Characterization of the Prediabetic State
Leif Groop, Carol Forsblom, and Mikko Lehtovirta

First degree relatives of patients with non–insulin-dependent diabetes mellitus (NIDDM) have a 40% risk of developing NIDDM during their lifetime and the risk seems to be greater if the disease is inherited from the mother than from the father. It has also become clear that metabolic abnormalities are demonstrable long before the disease becomes manifest. The prediabetic state is associated with a predisposition to abdominal obesity, insulin resistance, lipid disorders, high blood pressure, and microalbuminuria, ie, the metabolic or insulin resistance syndrome. It is, however, not yet known whether treatment of these abnormalities is able to prevent progression to manifest NIDDM. Am J Hypertens 1997;10:172S–180S © 1997 American Journal of Hypertension, Ltd.

KEY WORDS: Non–insulin-dependent diabetes mellitus, insulin resistance, hypertension, prediabetes, microalbuminuria.

About 100 million people in the world suffer from non–insulin-dependent diabetes mellitus (NIDDM).1 It has been predicted that this figure will be doubled within 10 years. Although NIDDM is one of the most common noncommunicable diseases in the world, there are large ethnic and geographic variations in the prevalence of NIDDM. In Scandinavia, where IDDM is common, NIDDM accounts for 85% of all cases with diabetes mellitus. In Asia and Japan, where IDDM is rare, NIDDM accounts for most cases of diabetes mellitus. In certain ethnic populations like the Pima Indians and the Nauruans, the prevalence approaches 40%.2,3 Are these ethnic differences due to genetic or environmental factors?

EVIDENCE THAT NIDDM IS INHERITED

There is plenty of evidence that NIDDM is inherited. In a study of NIDDM in male twins, the concordance rate of NIDDM approaches 90% when both twins have been examined.4 The lifetime risk of developing NIDDM is about 40% if one parent has NIDDM,5 but if both parents have NIDDM, the risk for offspring may be as high as 70%. Despite this, no clear-cut Mendelian inheritance has been demonstrated for the disease. Whereas MODY (maturity-onset–diabetes mellitus of the young) in general follows a clear autosomal dominant mode of inheritance, the picture in NIDDM is less clear.

Another problem is that NIDDM seems to have a predominant maternal mode of inheritance in whites.6,7 After adjustment for age, Finnish NIDDM patients are 1.5 to 2 times more likely to have mothers than fathers with NIDDM.8 This is not observed in high risk populations such as Pima Indians and Mexican Americans.9

WHAT IS INHERITED IN NIDDM?

In general, both insulin resistance and impaired insulin secretion are required to manifest NIDDM.10,11 Insulin resistance could represent a primary genetic defect in skeletal muscle or develop as the consequence of obesity. Insulin resistance by itself cannot cause diabetes mellitus, with the exception of some rare conditions with insulin receptor mutations.12 As long as the β-cell can compensate for the degree of insulin resistance, glucose tolerance remains normal. There-
fore, impaired β-cell function is always involved in the pathogenesis of NIDDM.

It is important to remember that hyperglycemia per se can impair insulin sensitivity and β-cell function. A vicious cycle ensures by which hyperglycemia is maintained, a situation also referred to as glucose toxicity.13 Because subjects with manifest hyperglycemia usually display all defects of diabetes mellitus it is not possible from studying NIDDM patients to decide what is inherited and what is acquired in NIDDM. To circumvent this problem we14 and others15,16 have studied persons at risk of NIDDM: that is, first-degree relatives of patients with NIDDM.

