Early Abnormalities in Coronary Heart Disease Risk Factors in Relatives of Subjects With Non–Insulin-Dependent Diabetes

Helena Sarlund, Kalevi Pyörälä, Ilkka Penttilä, and Markku Laakso

Coronary heart disease risk factor levels were studied in 184 first-degree relatives (sisters and brothers) of non-insulin-dependent diabetic subjects (124 relatives with normoglycemia, 34 relatives with impaired glucose tolerance [IGT], and 26 relatives with non-insulin-dependent diabetes mellitus [NIDDM]) and in 215 relatives of nondiabetic subjects (194 relatives with normoglycemia and 21 relatives with IGT). Subjects with IGT exhibited the highest insulin responses to an oral glucose load. Systolic blood pressure was significantly higher; serum high density lipoprotein cholesterol level was significantly lower; and total, low density lipoprotein, and very low density lipoprotein triglyceride levels were higher in the relatives with a family history of diabetes who had IGT or NIDDM than in the normoglycemic relatives without a family history of diabetes. These abnormal changes were not seen in normoglycemic relatives or relatives with IGT who had no family history of NIDDM. Thus, in relatives of diabetics, abnormal glucose tolerance seems to induce changes in cardiovascular heart disease risk factor levels that are similar to those observed in NIDDM. Therefore, a family history of diabetes adds substantially to the risk for atherosclerosis, particularly in subjects with IGT. (Arteriosclerosis and Thrombosis 1992;12:657–663)

KEY WORDS • coronary heart disease • impaired glucose tolerance • non–insulin-dependent diabetes mellitus • cardiovascular risk factors

Subjects with non–insulin-dependent diabetes mellitus (NIDDM) are at increased risk for the development of atherosclerotic vascular complications. At the time of diagnosis, the existence of atherosclerotic manifestations is already widespread, and furthermore, the prevalence of coronary heart disease shows virtually no correlation with the duration of NIDDM. Although the etiology of this excess risk is largely unexplained, many cardiovascular risk factors are abnormally high in patients with NIDDM. In particular, these factors include hypertension or elevated blood pressure levels, hyperinsulinemia, high serum total and very low density lipoprotein (VLDL) triglyceride levels, and low serum high density lipoprotein (HDL) cholesterol and apolipoprotein A-I levels.

It is widely accepted that frank clinical NIDDM is preceded by a long prediabetic stage. Impaired glucose tolerance (IGT), which can be assessed by an oral glucose tolerance test, is a widely accepted entity of the prediabetic stage. It is commonly believed that IGT represents a transitional stage between normal and diabetic glucose tolerance. Moreover, IGT is also a risk factor for cardiovascular disease, either by itself or as a consequence of its presumed precursor relation to diabetes. IGT is not, however, a homogeneous condition, and only some of these subjects are in the transition to frank diabetes. Although it is impossible by any clinical or laboratory means to identify different subtypes of IGT, those individuals having an IGT and a family history of NIDDM could be at greater risk for developing diabetes and atherosclerosis than are those individuals without any family history of NIDDM. Therefore, it could be expected that normoglycemic and IGT subjects with a family history of diabetes would have more aberrations in their cardiovascular risk factor profile than do corresponding subjects without a family history of diabetes. However, surprisingly few data exist with respect to the coronary heart disease risk factor levels of the relatives of diabetics, and these limited data are based on a study of Mexican-Americans, a hyperinsulinemic population with a high frequency of NIDDM. To investigate this issue in a population whose prevalence of NIDDM is of the same magnitude as that in many other westernized populations, we studied the insulin responses after an oral glucose load, serum lipid, lipoprotein, and apolipoprotein A-I and B concentrations, and blood pressure levels in the siblings of diabetic and nondiabetic probands.

