Asymptomatic Hyperglycemia Is Associated with Lipid and Lipoprotein Changes Favoring Atherosclerosis

Markku Laakso and Elizabeth Barrett-Connor

We studied lipid and lipoprotein concentrations and their relationships to insulin level in 994 men and 1246 women ages 50 to 91 years in the upper middle-class community of Rancho Bernardo in southern California. Altogether, 593 men and 741 women had normal glucose tolerance, 240 men and 348 women, impaired glucose tolerance (IGT), 104 men and 117 women, newly diagnosed noninsulin-dependent diabetes (NIDDM), and 57 men and 40 women, previously diagnosed NIDDM. In women but not men, total cholesterol and low density lipoprotein were significantly higher in those with newly diagnosed NIDDM, compared to subjects with normal glucose tolerance. In both men and women, high density lipoprotein (HDL) cholesterol was significantly lower, and total triglyceride significantly higher, in subjects with IGT and NIDDM compared to those with normal glucose tolerance; these differences persisted after adjusting for age, body mass index, smoking, alcohol intake, and exercise level. Multiple linear-regression analyses showed that fasting insulin (but not 2-hour insulin) was significantly associated with low HDL cholesterol and high total triglycerides independently from other variables (age, body mass index, waist/hip ratio, alcohol intake, smoking, exercise, and 2-hour glucose). Overall, these results show that asymptomatic hyperglycemia (IGT, newly diagnosed NIDDM) is associated with lipid and lipoprotein changes favoring atherosclerosis and that fasting hyperinsulinemia (insulin resistance) is the most important factor associated with these lipid and lipoprotein abnormalities.


Autopsy, clinical, and epidemiological studies have all shown an excess prevalence of atherosclerotic complications in patients with diabetes mellitus.1–4 This particularly applies to noninsulin-dependent diabetes (NIDDM). By the time of diagnosis of diabetes, these patients have more atherosclerotic complications, particularly coronary heart disease, than do non-diabetics of corresponding ages.6–7 An increased frequency of atherosclerotic events has also been reported in persons with impaired glucose tolerance (IGT).8–10 The mechanism for the increased risk of atherosclerosis in NIDDM and IGT is unknown. Disturbances in glucose and insulin metabolism and their adverse effects on lipids and lipoproteins and blood pressure have been suggested as possible explanations.11,12,13 Several reports on lipid and lipoprotein abnormalities in NIDDM have been published,14–20 and a few studies have dealt with persons with IGT.21–26 The main lipid and lipoprotein abnormalities in NIDDM are elevated total triglyceride and low high density lipoprotein (HDL) cholesterol levels.14–20 The results of studies of lipid and lipoprotein levels associated with IGT have all shown elevated total triglyceride levels, but reduced HDL cholesterol levels have not been found in all studies.21–26 To our knowledge, no studies on lipid and lipoprotein levels in persons with previously undiagnosed NIDDM have been published.

Recent studies on normoglycemic persons in which the euglycemic clamp technique was used have suggested that insulin resistance could be linked with lipid and lipoprotein abnormalities.27 No information is available for subjects with abnormal glucose tolerance. Previously published studies have shown that patients with IGT or NIDDM are markedly insulin resistant,28 and it has been suggested that insulin resistance could also be the primary defect for lipid and lipoprotein changes in NIDDM.29,30 Resistance to insulin-stimulated glucose uptake leads to a compensatory elevation of fasting and postprandial insulin levels in subjects with abnormal glucose tolerance. Therefore, if insulin resistance or high insulin level plays a major role in determining dyslipidemia in persons with normal glucose tolerance, its influence should also be seen in those with IGT or undiagnosed NIDDM. To study further the association of asymptomatic hyperglycemia and hyperinsulinemia and abnormalities in lipid and lipoprotein metabolism, we measured lipid and lipoprotein concentrations and studied their relationships to fasting insulin level in a large number of older adults who had varying degrees of glucose tolerance.

Methods

Subjects

Between 1984 and 1987, all surviving residents in a previously characterized older, upper middle-class Cau-
caspian population were invited to participate in a clinical evaluation for chronic diseases. At the time of their clinic visit, a history of diabetes and current medications, cigarette smoking, alcohol consumption, and physical exercise were obtained by standardized interview, and measurements were made of height, weight, and waist and hip circumference. Alcohol intake was evaluated on the basis of the frequency of alcohol consumption per month. A subject was classified as an alcohol user if the frequency of alcohol intake was at least twice a month. Physical activity was defined by a simple question, “Do you regularly engage in strenuous exercise or hard physical labor?” Height and weight were measured with participants in light clothing without shoes. A standard 75 g oral glucose tolerance test was obtained in the morning after a requested 12-hour fast.

