Hyperglycaemia is necessary for the diagnosis of diabetes. For more than 35 years there has been a spirited controversy about the diagnostic criteria for Type 2 diabetes, in particular about the oral glucose tolerance test (OGTT). In a 1975 paper Marvin Siperstein[1] referred to the OGTT as ‘a pitfall in the diagnosis of diabetes mellitus’. Now the controversy has returned in the wake of the 1997 recommendations by the American Diabetes Association to exclude this test from routine diagnostic and screening efforts[2]. This discussion has expanded beyond the best method to determine the level of glycaemia that defines diabetes, and now embraces questions of the best glucose level to predict an increased risk of future diabetes or future cardiovascular disease. The paper by Qiao et al. in this issue[3] is one of several recent publications that re-examine the OGTT question.

The history of the OGTT is instructive. By the 1960s it was recognized that a fasting glucose test would miss many persons who had obvious diabetes when their glucose was measured after a test meal. This led to the development of at least six different recommendations for oral glucose loads ranging from 50 to 100 g without regard to body size[4–7], or based on ideal body weight[8] or body surface[9]. Most of these early tests for diabetes required both 1 and 2 h post-challenge blood draws, and the level of glycaemia required for a diagnosis of diabetes varied depending on the protocol. Only one of these early protocols included a fasting blood glucose[4], and this protocol (with the diagnosis of diabetes based on a point score) required four blood tests, one at 0, 1, 2 and 3 h after an OGTT.

Several reasons for not testing post-challenge glycaemia were recognized early, including the poor reproducibility of post-challenge (compared to fasting) glucose levels[10] and the striking effect of age on post-challenge (compared to fasting) glucose[8]. In fact, the high prevalence of diabetes in older adults when the diagnosis was based on post-challenge glucose led to a reluctance to accept the OGTT — on the grounds that so many people could not possibly have diabetes! This led to the clinical concept that only patients whose disease was severe enough to cause fasting hyperglycaemia really had diabetes.

Toward the end of the 1970s, clinical and epidemiologic data on the fasting and post-challenge glucose levels associated with diabetic retinopathy led to recommendations for a single unifying protocol, proposed almost concurrently by the National Diabetes Data Group in the United States[11] and the World Health Organization[12]. These groups (which had some overlapping membership) proposed nearly identical criteria for the diagnosis of Type 2 diabetes: a fasting plasma glucose of \( \geq 7.8 \text{ mmol} \cdot \text{l}^{-1} \) or a 2-hour glucose (post 75 gm glucose challenge) \( \geq 11.1 \text{ mmol} \cdot \text{l}^{-1} \). The committees added criteria for impaired glucose tolerance (IGT=2 hour post-challenge glucose 7.8 to 11.1 mmol \cdot l^{-1} with normal fasting glucose) to reflect studies showing levels associated with an increased risk of worsening to diabetes.

Over the next 20 years, studies showed that IGT was not only a risk factor for progression to diabetes[13–17], but also for cardiovascular disease[18]. In a 1998 review, George Alberti[19] concluded that ‘IGT has come of age.’

In 1997, the American Diabetes Association[2] proposed new criteria for diabetes, lowering the fasting plasma glucose to 7.0 mmol \cdot l^{-1}; they also recommended adding an impaired fasting glucose category (6.1 to 7.0 mmol \cdot l^{-1}), and removing the glucose challenge from medical practice. In 1999 the World Health Organization advanced similar criteria but was less restrictive about the use of the OGTT[20]. The rationale for these changes was complex, but the main purpose was to preclude the need for the unpleasant, inconvenient, and poorly reproducible OGTT by lowering the fasting plasma glucose to a level that was expected to include most persons whose OGTT would be 11.1 mmol \cdot l^{-1} or greater. It was hoped that eliminating the OGTT would lead more individuals to be screened, diagnosed, and treated.