Methods

This investigation is part of a larger study of the risk factors and prevalence of coronary heart disease in the first-degree relatives of non–insulin-dependent diabetics with and without coronary heart disease. The original study population consisted of 1,113 probands, their spouses, siblings, and children. The probands (114...
men, 47 women) were randomly selected from a previous study of the prevalence of coronary heart disease and its risk factors in 564 45–64-year-old patients with NIDDM and 649 nondiabetic control subjects in the Kuopio University Hospital district, East Finland. This study reports the levels of cardiovascular risk factors in 184 siblings (sisters and brothers; 80 men, 104 women) of 85 probands with NIDDM and 215 siblings (85 men, 130 women) of 76 probands without NIDDM grouped by glucose tolerance status. The probands without NIDDM did not have a family history of diabetes. All diabetic subjects fulfilled the World Health Organization diagnostic criteria for NIDDM. Of 26 patients with NIDDM, 18 were being treated with orally administered drugs and eight with diet only.

The subjects were classified as having IGT if the fasting plasma glucose level was less than 8.0 mmol/l and if the 2-hour plasma postglucose load value was between 8.0 and 11.0 mmol/l or as having normal glucose tolerance if both fasting and 2-hour plasma postglucose load values were less than 8.0 mmol/l, according to the criteria of the World Health Organization. None of the subjects received hypolipidemic drug therapy or had any renal, hepatic, or thyroid disease affecting glucose or lipid metabolism.

Methods

The study program included an interview to assess the history of smoking, alcohol intake, physical activity, and the use of medications. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. Blood pressure was measured with a mercury sphygmomanometer with the subject in a sitting position (after a 5-minute rest) and was read to the nearest 2 mm Hg. An oral glucose tolerance test was performed in the morning after a 12-hour fast by administration of a 75-g glucose load. The blood samples for the determination of plasma glucose and insulin values were taken before and 1 and 2 hours after the glucose load. Plasma glucose was determined by the glucose dehydrogenase method (Merck Diagnostica, Darmstadt, FRG) and plasma insulin by a commercial double-antibody solid-phase radioimmunoassay (Phadeseeph, Pharmacia Diagnostics, Uppsala, Sweden). Samples for the determination of serum lipids, lipoproteins, and apolipoproteins were taken after a 12-hour fast but before the oral glucose tolerance test. Lipid and lipoprotein values were determined from fresh, unfrozen serum samples. Lipoprotein fractionation was performed using ultracentrifugation at 10°C with a Kontron TGA 65 ultracentrifuge and selective precipitation.22

VLDL subfraction was selected by centrifuging the serum samples at 11,000 g/ml (105,000g for 18 hours). HDL was determined directly with dextran sulfate and magnesium chloride precipitation. Low density lipoprotein (LDL) cholesterol was calculated as the difference between total serum cholesterol and the determined subfraction values. Cholesterol and triglyceride levels were determined by enzymatic methods (Boehringer GmbH, Mannheim, FRG). Apolipoprotein A-I and B contents were determined by a commercial immunoturbidimetric method (Orion Diagnostica, Helsinki, Finland).

Statistical Analysis

Data are presented as mean±SEM. First, all five groups of siblings were compared by the analysis of covariance (ANCOVA) after adjustment for age, sex, and BMI (NGT/D−, normal glucose tolerance and no family history of diabetes; NGT/D+, NGT and a family history of diabetes; IGT/D−, IGT and no family history of diabetes; IGT/D+, IGT and a family history of diabetes; and NIDDM/D+, NIDDM and a family history of diabetes). If the groups differed significantly (p<0.05), all other groups of relatives were compared separately with the NGT/D− group by ANCOVA with age, sex, and BMI as covariates. Finally, the IGT/D− and IGT/D+ groups were compared by ANCOVA using age, sex, and BMI as covariates. Data for men and women were combined because no significant gender differences in cardiovascular risk factors were found by glucose tolerance status. Comparisons of serum total and VLDL triglyceride and plasma insulin values were done after logarithmic transformations. Correlations were calculated by Pearson’s correlation coefficients. Statistical analyses were carried out using the SPSSX programs.

Approval of Ethics Committee

This study was approved by the Ethics Committee of the Kuopio University Central Hospital.