**Measurements**

Total cholesterol and triglycerides were measured by enzymatic techniques with an ABA-200 biochromat analyzer (Abbott Laboratories, Irving, TX), high-performance cholesterol reagent (No. 236691, Boehringer-Mannheim Diagnostics, Indianapolis, IN), and triglyceride agent (No. 6097, Abbott Laboratories). Low density lipoprotein (LDL) cholesterol (containing intermediate density lipoprotein, \( d=1.006 \) to 1.063) and HDL cholesterol were measured according to the standardized procedures of the Lipid Research Clinics Manual. Our laboratory is under the continuous standardization program of the Centers for Disease Control, Atlanta, Georgia. Fasting and 2-hour plasma glucose and insulin were measured in a diabetes research laboratory. Glucose was determined on the Beckman Astra-8 (Beckman Instruments, Fullerton, CA) automated system by the glucose oxidase method, and insulin was measured in triplicate by a double-antibody radioimmunoassay. Insulin values are reported for all consecutive participants seen after the laboratory had been standardized.

The following analysis is based on all clinic participants who were 50 years old or older, had fasted at least 12 hours before the visit, were not taking insulin, and had both fasting and 2-hour post-challenge glucose values. According to World Health Organization criteria, diabetes was defined by any of the following: fasting plasma glucose \( \geq 140 \) mg/dl, 2-hour post-challenge glucose \( >200 \) g/dl, or a personal history of diabetes diagnosed by a physician. The 16 persons who were taking insulin were excluded, so that we only describe persons with NIDDM. Previous history of NIDDM was validated by glucose tolerance test or record review in 98% of the participants. Persons who met glucose tolerance criteria for NIDDM without a previous history of diabetes were called newly diagnosed diabetics. Impaired glucose tolerance was defined as a 2-hour post-challenge plasma glucose of 140 to 199 mg/dl with a fasting glucose of \(<140 \) mg/dl and no personal history of diabetes. Body mass index (BMI) was defined as weight (kg)/height (m)².

**Statistical Methods**

The results are presented as means±SEM. Differences between groups were assessed with an analysis of variance and with a \( \chi^2 \) test when appropriate. Adjustment for confounding factors was done by an analysis of covariance. The relationships between variables were calculated by using Pearson correlation coefficients. Multiple linear-regression analysis was used to investigate the independent associations of age, BMI, waist/hip ratio, smoking (smokers, nonsmokers), alcohol intake, exercise (actives, nonactives), and insulin with lipids and lipoproteins. In all statistical analyses, logarithmic values for total triglycerides and insulin were used.

**Results**

Table 1 shows the characteristics of the 994 men and 1246 women (ages 50 to 91 years) in the study groups. Both men and women with IGT or NIDDM were significantly older than men and women with normal glucose tolerance. Men with NIDDM did not differ from men with normal glucose tolerance with regard to BMI but had higher waist/hip ratios. Women with NIDDM or IGT had significantly higher BMI and waist/hip ratios than did women without these problems. Fasting and 2-hour insulin levels tended to be higher in subjects with IGT and NIDDM compared with those of subjects with normal glucose tolerance, but the difference was not always statistically significant. There were no significant differences in cigarette smoking by glucose tolerance status, but a smaller percent of known diabetics reported use of alcohol within the past week, and this difference was statistically significant in women. A significantly smaller proportion of those found to have NIDDM (both sexes) and IGT (men) were physically active.

Table 2 shows the total and LDL and HDL cholesterol levels, total triglyceride levels, and the LDL/HDL cholesterol ratios in men and women according to glucose tolerance, before and after adjusting for age, BMI, smoking, alcohol, exercise, and estrogen use in women. In men, total cholesterol did not differ significantly by glucose tolerance, although LDL was significantly lower in men with previously known diabetes compared to men with normal glucose tolerance. In contrast, in women, total cholesterol and LDL were significantly higher only in newly diagnosed diabetics. In both men and women, HDL cholesterol was significantly lower, and total triglyceride level higher, in subjects with IGT and NIDDM compared to those with normal glucose tolerance, and these differences persisted after adjusting for all covariates. In men, LDL/HDL cholesterol ratio did not differ by glucose tolerance, but women with IGT or NIDDM had higher LDL/HDL cholesterol ratios than did women with normal glucose tolerance. When lipid and lipoprotein levels were compared between IGT and NIDDM subjects, the differences were not significant in either men or women (data not shown). All analyses reported in Table 2 were done after excluding subjects taking medication for hypertension. In men, all the differences in lipid and lipoprotein concentrations persisted, but in women, the differences in total cholesterol, LDL cholesterol, and total cholesterol/LDL cholesterol ratio between newly diagnosed patients with NIDDM and subjects with normal tolerance disappeared. The use of antihypertensive medication did not, however,
have any significant influence on HDL cholesterol and total triglyceride levels.

