin resistance, the major etiological factor responsible for the development of diabetes.[17,18] 4. Conceptually, at least to us, 60 minutes after the ingestion of a meal, not several hours afterwards, represents the maximal point of metabolic and digestive events and therefore, potentially is a better time to choose to detect the earliest signs of metabolic dysfunction. Moreover, in temporal terms at least, what happens at one hour is bound to affect the 2-hour glucose concentration (spill-over effect) and not the other way around. 5. Historically, we are not aware of any published work which would discredit the one-hour glucose concentration or show it to be in anyway inferior to that of 2-hour glucose concentration, either as a predictor of glucose intolerance or of macrovascular complications. It is indeed a pity how some of the early landmark studies, where both the one-hour and 2-hour glucose concentrations had been measured simultaneously, failed to explore the outcome in terms of these 2 set points. We would urge investigators with access to such data to re-examine their data and where possible to compare the predictive value of plasma glucose measured at one-hour versus that at 2-hour time points. 6. We are aware however, of a number of prospective studies that have shown a close relationship between one-hour glucose concentration post-challenge and the risk of cardiovascular complications. This is perhaps best illustrated by the findings of the Honolulu series of studies, which showed the one-hour plasma glucose concentration to be an independent risk factor for ischemic heart disease, stroke, and sudden death.[19-22] Even more interesting, is the observation reported in these studies that the vascular risk attached to the one-hour glucose concentration closely followed a gradient pattern with, a direct dose-response relationship. It is not known however, what one-hour glucose value would separate those who will and those who will not develop

complications, although in one study cardiovascular mortality was reported to accelerate once the one-hour blood glucose concentration exceeded the 200 mg% mark.[23]

In conclusion, over the years, the diagnosis of diabetes has been a constant source of debate. A combination of factors seem to undermine the outcome each time new criteria were established: existing scientific evidence (often modest or inconsistent), overwhelming tradition (enshrined in the eternal use of the OGTT) and clinical consensus (often hardest to get of all human commodities). In other words, a mix of ingredients to ensure a permanent settlement is never close at hand. The one-hour postchallenge glucose concentration appears to be a casualty of this process. Our observations in Saudi Arabians suggest that at least in this ethnic group, hyperglycemia one-hour postprandially is relatively common and may not be benign. Given the reasons and observations described above, we would urge the diabetes community to seriously reconsider the one-hour glucose concentration as a point of relevance in the detection and classification of glucose tolerance.

Acknowledgment. We are grateful to Dr. Robert Rizza for critical review of the manuscript and general support and encouragement.

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