Results

Characteristics of the Study Groups

Characteristics of the study groups are given in Table 1. The relatives of the IGT groups and the NIDDM group were significantly older than the relatives of the NGT/D− group. The relatives of the IGT/D+ group and the NIDDM/D+ group were significantly more obese and had higher systolic blood pressures than the relatives of the NGT/D− group. After exclusion of the data for previously diagnosed and treated hypertensive subjects, systolic blood pressure was still significantly higher in both IGT groups and diastolic blood pressure was higher in the relatives of the IGT/D− group than in the relatives of the NGT/D− group. Despite normal glucose tolerance, the 1-hour plasma glucose level was significantly higher in the relatives of the NGT/D+ group than in the relatives of the NGT/D− group. No differences among the study groups were found in alcohol intake, smoking habits, or physical activity.

Plasma Insulin Levels

Age-, sex-, and BMI-adjusted fasting plasma insulin levels were significantly higher in both IGT groups and the NIDDM/D+ group than in the control group (Figure 1A). Two-hour insulin levels were highest in the relatives with IGT (Figure 2, lower panel).

Serum Lipids, Lipoproteins, and Apolipoproteins

Unadjusted levels of serum lipids, lipoproteins, and apolipoproteins A-I and B are shown in Table 2. Serum total and LDL cholesterol levels did not differ among the study groups. Serum HDL cholesterol level was significantly lower in all groups of relatives with a family history of diabetes compared with the NGT/D− group. Serum VLDL cholesterol level and serum total and lipoprotein triglyceride levels were significantly higher.
TABLE 1. Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NGT/D−</th>
<th>NGT/D+</th>
<th>IGT/D−</th>
<th>IGT/D+</th>
<th>NIDDM/D+</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men/women</td>
<td>76/118</td>
<td>53/71</td>
<td>9/12</td>
<td>17/17</td>
<td>10/16</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>53.6±0.7</td>
<td>55.3±0.9</td>
<td>61.5±1.7t</td>
<td>57.7±1.5t</td>
<td>59.2±1.6t</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.6±0.3</td>
<td>27.1±0.4</td>
<td>27.7±0.6</td>
<td>29.8±0.7t</td>
<td>29.0±0.9t</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting glucose (mmol/l)</td>
<td>5.1±0.1</td>
<td>5.2±0.1</td>
<td>5.4±0.2</td>
<td>5.9±0.1§</td>
<td>10.7±0.7§</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1-Hour glucose (mmol/l)</td>
<td>6.9±0.1</td>
<td>7.8±0.2§</td>
<td>11.0±0.5§</td>
<td>11.2±0.4§</td>
<td>20.2±1.2§</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2-Hour glucose (mmol/l)</td>
<td>5.5±0.1</td>
<td>5.8±0.1</td>
<td>9.1±0.2§</td>
<td>9.2±0.1§</td>
<td>19.9±1.5§</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>145±2</td>
<td>144±2</td>
<td>155±4</td>
<td>165±2§</td>
<td>161±4t</td>
<td>0.01</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>86±1</td>
<td>85±1</td>
<td>93±2†</td>
<td>91±2†</td>
<td>90±2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Alcohol intake (g/wk)</td>
<td>40±5</td>
<td>39±7</td>
<td>48±27</td>
<td>42±3</td>
<td>19±2</td>
<td>NS</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>17.0</td>
<td>14.5</td>
<td>9.5</td>
<td>23.5</td>
<td>15.4</td>
<td>NS</td>
</tr>
<tr>
<td>Physically active (%)</td>
<td>73.2</td>
<td>72.6</td>
<td>76.2</td>
<td>67.7</td>
<td>80.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean±SEM.
NGT, normal glucose tolerance; IGT, impaired glucose tolerance; NIDDM, non–insulin-dependent diabetes mellitus; D−, nondiabetic proband; D+, diabetic proband.
* Difference over the five groups (χ² test or analysis of variance).
†p<0.05, §p<0.01, †p<0.001 compared with the NGT/D− group (Student's two-tailed t test).

in the relatives of the IGT/D+ group and the NIDDM/D+ group than in the NGT/D− group. No significant differences were found in serum apolipoprotein A-I and B levels among the five study groups.

The lipoprotein fractions that differed among the five groups are shown in Figures 2 and 3 after adjustment for age, sex, and BMI. All differences given in Table 2 remained statistically significant.