THE BOTNIA STUDY

The Botnia study represents a large family study in Western Finland that was started in 1990 to identify early metabolic defects in families with NIDDM and to relate these metabolic defects to alterations in DNA. The region was settled about 1,000 years ago by Swedish and Finnish ancestors, whose descendants have remained in this area ever since. Approximately 4,500 family members, including 1,250 patients with NIDDM from 750 families, have been studied to date. Six hundred spouses without a family history of NIDDM served as controls. In this paper we will compare nondiabetic first-degree relatives of patients with NIDDM (REL) with their nondiabetic spouses (CON) sharing the same environment.8

TABLE 1. CLINICAL CHARACTERISTICS OF FEMALE FIRST-DEGREE RELATIVES OF PATIENTS WITH NIDDM AND FEMALE CONTROL SUBJECTS WITHOUT A FAMILY HISTORY OF NIDDM

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Relatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>274</td>
<td>1,072</td>
</tr>
<tr>
<td>Age (years)</td>
<td>50 ± 14</td>
<td>51 ± 15</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.6 ± 4.3</td>
<td>26.0 ± 4.6</td>
</tr>
<tr>
<td>FFM (kg)</td>
<td>47 ± 7</td>
<td>47 ± 7</td>
</tr>
<tr>
<td>WHR</td>
<td>0.82 ± 0.07</td>
<td>0.84 ± 0.05</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>127.5 ± 17.4</td>
<td>131.6 ± 19.7</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>77.1 ± 8.6</td>
<td>78.6 ± 9.8</td>
</tr>
<tr>
<td>FBG (mmol/L)</td>
<td>4.9 ± 0.1</td>
<td>5.0 ± 0.6</td>
</tr>
<tr>
<td>Glucose area</td>
<td>144 ± 123</td>
<td>190 ± 141</td>
</tr>
<tr>
<td>β-insulin (pmol/L)</td>
<td>48 ± 30</td>
<td>49 ± 29</td>
</tr>
<tr>
<td>Insulin area (pmol/L)</td>
<td>34 ± 19</td>
<td>42 ± 26</td>
</tr>
</tbody>
</table>

Values are mean ± SD. Abbreviations: BMI, body mass index; FFM, fat-free mass; WHR, waist–hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; β-insulin, fasting serum insulin.

FIGURE 1. Influence of a family history of NIDDM on energy expenditure. FH+, family history of NIDDM; FH−, no family history of NIDDM. Standard errors of the mean (SEM) are indicated above the bars.

OBESITY

Obesity is considered to be a risk factor for NIDDM, but the question is whether a family history of NIDDM is a risk factor for weight gain and obesity. To address this question we compared anthropometric measurements and metabolic rates between REL and CON from the Botnia study (Table 1). Despite similar body mass index (BMI) and total body fat, women and men with a family history of NIDDM had greater waist–hip ratios (WHR) than did their spouses without a family history of NIDDM.8 This increase in abdominal obesity in first-degree relatives of patients with NIDDM was independent of the degree of glucose tolerance and was seen across all quartiles of 2 h glucose values during an oral glucose tolerance test.

Indirect calorimetry with measurements of metabolic rates in the basal and insulin-stimulated state (clamp) was performed in a subset of the subjects. The metabolic rates expressed per kilogram of fat-free mass was decreased in REL as compared with CON, but this difference disappeared when data were adjusted for differences in WHR (Figure 1). Taken together these data suggest that a family history of NIDDM influences body fat distribution and energy expenditure. Therefore, it is quite possible that a family history of NIDDM is a risk factor for abdominal obesity and weight gain through a reduced energy expenditure.

INSULIN RESISTANCE

Insulin resistance can be defined as a condition in which insulin is no longer able to exert a normal
biological effect on the three major substrates, glucose, free fatty acids, and amino acids in target tissues such as skeletal muscle, adipocytes, and liver. Quantitatively, the glucoregulatory effect of insulin on skeletal muscle is the most important determinant of whole-body insulin sensitivity.

