Features of Syndrome X in First-Degree Relatives of NIDDM Patients

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OBJECTIVE — To determine whether the features of syndrome X are more common in first-degree relatives of non-insulin-dependent diabetes mellitus (NIDDM) patients than in control subjects with no family history of diabetes.

RESEARCH DESIGN AND METHODS — A total of 154 first-degree relatives from 60 families with two or more NIDDM patients and 154 age- and sex-matched control subjects were studied. All subjects underwent a 75-g oral glucose tolerance test and baseline lipid blood and anthropometric measures. The features of syndrome X that were studied were obesity, hypertension, dyslipidemia (high triglyceride levels and low high-density lipoprotein [HDL] cholesterol concentrations), impaired glucose tolerance (World Health Organization criteria), and insulin resistance (as assessed by the homeostasis model assessment).

RESULTS — Relatives were heavier than control subjects (body mass index 27.5 ± 5.2 vs. 25.2 ± 4.6 kg/m^2, respectively [mean ± SD], $P < 0.0002$), had lower HDL cholesterol concentrations (1.2 ± 0.3 vs. 1.4 ± 0.4 mmol/l, $P < 0.001$), were more insulin-resistant (2.3 [0.7–7.6] vs. 1.6 [0.5–5.1], geometric mean [95% confidence intervals], $P < 0.0001$), and had more individuals classified as having impaired glucose tolerance (28 of 154 [18%] vs. 7 of 154 [7%], χ^2, $P < 0.001$). The differences in insulin resistance and HDL cholesterol concentrations between the groups were independent of obesity.

CONCLUSIONS — Features of syndrome X occur more frequently in relatives of NIDDM patients than in control subjects with no family history of diabetes.

It is now well recognized that obesity, hypertension, dyslipidemia, and abnormal glucose tolerance frequently coexist in the same individuals (1). Insulin resistance is a common factor associated with these conditions, and together this clustering of cardiovascular risk factors is known as syndrome X (2).

First-degree relatives of non-insulin-dependent diabetes mellitus (NIDDM) patients have a 40% lifetime risk of developing diabetes (3); this risk becomes greater when there are two or more diabetic family members. Insulin resistance has been implicated as a major factor in the pathogenesis of NIDDM (4). As insulin resistance may be the common underlying defect in both syndrome X and NIDDM, we determined whether the features of syndrome X were more common in first-degree relatives of NIDDM patients than in control subjects with no family history of diabetes.

RESEARCH DESIGN AND METHODS

We studied 154 first-degree relatives of NIDDM patients identified from 60 Caucasian families with two or more living first-degree relatives with the disease. These subjects were closely matched for age and sex with 154 control subjects who had no family history of diabetes and were chosen from a population-based sample recruited in Newcastle upon Tyne. Informed written consent was obtained from all the participants, and the study was approved by the Newcastle Health Authority and University of Newcastle upon Tyne Joint Ethics Committee.

After an overnight fast, blood samples were taken to measure serum lipids, serum insulin, and blood glucose, after which a 75-g oral glucose tolerance test was performed. Serum cholesterol and serum triglyceride concentrations were measured using commercial kits (Roche, U.K.). High-density lipoprotein (HDL) cholesterol was isolated after precipitation of apolipoprotein B containing lipoproteins with heparin and manganese. The supernatant HDL cholesterol was then measured, as described above. Blood glucose was measured by the glucose oxidase method (YSI, Yellow Springs, OH). Serum insulin concentrations were determined using a two-site

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HDL, high-density lipoprotein; HOMA, homeostasis model assessment; NIDDM, non-insulin-dependent diabetes mellitus.

Table 1—*Features of syndrome X in relatives of NIDDM patients and control subjects with no family history of diabetes*

	Relatives	Control subjects	*P* values
Age (years)	39 ± 10	41 ± 10	NS
Sex (M/F)	68/86	74/80	NS
Body mass index (kg/m^2)	27.5 ± 5.2	25.2 ± 4.6	0.0002
Systolic BP (mmHg)	126 ± 16	125 ± 15	NS
Diastolic BP (mmHg)	78 ± 11	76 ± 10	NS
Triglycerides (mmol/l)	1.3 ± 0.9	1.2 ± 0.7	NS
HDL cholesterol (mmol/l)	1.2 ± 0.3	1.4 ± 0.4	0.001
Insulin resistance (HOMA) (mmol · mU^{-1} · l^{-2})	2.3 (0.7–7.6)	1.6 (0.5–5.1)	0.0001

Data are means ± SD and (for insulin resistance) geometric mean (95% confidence interval). Analysis performed by Student's *t* test. BP, blood pressure.

monoclonal enzyme-linked immunosorbent assay highly specific for intact human insulin (5). Insulin resistance was calculated from fasting blood glucose and serum insulin concentrations using the computer-solved homeostasis model assessment (HOMA) method described by Matthews et al. (6). The features of syndrome X considered in this study were obesity, hypertension (systolic and diastolic), serum lipids (triglyceride concentrations and HDL cholesterol concentrations), impaired glucose tolerance, and insulin resistance.

Statistical analysis

The Student's *t* test was used to compare variables between the relatives and controls. The results are expressed as mean ± SD except for HOMA values, which were log-transformed to normalize distribution and expressed as geometric means with confidence intervals. The χ^2 test was used to compare the number of individuals in each group with impaired glucose tolerance. Analysis of variance was performed to correct for difference in body mass index using the General Linear Model on Minitab Statistics.

RESULTS — The results show that the relatives were heavier, more insulin resistant, and had lower HDL cholesterol concentrations than the control subjects (Table 1). After correction for body mass index, the relatives were still more insulin resistant ($P < 0.02$) and had lower HDL cholesterol concentrations than the control subjects ($P < 0.03$). The relatives were also more likely to have impaired glucose tolerance than the control subjects (28 of 154 [18%] vs. 7 of 154 [5%], $P < 0.001$).

CONCLUSIONS — This study has shown that first-degree relatives of NIDDM patients have more features of syndrome X (specifically higher weight, insulin resistance, lower HDL cholesterol concentrations, and impaired glucose tolerance) than in age- and sex-matched individuals with no family history of diabetes.

McCance et al. (7) have recently found that weight was the variable most strongly associated with parental diabetes and was highly predictive of the development of diabetes in adolescent Pima Indians. The importance of the present study is that although the relatives were heavier than the control subjects, the relatives were still more insulin resistant and had lower HDL cholesterol concentrations after correcting for obesity. Insulin resistance may be the common link between NIDDM and syndrome X. Insulin resistance has been shown to predict the development of NIDDM in unaffected first-degree relatives (8), and Haffner et al. (9) demonstrated that elevated insulin levels precede the development of the other features of syndrome X, including lower HDL cholesterol concentrations. Although blood pressure was not elevated in the relatives or the control subjects, there is evidence to suggest that prehypertensive individuals have metabolic abnormalities before the development of their hypertension (10). Thus the lack of difference in blood pressure between the groups may represent a "prehypertensive" phase in the relatives and may also be accounted for by their relatively young age.

In conclusion, first-degree relatives of NIDDM patients who are at risk of developing diabetes have more features of syndrome X than control subjects with no family history of diabetes. The underlying defect in the two conditions may well be insulin resistance. It is important to identify family members of NIDDM patients with features of syndrome X because of the increased risk of developing coronary heart disease and diabetes.

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