Fasting insulin level was inversely correlated with HDL cholesterol in all five groups of relatives (Table 3). Furthermore, fasting insulin level had a significant positive correlation with LDL and VLDL triglycerides in a majority of these groups. Two-hour insulin levels were less strongly correlated with lipoprotein fractions. All correlations between VLDL cholesterol and insulin levels failed to reach statistical significance.

Comparison of Relatives With Impaired Glucose Tolerance

The relatives of the IGT/D+ group were significantly more obese and had higher fasting plasma glucose levels and systolic blood pressure levels than the relatives of the NGT/D− group (p<0.05) (Table 1). Age-, sex-, and BMI-adjusted plasma insulin levels did not differ (fasting insulin, p=0.432; 2-hour insulin, p=0.827) between these two IGT groups (Figure 1), but the serum HDL cholesterol level was significantly lower in the relatives of the IGT/D+ group than in the relatives of the IGT/D− group (p<0.05, Figure 2). No other differences were found between the IGT groups with respect to lipids, lipoproteins, or apolipoproteins.

Discussion

The major finding of this study was that subjects with IGT and NIDDM had multiple abnormalities in their cardiovascular risk factor profiles if they had a family history of diabetes. They were more obese; had higher systolic blood pressures; higher insulin responses in the fasting state and after an oral glucose load; lower HDL cholesterol levels; and higher total, LDL, and VLDL triglyceride levels compared with those of normoglycemic relatives without a family history of diabetes. In contrast, if subjects with IGT or normoglycemia did not have a family history of diabetes, adverse changes in lipids and lipoproteins were minimal. Our findings...
TABLE 2. Serum Cholesterol, Triglyceride, and Apolipoprotein Levels in the Relatives of Nondiabetic and Diabetic Subjects

<table>
<thead>
<tr>
<th></th>
<th>NGT/D−</th>
<th>NGT/D+</th>
<th>IGT/D−</th>
<th>IGT/D+</th>
<th>NIDDM/D+</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol (mmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>6.29±0.09</td>
<td>6.79±0.11</td>
<td>6.87±0.37</td>
<td>6.76±0.22</td>
<td>6.84±0.30</td>
<td>NS</td>
</tr>
<tr>
<td>HDL</td>
<td>1.45±0.03</td>
<td>1.35±0.03†</td>
<td>1.43±0.08</td>
<td>1.20±0.05§</td>
<td>1.19±0.05§</td>
<td>0.001</td>
</tr>
<tr>
<td>LDL</td>
<td>4.59±0.07</td>
<td>4.48±0.09</td>
<td>4.37±0.27</td>
<td>4.49±0.17</td>
<td>4.37±0.22</td>
<td>NS</td>
</tr>
<tr>
<td>VLDL</td>
<td>0.88±0.03</td>
<td>0.95±0.04</td>
<td>1.07±0.18</td>
<td>1.07±0.09†</td>
<td>1.28±0.10†</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1.31±0.04</td>
<td>1.36±0.06</td>
<td>1.62±0.16</td>
<td>1.95±0.16‡</td>
<td>2.47±0.35‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL</td>
<td>0.09±0.01</td>
<td>0.09±0.01</td>
<td>0.11±0.01</td>
<td>0.10±0.01</td>
<td>0.14±0.01‡</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LDL</td>
<td>0.34±0.01</td>
<td>0.36±0.01</td>
<td>0.41±0.04</td>
<td>0.44±0.03‡</td>
<td>0.45±0.06‡</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>VLDL</td>
<td>0.88±0.04</td>
<td>0.91±0.05</td>
<td>1.10±0.12</td>
<td>1.41±0.14‡</td>
<td>1.87±0.30‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Apolipoproteins (g/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A-I</td>
<td>1.47±0.02</td>
<td>1.43±0.02</td>
<td>1.50±0.07</td>
<td>1.34±0.04</td>
<td>1.38±0.04</td>
<td>NS</td>
</tr>
<tr>
<td>B</td>
<td>1.34±0.04</td>
<td>1.26±0.04</td>
<td>1.43±0.13</td>
<td>1.36±0.07</td>
<td>1.40±0.09</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean±SEM.
NGT, normal glucose tolerance; IGT, impaired glucose tolerance; NIDDM, non-insulin-dependent diabetes mellitus; D−, nondiabetic proband; D+, diabetic proband; HDL, high density lipoprotein; LDL, low density lipoprotein; VLDL, very low density lipoprotein.