Unfortunately, the premise that 7.0 mmol \cdot l^{-1} fasting glucose is equivalent to 11.1 mmol \cdot l^{-1} or greater post-challenge glucose was based on few studies and included almost no older adults. It is now
abundantly clear that different populations show a wide range of the mean fasting plasma glucose corresponding to a ‘diabetic 2 h glucose level’. For example, the mean fasting plasma glucose corresponding to a 2-h glucose of 11·1 mmol·l⁻¹ or greater has been between 5·3 and 5·7 mmol·l⁻¹ in middle-aged Swedish Caucasians, Brazilian, and Chinese, 6·4 mmol·l⁻¹ in Northern Europeans, 6·8 mmol·l⁻¹ in Pima Indians and at least 7·1 mmol·l⁻¹ in South Asians. Further, a significant proportion of older adults have diabetes manifest only as isolated post-challenge hyperglycaemia, diabetes that would be missed if only fasting glucose were assessed.

After the 1997 ADA revision, many papers showed that the 2-h post challenge glucose levels predict the risk of future heart disease more effectively than fasting glycaemia. The paper by Qiao et al. in this issue, based on five Finnish cohort studies, shows that post-challenge glucose is a better predictor of CHD than fasting glucose, even in populations at very high risk of cardiovascular disease.

Is glycosylated hemoglobin an alternative? Probably not. Although it is more physiologic, and does not require fasting, drinking a glucose solution, or waiting hours for blood samples to be drawn, it is also expensive, not available in much of the world, and poorly standardized in most places where it is available. In 1984 Michaella Modan reported that 2-h post load glucose was superior to HbA1 (and fasting glucose) for the detection of diabetes, and a recent meta-analysis (of 34 studies with nearly 9000 subjects) found that only 42% of persons with diabetes by OGTT had a glycosylated hemoglobin level of 7-0% or higher.

The finding that post-challenge glucose identifies many individuals with diabetes who would be missed by fasting glucose or glycosylated hemoglobin is disappointing. Replacing the cumbersome, costly OGTT with a fasting glucose would have been welcomed by physicians and patients alike. It would have facilitated mass screening for early identification of persons at risk of diabetes and heart disease — shown to be preventable in high-risk individuals. The rules of screening for diagnosis or risk factor status are clear: quick, simple, cheap, reliable, valid, and acceptable to the population/patient. The OGTT does not fit any of these criteria very well. Nevertheless, it remains our most valuable tool for the early recognition of persons with diabetes or who are at increased risk for diabetes and heart disease. Clinical criteria based on family history, body size, ethnic group, and casual glucose may reduce the number who need to be tested but do not remove the advantages of the OGTT.

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References


Eur Heart J, Vol. 23, issue 16, August 2002
Fibrinogen — the key to familial CHD or just another shadow in Plato’s Allegory?

See doi:10.1053/euhj.2001.3117 for the article to which this Editorial refers.

Fibrinogen is one of the major determinants of platelet aggregation and when its level is elevated it is a risk for cardiovascular disease, independent of more traditional risk factors such as cigarette smoking, dyslipidemia, hypertension or diabetes. Fibrinogen and other procoagulatory plasma constituents might be the missing link to severe premature familial CHD. The latter condition may be caused to some extent by an accumulation of adverse risk factors based on unhealthy lifestyle, unfavourable genetics, or on both, but in some instances apparently it is unrelated to common risk factors. Is fibrinogen or another coagulation factor or an associated genetic polymorphism the key to this situation?

The problems each investigator trying to tackle this issue finds himself confronted with are difficulties in identifying patients with premature CHD unrelated to common risk factors, in recruiting relatives free of atherosclerosis, in finding a suited control population and, finally, in compensating for the host of factors influencing fibrinogen levels (Table 1).

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<th>Higher</th>
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<td>Women</td>
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<td>Sports participation</td>
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<td>Blacks</td>
<td>Oestrogen use</td>
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<td>Cigarette smoking</td>
<td>Plasma triglycerides</td>
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<td>HDL-cholesterol</td>
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