Prediction of type 2 diabetes: A natural history perspective

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Introduction

Type 2, non-insulin dependent diabetes mellitus (NIDDM) is the most common form of diabetes and one of the most frequent metabolic disorders worldwide. About 5% of individuals of European ancestry are affected, while epidemics of NIDDM have recently appeared among non-white populations that have traditionally lived in harsh environmental conditions, once they had adopted a modern lifestyle. In such populations, which may soon include many rapidly developing middle eastern countries, the prevalence of NIDDM may be as high as 50% among the adults. In the relatively lower risk of Caucasian populations, the plasma glucose concentrations display a near-normal distribution. In high-risk populations such as Pima Indians of South-Western Arizona, USA, and the Micronesians of the South Pacific Island of Nauru, the frequency distribution of plasma glucose concentrations is bimodal, and the intersection of the two modes occurs near a plasma glucose concentration of 7.8 mmol/l fasting or 11.1 mmol/l 2 hours after an oral glucose tolerance test (OGTT). Furthermore, there is an increased frequency of microvascular diseases in the second mode, justifying the choice of these cut-off points for the diagnosis of diabetes.

The bimodal distribution of the plasma glucose concentration also means that diabetes in these populations might be caused by a major gene with a high frequency in the populations. This disorder is clearly becoming a burden to the public health systems of developing countries, causing an excess morbidity and mortality mainly through cardiovascular and cerebrovascular complications. NIDDM is believed to be a genetic disorder, whose expression is greatly affected by environmental factors. This disorder has an insidious onset and its characteristic over hyperglycaemia is preceded by a period of normoglycaemia associated with hyperinsulinaemia, which in itself is associated with macrovascular complications. Hyperglycaemia results from a combination of insulin resistance (decreased effectiveness of insulin on its target tissues) and impaired glucose secretion. Predicting this disorder at an early stage would help to initiate preventive measures, thus avoiding the morbidity and mortality associated with chronic hyperinsulinaemia and hyperglycaemia. Abnormalities found in both clinically overt disease and its prodromal phase could be used to identify those subjects who are likely to manifest overt hyperglycaemia during their lifetime. It would be most beneficial, however, to identify genetic carriers when no physiological alterations are present, i.e. at the time when environmental triggers can be avoided. In this paper, I will discuss the possibility of predicting NIDDM in the light of its natural history.
Natural history of Type 2 Diabetes

Cross-sectional and longitudinal studies in Pima Indians, Nauruans, and other populations have all found that type 2 diabetes progresses to overt hyperglycaemia through a series of characteristic stages. 6,8-10. A plot of plasma insulin levels versus glucose concentrations shows an inverted U relationship. Within the normoglycaemic range increasing plasma glucose levels are associated with increasing insulin concentrations. In the diabetic range, however, increasing glucose levels are associated with a progressive decrease in the plasma insulin concentrations. Maximal insulin concentrations typically correspond to glucose levels that define a category of glucose intolerance intermediate between normal and diabetic, viz. Impaired Glucose Tolerance (IGT). Plasma glucose level in IGT is below 7.8 mmol/l fasting, but between 7.8 and 11.1 two hours after ingestion of 75 grams of glucose.11 Studies using euglycemic hyperinsulinaemic clamp techniques to measure insulin sensitivity have demonstrated that the ascending, hyperinsulinaemic limb of the inverted U-curve is caused by the development of tissue insulin resistance, mainly in the skeletal muscle, and that hyperinsulinaemia at this stage is very compensatory response to preserve normoglycaemia.. 6,12 Insulin resistant subjects also have low metabolic rate,13 in spite of their hyperinsulinaemia probably because of the insulin resistance of muscle, the metabolically most active tissue. As a result, the development of IGT is usually associated with increasing body weight.

Insulin resistance in type 2 diabetes.