*p<0.05, †p<0.01, §p<0.001 compared with the NGT/D− group (Student's two-tailed t test).

suggest that the prediabetic phase significantly modulates cardiovascular risk factors in an atherogenic direction. These adverse changes in cardiovascular risk factors probably make a significant contribution to the subsequent development of atherosclerotic manifestations and help to explain why the duration of clinical
relatives of patients with NIDDM are more insulin aggregation as has been proposed, one would expect patients with NIDDM. Our results are compatible with insulin resistant than subjects without a family history of dia-

resistant association with NIDDM and IGT. Even first-degree

insulin response decreases.34 The relatives of the patients with NIDDM are also at increased risk of developing diabetes23-25 as well as atherosclerosis.26 An early sign that characterizes this risk is hyperinsulinemia, and indeed, prospective population studies have indicated that elevated insulin levels and insulin resistance predict conversion to NIDDM12,28-30 and that hyperinsulinemia also appears to be a risk factor for coronary heart disease.31-33 A family history of diabetes was associated with an insignificant increase in insulin levels in normoglycemic subjects in our study, but frank hyperinsulinemia was seen only in subjects with IGT. The lowest insulin levels in the oral glucose tolerance test were observed in patients with NIDDM. Our results are compatible with those of previous studies, which have demonstrated that hyperinsulinemia characterizes subjects with IGT and that when glucose tolerance worsens toward diabetes, insulin response decreases.34 Elevated insulin levels are usually an indicator for insulin resistance, one of the underlying mechanisms associated with NIDDM and IGT.34 Even first-degree relatives of patients with NIDDM are more insulin resistant than subjects without a family history of diabetes.35 If insulin resistance and NIDDM show familial aggregation as has been proposed, one would expect that subjects with a family history of diabetes are particularly susceptible to abnormalities in the cardio-

vascular risk factors that are mediated by insulin resistance. Of the known cardiovascular risk factors, high VLDL triglyceride and low HDL cholesterol levels have been shown to be associated with not only hyperinsu-

linemia38-40 (as demonstrated in this study; Table 3) but also insulin resistance as measured by the euglycemic clamp technique in normoglycemic subjects32-34 and subjects with abnormal glucose tolerance.44 Furthermore, the elevation of blood pressure levels has been shown to be related to impaired insulin-mediated glu-

cose uptake in both nondiabetic45 and diabetic46 subjects. Therefore, it is tempting to speculate that a high degree of insulin resistance in the relatives of diabetic probands could explain at least in part the adverse changes in lipoprotein and blood pressure levels in these subjects. Indeed, our unpublished data based on the measurement of insulin resistance by the euglycemic clamp technique in a subgroup of subjects included in this report supports this notion. Rates of whole-body glucose uptake were 22% lower in subjects of the IGT/D− group (n=8) but were 45% lower in subjects of the IGT/D+ group (n=9) compared with the rates of whole-body glucose uptake in subjects of the NGT/D− group (n=9).

Serum total and LDL cholesterol as well as apolipo-

protein B levels did not differ among the study groups, a finding that confirms the notion that IGT and NIDDM do not have a major influence on LDL cholesterol concentration.11 However, we measured only the levels of LDL cholesterol and did not characterize the qualitative changes in lipoprotein composition in greater detail. In particular, levels of small, dense LDL particles, which are increased in the serum of survivors of myocardial infarction47 and subjects with combined hyperlipidemia,48 were not determined. These lipoprotein particles may be related to the prediabetic or diabetic state and remain unnoticed if only LDL cholesterol levels are measured. Furthermore, we observed