Table 3 shows correlation coefficients of selected variables with lipids and lipoproteins in subjects with normal glucose tolerance, IGT, or newly diagnosed NIDDM. In men, age correlated negatively with total and LDL cholesterol and total triglyceride level. In women, BMI, waist/hip ratio, 2-hour glucose, and fasting insulin were associated positively with total and LDL cholesterol. Alcohol intake and exercise were positively associated with HDL cholesterol in subjects with normal glucose tolerance status (Table 4). In men, age was negatively associated with total and LDL cholesterol, and alcohol intake was positively associated with total cholesterol. In women, BMI and waist/hip ratio were positively associated with total and LDL cholesterol levels. In both men and women, BMI, 2-hour glucose, and fasting insulin were negatively associated with HDL cholesterol and were positively associated with total triglycerides. In addition, alcohol intake and physical exercise were positively associated with HDL cholesterol. In men, but not women, age and alcohol intake were positively associated with HDL cholesterol and negatively associated with total triglycerides. All regression analyses were also carried out separately in each glucose tolerance status group (normal glucose tolerance, IGT, newly diagnosed NIDDM, previously diagnosed NIDDM) in both men and women to investigate whether the association of fasting insulin with lipid and lipoproteins is independent of other variables (age, BMI, waist/hip ratio, alcohol intake, exercise level, and smoking (data not shown). In men, highest correlation was between BMI and waist/hip ratio (r=0.42, p<0.001) and in women, between BMI and fasting insulin level (r=0.36, p<0.001).

Multiple regression analyses were carried out to investigate the associations of age, BMI, waist/hip ratio, alcohol intake, smoking, exercise, 2-hour glucose, and fasting insulin level with lipids and lipoproteins in subjects with normal glucose tolerance, IGT, and with newly diagnosed NIDDM (Table 4). In men, age was negatively associated with total and LDL cholesterol, and alcohol intake was positively associated with total cholesterol. In women, BMI and waist/hip ratio were positively associated with total and LDL cholesterol levels. In both men and women, BMI, 2-hour glucose, and fasting insulin were negatively associated with HDL cholesterol and were positively associated with total triglycerides. In addition, alcohol intake and physical exercise were positively associated with HDL cholesterol. In men, but not women, age and alcohol intake were positively associated with HDL cholesterol and negatively associated with total triglycerides.
Table 2. Lipid and Lipoprotein Levels before and after Adjustment for Confounding Factors in Rancho Bernardo Men and Women Grouped by Glucose Tolerance Status (1984–1987)

<table>
<thead>
<tr>
<th></th>
<th>Normal glucose tolerance</th>
<th>Impaired glucose tolerance</th>
<th>Newly diagnosed NIDDM</th>
<th>Previously diagnosed NIDDM</th>
<th>ANCOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted (mean)</td>
<td>Adjusted for age, BMI, smoking, alcohol intake, exercise</td>
<td>Unadjusted (mean)</td>
<td>Adjusted for age, BMI, smoking, alcohol intake, exercise</td>
<td>Unadjusted (mean)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>212.8</td>
<td>208.7</td>
<td>209.9</td>
<td>200.3*</td>
<td>0.081</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>135.3</td>
<td>131.7</td>
<td>129.6</td>
<td>123.5*</td>
<td>0.044</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>55.2</td>
<td>51.6‡</td>
<td>52.0*</td>
<td>46.8‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total triglycerides (mg/dl)</td>
<td>115.0</td>
<td>126.9‡</td>
<td>148.6‡</td>
<td>165.9‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL/HDL cholesterol ratio</td>
<td>2.63</td>
<td>2.72</td>
<td>2.69</td>
<td>2.85</td>
<td>0.347</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>227.7</td>
<td>230.4</td>
<td>240.1‡</td>
<td>217.9</td>
<td>0.002</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>135.8</td>
<td>138.8</td>
<td>148.2†</td>
<td>130.6</td>
<td>0.006</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>71.0</td>
<td>66.2‡</td>
<td>62.8‡</td>
<td>57.4‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total triglycerides (mg/dl)</td>
<td>105.1</td>
<td>129.8‡</td>
<td>150.1‡</td>
<td>160.5†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL/HDL cholesterol ratio</td>
<td>2.09</td>
<td>2.33‡</td>
<td>2.59‡</td>
<td>2.43*</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*p<0.05, †p<0.01, ‡p<0.001. Other groups are compared with normal glucose tolerance.