The total amount of glucose metabolized by the whole body in response to insulin (insulin-mediated glucose metabolism) is reduced by about 40% in NIDDM compared with normal subjects.6,8 Insulin mediated glucose metabolism is also reduced in normoglycaemic subjects at high risk for developing diabetes, eg. first-degree relatives of NIDDM patients, indicating pre-diabetic insulin resistance. 14,15 In a longitudinal study of Pima Indians the development of IGT was associated with a worsening of insulin resistance, but the same degree of insulin resistance was present during the transition from IGT to NIDDM.6 In addition, insulin resistance in this population may be genetically determined.16-18

The whole body glucose metabolism is mainly explained by its metabolism in skeletal muscle.19 Cellular pathways of glucose metabolism in this tissue have therefore been explored. In normal target cells, insulin action is initiated by insulin binding to its receptor in the plasma membrane. This is followed by activation of receptor-associated tyrosine kinase, which then initiates a cascade of reactions ending in glucose metabolism. 20,21 Under the influence of insulin a glucose transporter (GLUT4) present in muscle and fat cells facilitates glucose entry in to the cells, 22 while glycogen synthetase present in muscle and liver synthesizes glycogen from the glucose.23,24 In muscle, the insulin receptor tyrosine kinase has a low activity in NIDDM, but not in prediabetic insulin resistance, indicating that the kinase defect is secondary to the diabetic state.25,26 The stimulation of glycogen synthetase by insulin is defective in NIDDM as well as in prediabetic insulin resistance. 27-29 Moreover, our more recent studies in Pima Indians show a reduced activity of muscle
type-1 protein phosphatase, an enzyme that activates glycogen synthetase upon insulin stimulation.

**Insulin secretion in Type 2 Diabetes**

In most NIDDM patients the plasma concentrations of insulin in the fasting state and in response to glucose are usually in the normal range when considered in terms of absolute values. In fact, these insulin values are low for the prevailing glucose levels, and the inverted U-curve clearly shows a loss of the normal positive relationship between plasma glucose levels and insulin concentrations. Moreover, the insulin values in NIDDM are clearly subnormal when corrected for the cross-reactivity of proinsulin in the insulin assay. The early phase of insulin release during both the OGTT and intravenous glucose tolerance test (IVGTT) is reduced and the overall insulin release is delayed, which may contribute to the delay in post-prandial glucose metabolism in NIDDM. The early insulin response to non glucose secretagogues is not affected, but the glucose potentiation of the pancreatic response to these secretagogues is impaired. This selective glucose insensitivity is thought to result from the down-regulation of the beta-cell glucose-transporter (GLUT 2) by hyperglycemia ("a mechanism known as glucose toxicity"). GLUT2 constitutes with the enzyme glucokinase the so called “pancreatic glucose sensor system”. A new dimension of the pancreatic function was introduced by studies of the pulsatility of insulin secretion. Normal insulin secretion displays a pattern of rapid oscillations occurring every 10-15 minutes, and large-amplitude pulses released every 1-3 hours mostly during the post-prandial period. Subjects with NIDDM do not have this normal pattern of insulin delivery, which is thought to maximize insulin effectiveness: the rapid oscillations are gone and the post-prandial pulses are small and irregular.

Whether the pancreatic beta-cell function is normal in prediabetes is still controversial. In most subjects with prediabetic insulin resistance neither the first nor the second phase of insulin secretion is reduced, there is a characteristic hyperinsulinaemia both in the fasting state and after glucose stimulation. Recently, however, Mitakou et al reported reduced insulin levels 30 minutes after the ingestion of glucose in subjects with IGT. In fact, many of these subjects had a 2-hour plasma glucose of more than 11.1 mmol/l, i.e. diagnostic of diabetes. Also O’Rahilly et al reported abnormal pulsatile insulin secretion in first-degree relatives of patients with NIDDM at a time when their first-phase insulin response to intravenous glucose was still normal. Insulin sensitivity was not measured in this study. Since these subjects had (mild) glucose intolerance, they were probably also insulin resistant.