### Table 3. Correlation of Fasting and 2-Hour Plasma Insulin Levels With Lipoprotein Fractions

<table>
<thead>
<tr>
<th>Study group</th>
<th>HDL cholesterol</th>
<th>VLDL cholesterol</th>
<th>LDL triglycerides</th>
<th>VLDL triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGT/D−</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting insulin level</td>
<td>-0.24†</td>
<td>0.13</td>
<td>0.19*</td>
<td>0.40†</td>
</tr>
<tr>
<td>2-Hour insulin level</td>
<td>-0.27†</td>
<td>0.14</td>
<td>0.20*</td>
<td>0.40†</td>
</tr>
<tr>
<td>NGT/D+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting insulin level</td>
<td>-0.30†</td>
<td>0.18</td>
<td>0.16</td>
<td>0.31†</td>
</tr>
<tr>
<td>2-Hour insulin level</td>
<td>-0.29†</td>
<td>0.17</td>
<td>0.22*</td>
<td>0.32†</td>
</tr>
<tr>
<td>IGT/D−</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting insulin level</td>
<td>-0.65†</td>
<td>0.18</td>
<td>0.52*</td>
<td>0.55*</td>
</tr>
<tr>
<td>2-Hour insulin level</td>
<td>-0.67†</td>
<td>0.16</td>
<td>0.57*</td>
<td>0.53</td>
</tr>
<tr>
<td>IGT/D+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting insulin level</td>
<td>-0.50*</td>
<td>0.16</td>
<td>0.31</td>
<td>0.14</td>
</tr>
<tr>
<td>2-Hour insulin level</td>
<td>-0.29</td>
<td>-0.04</td>
<td>-0.07</td>
<td>-0.01</td>
</tr>
<tr>
<td>NIDDM/D+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting insulin level</td>
<td>-0.69†</td>
<td>0.13</td>
<td>0.27</td>
<td>0.48*</td>
</tr>
<tr>
<td>2-Hour insulin level</td>
<td>-0.49*</td>
<td>-0.10</td>
<td>-0.01</td>
<td>0.12</td>
</tr>
</tbody>
</table>

HDL, high density lipoprotein; VLDL, very low density lipoprotein; LDL, low density lipoprotein; NGT, normal glucose tolerance; IGT, impaired glucose tolerance; NIDDM, non-insulin-dependent diabetes mellitus; D−, nondiabetic proband; D+, diabetic proband.

*p<0.05, †p<0.01.
increased VLDL cholesterol and LDL triglyceride levels in NIDDM and IGT groups if the relatives had a family history of diabetes. These changes reflect an altered composition of VLDL and LDL particles.\(^4\)

With respect to the risk of atherosclerosis, these abnormalities may be of great importance because LDL triglycerides and the VLDL remnants or intermediate density lipoproteins that are produced during catabolism of VLDL to intermediate density lipoproteins and LDL are atherogenic\(^2\,\^3\) and have been shown to be associated with atherosclerosis in animal\(^2\) and human\(^3\) studies.

The current study, demonstrating a clustering of cardiovascular risk factors among relatives with a family history of NIDDM, suggests a “natural history” of the influence of NIDDM on cardiovascular risk factors before the development of frank hyperglycemia. The earliest changes in the cardiovascular risk factor profile can be observed in the relatives of patients with NIDDM even if their glucose tolerance is still normal.

The presence of IGT introduces more aberrations in cardiovascular risk factors, but these changes are minimal if these subjects do not have a family history of diabetes. This is probably due to the fact that IGT subjects with a family history of diabetes are more insulin resistant and at greater risk for developing NIDDM than are IGT subjects without a family history of diabetes. It is important to note that these individuals were characterized not only by hyperinsulinemia, high blood pressure, high total and VLDL triglyceride levels, and reduced HDL cholesterol levels but also by high LDL triglyceride and VLDL cholesterol levels. The significance of these changes in cardiovascular risk factors in prediabetic individuals indicates a disturbance in VLDL and LDL metabolism and should be carefully evaluated in prospective population studies because these abnormalities in lipoprotein metabolism may be closely linked to the mechanisms underlying the effect of insulin resistance on atherosclerosis.

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H Sarlund, K Pyörälä, I Penttilä and M Laakso

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