Using the euglycemic clamp technique we quantitated insulin sensitivity in REL and CON and in patients with NIDDM (Figure 2). As shown in Figure 2, the persons with a family history of NIDDM showed a 30% reduction in their rate of insulin-stimulated glucose metabolism, which is in the same range as found in other studies.15–17 It should be kept in mind that not every first-degree relative of an NIDDM patient is insulin-resistant. If insulin resistance is defined as the mean ± the standard deviation (SD) of the CON group, approximately 45% of the REL group, compared with 20% of the CON group, is insulin resistant.8 After entering the cell the glucose is phosphorylated to glucose-6-phosphate. Thereafter it can take one of two pathways: it can either go through glycolysis and Krebs cycle to produce ATP, CO2, and H2O, or be stored as glycogen (Figure 3). The studies were combined with indirect calorimetry, which allowed us to obtain separate estimates of glucose oxidation and glucose storage (>90% glycogen synthesis in skeletal muscle). Glucose oxidation was normal in the prediabetic state; therefore, the defect in glucose metabolism was evidently due to a marked impairment in the rate of glycogen formation. This, in turn, was associated with impaired stimulation of the key enzyme of this pathway, glycogen synthase, but this does not localize a priori the defect to the glycogen synthase step. Studies using the NMR technique have shown decreased rather than increased levels of glucose-6-phosphate after insulin stimulation in offspring of NIDDM patients, suggesting that the defect may be at the level of glucose transport/phosphorylation.16 If glycogen synthase was rate limiting one would expect an increase in glucose-6-phosphate. However, exercise normalized the phosphorylation step, leaving glycogen synthesis.19 This, in turn, would imply that there is an inherited defect in the glycogen synthase step in nondiabetic relatives of patients with NIDDM.

In studies in Pima Indians an increased, rather than decreased, rate of glucose oxidation in association with a decreased metabolic rate has been considered a risk factor for subsequent weight gain.20 With the accumulation of body fat (especially in the abdominal region), more free fatty acids (FFA) are provided for oxidation, and the body may switch from using preferentially glucose to fat for oxidation. Longitudinal studies are required to confirm whether this hypothesis is correct.

HETEROGENEITY OF INSULIN RESISTANCE

Contrary to earlier views, not all NIDDM patients are insulin resistant. Insulin resistance is primarily seen in patients with hypertension and/or microalbuminuria21,22 (Figure 4). Insulin resistance is associated with essential hypertension independently of glucose tolerance,23 and this link seems to be under genetic control. Offspring of hypertensive patients are more insulin resistant than offspring of normotensive patients. First-degree female relatives of patients with NIDDM had higher blood pressure than did women without a family history of NIDDM.8 Similarly, nondiabetic persons with increased albumin excretion rate (AER) are more insulin resistant than persons with normal AER.24

In contrast, many normotensive NIDDM patients with normal AER show an almost normal insulin sensitivity, provided that their glucose control is not severely deteriorated. Some of these patients may represent subgroups characterized by unique genetic defects such as MODY325 or NIDDM2.26

THE INSULIN RESISTANCE SYNDROME

Taken together these data suggest that insulin resistance is not unique to NIDDM, as it is also observed in association with hypertension,23 hypertriglyceridemia,27 abdominal obesity,8 microalbuminuria,21,22,24

FIGURE 2. Insulin sensitivity in NIDDM patients and in subjects with (FH+) and without (FH−) a family history of NIDDM. Open areas, glucose oxidation; shaded areas, nonoxidative glucose metabolism. FBG, fasting blood glucose; BMI, body mass index. *P = .002; **P = .0001. Standard errors of the mean (SEM) are indicated above the bars.
and hyperuricemia. These conditions tend to cluster together. This syndrome has been referred to as syndrome X, or the insulin resistance syndrome, which suggests that insulin resistance is a common denominator for the different components (Figure 5). The sequence of events by which insulin resistance would lead to these abnormalities is not clear. Nevertheless, the simultaneous occurrence of these conditions is associated with a markedly increased risk for cardiovascular disease.

**BLOOD FLOW AND INSULIN RESISTANCE**

Decreased capillary density has been found in muscle biopsies from obese, insulin-resistant Pima Indians. Theoretically, impaired transport of substrates and insulin to the target tissue through reductions in blood flow could explain insulin resistance. Three findings argue against a major role for blood flow in determining insulin-stimulated glucose metabolism in skeletal muscle. First, the defect in glycogen synthesis is demonstrable in cultured fibroblasts and muscle cells from patients with NIDDM. Second, impaired blood flow should affect the effect of insulin on all substrates in the same way. This is not the case. Third, it was observed in a prospective study that increased rather than decreased capillary density preceded the development of NIDDM, suggesting an attempt to compensate for an intracellular defect in glucose metabolism.