**Predictor of Type 2 diabetes**

It appears from the above discussion that the natural history of type 2 diabetes evolves in 4 main stages: genetic susceptibility, insulin resistance, IGT and overt diabetes. The temporal profile of insulin secretion in NIDDM, on the other hand, exhibits 3 main features: loss of pulsatility, disappearance the first phase, and diminished responsiveness to glucose. Eriksson et al have shown that insulin resistance precedes the alterations of the first-phase insulin secretion, leaving insulin resistance and loss of insulin secretion pulsatility as the earliest functional lesions in the course
A. Clinical and Physiological Predictors of NIDDM

Since the period preceding overt hyperglycemia is accompanied by physiological alterations (obesity, hyperinsulinemia, impaired glucose tolerance), these have been used as predictors of NIDDM in a few studies. It is a common belief that obesity, especially central or truncal obesity, predisposes to NIDDM. Studies in high risk populations have found that the predictive power of obesity for diabetes becomes negligible when other predictors such as plasma glucose and insulin, i.e. metabolic factors related to insulin resistance, are taken into account. 38,39

Insulin secretion pulsatility has not been used in predicting type 2 diabetes. However, Warram et al 40 found that, in contrast with glucose disposal rate (a measure of insulin action), the acute insulin response does not predict diabetes in glucose tolerant offspring of diabetic parents. In contrast, in individuals who already have IGT, hypoinsulinaemia predicts the development of NIDDM, as shown in Pima Indians, Nauruans, Japanese and Caucasians.32 In other studies, hypoinsulinaemia was less powerful predictor than insulin resistance, 41 offering support for the hypothesis that it is insulin resistance that remains the most important determinant of the development of type 2 diabetes. Plasma glucose concentration is a predictor of diabetes; the higher the glucose concentration the higher the risk of developing diabetes. In particular, IGT individuals have about a 6-fold increased risk of developing diabetes compared with individuals with normal glucose tolerance.3,4,39

Fasting plasma insulin levels have been found to predict the development of diabetes in Pima Indians, 41 Pacific Islanders3 and Mexican Americans.39 Subjects with fasting hyperinsulinaemia have about a 7-fold increased risk of developing diabetes. The predictive power of hyperinsulinaemia is no longer statistically significant when insulin resistance, as measured in vivo by clamp techniques, is taken into account. Studies using clamps in Pima Indians have demonstrated that insulin resistance per se is an independent predictor of the development of NIDDM.41 Clamp techniques are still considered too specialized and time consuming for clinical use. The simpler modified IVGTT may be an earlier substitute in the clinical setting, as it measures insulin sensitivity with a comparable accuracy.42 Assay of enzymes of the insulin action pathways may soon become available for the detection of insulin resistance.

B. Genetic predictors of type 2 diabetes

Genetic factors significantly contribute to the development of type 2 diabetes. The disorder shows a strong familial aggregation and 10 to 30% of first degree relatives of diabetic individuals are affected. The prevalence of this disorder varies among different ethnic groups living in the same environment. More importantly, its concordance rate has been found to be about 100% among monzygotic twins, whid 10 to 30% in dizygotic twins. 43,44 A recent population survey in Finland, however, suggests that the concordance rate of NIDDM in identical twins may be much lower than previously thought.45 Thus, although NIDDM is believed to be caused by a major gene in some populations, this may not be universal, and its mode of
inheritance remains unknown. There is no clear association with the HLA system as in type 1 diabetes.44

Analysis of molecular genetic materials has been pursued in recent years, mainly based on genes that code for known pathways of insulin secretion (insulin, GLUT2, glukokinase) and insulin action (insulin receptor, GLUT4, glycogen synthase), the so-called “candidate genes”. Polymorphism or mutations were rarely found in most of these genes in NIDDM subjects.43,44,46 Recently, polymorphisms in the glycogen synthetase47 and the glukokinase 48-50 genes were reported in subsets of NIDDM subjects but for the majority of the patients no genetic information is available.

**Conclusion**

For the clinicians, early prediction of NIDDM is based on historical data such as obesity and parental diabetes. The predictive power could be increased by additional diagnostic techniques such as OGTT or modified IVGTT with a determination of plasma insulin. IGT with its associated hyperglycaemia and hyperinsulinaemia is currently the best predictor of NIDDM. Future developments may allow routine assays of insulin-responsive enzymes such as glycogen synthase and type-1 protein phosphatase, whose biochemical defects are demonstrated early in the course of type 2 diabetes.

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