**THRIFTY GENOTYPE**

Why do insulin resistance, obesity, and NIDDM markedly increase in populations switching from a rural to an urban lifestyle? The thrifty gene hypothesis was put forward in 1962 by Neel who proposed that individuals living in a harsh environment with unstable food supply would maximize their probability of surviving if they could maximize storage of surplus energy. Genetic selection would favor energy conserving genotypes in such environments. Storage of energy as fat, especially as intra-abdominal fat, is a more efficient way of storing energy than as glycogen in skeletal muscle. Support for this hypothesis comes from a study in the obese and diabetic mouse. Normal weight heterozygous animals (only homozygous animals will develop obesity or diabetes mellitus) survived longer during total fasting than did their insulin-sensitive littermates. When this energy storing genotype is exposed to the abundance of food typical of the Western society, it becomes detrimental, causing insulin resistance, obesity, glucose intolerance, and NIDDM.

**ABDOMINAL OBESITY AND INSULIN RESISTANCE**

As pointed out earlier, both abdominal obesity and insulin resistance are under genetic control in relatives of patients with NIDDM. These two variables are also found to be strongly related regardless of whether the
The amount of intraabdominal fat is measured by computed tomography (CT) scan or WHR (Figure 6). What is the “chicken” and what is the “egg” in this scenario? Although abdominal obesity and insulin resistance could be coincidental expressions of a third unknown factor, the possibility that they are causally related must be considered. Abdominal fat tissue could provide a signal for the chain of events leading to skeletal muscle insulin resistance. One such candidate could be the recently described fat tissue hormone leptin. However, although leptin shows a strong positive correlation with total fat mass, there is no correlation with WHR. Intraabdominal free fatty acid (FFA) metabolism is relatively resistant to the effect of insulin in persons with abdominal obesity. Instead, the β3-adrenergic receptor of visceral fat is sensitive to stimulation by catecholamines. This in turn will ensure a large supply of FFA to the portal vein for further transport to the liver and other tissues such as muscle. In contrast, lipolysis in subcutaneous fat is more sensitive to the inhibitory effect of insulin, which will favor reesterification of FFA to triglycerides. Changes in the β3-adrenergic receptor could alter this scenario. A mutation in the first intracellular loop of the β3-receptor (Arg64Trp) was recently demonstrated. Pima Indians and Japanese with the mutation had a lower metabolic rate than did those with the Trp alleles. Moreover, there was a greater weight gain in French subjects with the mutation. After the initial report, several studies have shown that persons with the Arg64 mutation are more insulin resistant than are those with the Trp64 Trp genotype. There are still a number of unanswered questions regarding the role of the β3-receptor gene as a thrifty gene. The biological consequences of the mutation on visceral fat lipolysis have been small. On the other hand, some recent studies have linked the β3-receptor with an agonist results in ectopic expression of the ucp gene in white adipose tissue and an increased metabolic rate in rodents, which normally express the ucp gene only in brown adipose tissue. In fact, preliminary data suggest that there may be an interaction between the Arg64 mutation and a polymorphism in the promoter region of the ucp gene.

Finally, an increased supply of FFA in abdominal fat could result in increased FFA uptake and reesterification in muscle. In fact, increased intramuscular triglyceride concentrations have been reported in patients with NIDDM, and changes in fatty acid composition of the muscle cell membrane have been reported in insulin-resistant individuals. In experimental animals, the muscle triglyceride content correlates with the rate of insulin-stimulated glucose metabolism. An increased FFA turnover within the muscle could, through activation of the FFA/glucose cycle, lead to impaired insulin-stimulated glycogen synthesis. In this sequence of events, intraabdominal obesity would be the consequence of attempts to conserve and store energy. In this scenario, skeletal muscle insulin resistance would be secondary to abdominal obesity.

**INSULIN SECRETION**

There is still an intensive debate as to whether insulin resistance or impaired insulin secretion represents the

![FIGURE 4. Rates of insulin-stimulated total glucose metabolism (shown by the total height of the bars), glucose oxidation (open areas) and nonoxidative glucose metabolism (shaded areas) in normotensive and hypertensive NIDDM patients with (MA+) and without (MA−) microalbuminuria. Values are mean ± SEM. *P < .001, significantly different from control subjects; +, P < .05, significantly different from NIDDM patients with normal blood pressure and normal albumin excretion rate. LBM, lean body mass. Reproduced from Groop et al.](https://academic.oup.com/ajh/article-abstract/10/S6/172S/161819)
primary defect in NIDDM. This is, to some extent, an artificial debate. If one defect is timely manifested before another, for example, insulin resistance preceding impaired \( \beta \)-cell function, it does not mean that insulin resistance is inherited and impaired \( \beta \)-cell function acquired. Both defects can be inherited, although the presence of the former is a prerequisite for the manifestation of the latter. Inability to detect the 'inborn error' may be due to error of methods rather than of metabolism. The methods used to measure insulin secretory capacity are usually less refined than are the methods used to measure insulin sensitivity, which means that subtle, early defects in insulin secretion may be overlooked. Available data suggest that the 2 h blood glucose value during an oral glucose tolerance test must rise above 9 mmol/L before any defects in any secretion become discernible. Interestingly, this value coincides with the 2 h glucose value indicating gestational diabetes mellitus.

Some patients show a more severe degree of insulin deficiency than do the majority of NIDDM patients. Approximately 10% to 15% of patients above the age of 40 who are diagnosed with diabetes mellitus and initially treated with diet and oral antidiabetic agents have islet cells (ICA) or glutamic acid decarboxylase (GAD) antibodies. They are often women with other endocrine disorders, and most of them will require insulin treatment sooner or later. The patients represent a subgroup of IDDM rather than of NIDDM and have therefore been called latent autoimmune diabetes mellitus in adults (LADA). It seems justified to consider LADA as a unique disease entity, as the genetic background seems to differ from that in early-onset IDDM.

WHAT PREDICTS PROGRESSION TO NIDDM?

In the transition from normal to impaired glucose tolerance and NIDDM, only a moderate deterioration of insulin sensitivity is observed, whereas insulin secretion deteriorates in the transition from impaired glucose tolerance (IGT) to diabetes mellitus. Despite this, studies aiming at identifying predictors of NIDDM have given discrepant results. Insulin-resistant offspring of conjugal parents from the Joslin clinic in Boston had a 80% risk of developing diabetes mellitus during a 25-year follow-up period. In contrast, three studies have shown that both impaired early insulin response to an oral and intravenous glucose tolerance test,
together with a hyperinsulinemic response to the oral glucose tolerance test (OGTT)\textsuperscript{40} or insulin resistance as demonstrated with the euglycemic insulin clamp,\textsuperscript{63} predict diabetes mellitus. Taken together, available data clearly indicate that both insulin resistance and impaired $\beta$-cell function predict diabetes mellitus.

Importantly, NIDDM begins years and probably decades before the diagnosis is made based upon current WHO criteria. These criteria, which define the risk for developing microangiopathy, may have little predictive value for the risk to develop macroangiopathy, the “secret killer” of NIDDM. At diagnosis, already about 50% of the patients show hypertension or signs of macroangiopathy.\textsuperscript{67} NIDDM thus only represents the proverbial tip of the iceberg. We clearly come in on the stage in the epilogue of a Shakespearean tragedy, and it is no wonder therefore that the history of treatment of NIDDM has been a history of failures. The challenge for the future is—in analogy with the treatment of hypertension—to consider the prediabetic state as a pathological condition requiring early treatment, in the hope that this will prevent the devastating macrovascular complications.

**REFERENCES**