NIDDM=noninsulin-dependent diabetes, BMI=body mass index, ANCOVA=analysis of covariance, LDL=low density lipoprotein, HDL=high density lipoprotein.
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Table 3. Correlation Coefficients of Selected Variables with Lipids and Lipoproteins in Rancho Bernardo Men and Women with Normal and Impaired Glucose Tolerance and with Newly Diagnosed NIDDM (1984–1987)

<table>
<thead>
<tr>
<th>variable</th>
<th>Age</th>
<th>BMI</th>
<th>W/H ratio</th>
<th>Alcohol intake</th>
<th>Smoking</th>
<th>Exercise</th>
<th>2-hour glucose</th>
<th>Log serum insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>-0.131†</td>
<td>0.038</td>
<td>0.061</td>
<td>0.088</td>
<td>0.048</td>
<td>-0.010</td>
<td>-0.066</td>
<td>0.031</td>
</tr>
<tr>
<td>Women</td>
<td>0.048</td>
<td>0.143†</td>
<td>0.158†</td>
<td>0.019</td>
<td>-0.015</td>
<td>0.011</td>
<td>0.090*</td>
<td>0.095*</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>-0.152‡</td>
<td>0.027</td>
<td>0.037</td>
<td>0.078</td>
<td>0.055</td>
<td>0.003</td>
<td>-0.076</td>
<td>-0.036</td>
</tr>
<tr>
<td>Women</td>
<td>0.065</td>
<td>0.176‡</td>
<td>0.196‡</td>
<td>-0.050</td>
<td>-0.046</td>
<td>0.083*</td>
<td>0.097*</td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Men</td>
<td>0.116*</td>
<td>-0.241‡</td>
<td>-0.140†</td>
<td>0.109*</td>
<td>-0.037</td>
<td>0.010*</td>
<td>-0.150†</td>
<td>-0.273‡</td>
</tr>
<tr>
<td>Women</td>
<td>-0.035</td>
<td>-0.290‡</td>
<td>-0.264‡</td>
<td>0.228‡</td>
<td>0.080</td>
<td>0.124*</td>
<td>-0.159†</td>
<td>-0.265‡</td>
</tr>
<tr>
<td>Log total triglycerides</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Men</td>
<td>-0.146†</td>
<td>0.286‡</td>
<td>0.271‡</td>
<td>-0.049</td>
<td>0.072</td>
<td>0.140†</td>
<td>0.140†</td>
<td>0.401‡</td>
</tr>
<tr>
<td>Women</td>
<td>0.028</td>
<td>0.316‡</td>
<td>0.301‡</td>
<td>-0.116*</td>
<td>-0.027</td>
<td>-0.033</td>
<td>0.239‡</td>
<td>0.317‡</td>
</tr>
</tbody>
</table>

*p<0.05, †p<0.01, ‡p<0.001.

BMI = body mass index, W/H ratio = waist/hip ratio, insulin = fasting insulin, LDL = low density lipoprotein, HDL = high density lipoprotein, NIDDM = noninsulin-dependent diabetes.

Table 4. Multiple Regression Coefficients (Beta Coefficients) of Selected Variables Related to Lipids and Lipoproteins in Rancho Bernardo Men and Women with Normal and Impaired Glucose Tolerance and with Newly Diagnosed NIDDM (1984–1987)

<table>
<thead>
<tr>
<th>variable</th>
<th>Multiple R²</th>
<th>Age</th>
<th>BMI</th>
<th>W/H ratio</th>
<th>Alcohol intake</th>
<th>Smoking</th>
<th>Exercise</th>
<th>2-hour glucose</th>
<th>Log serum insulin</th>
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</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
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<tr>
<td>Men</td>
<td>0.030</td>
<td>-0.121†</td>
<td>-0.014</td>
<td>0.051</td>
<td>0.082*</td>
<td>0.011</td>
<td>-0.028</td>
<td>-0.049</td>
<td>0.022</td>
</tr>
<tr>
<td>Women</td>
<td>0.041</td>
<td>0.027</td>
<td>0.095*</td>
<td>0.109†</td>
<td>0.040</td>
<td>-0.001</td>
<td>0.025</td>
<td>0.045</td>
<td>0.039</td>
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<tr>
<td>LDL cholesterol</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Men</td>
<td>0.036</td>
<td>-0.154‡</td>
<td>0.001</td>
<td>0.037</td>
<td>0.070</td>
<td>0.013</td>
<td>-0.023</td>
<td>-0.036</td>
<td>0.060</td>
</tr>
<tr>
<td>Women</td>
<td>0.057</td>
<td>0.026</td>
<td>0.114†</td>
<td>0.146‡</td>
<td>-0.023</td>
<td>-0.024</td>
<td>-0.028</td>
<td>0.019</td>
<td>0.022</td>
</tr>
<tr>
<td>HDL cholesterol</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Men</td>
<td>0.373</td>
<td>0.106†</td>
<td>-0.149‡</td>
<td>-0.022</td>
<td>0.105†</td>
<td>-0.053</td>
<td>0.086*</td>
<td>-0.137‡</td>
<td>-0.161‡</td>
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<tr>
<td>Women</td>
<td>0.191</td>
<td>0.040</td>
<td>-0.150‡</td>
<td>-0.173‡</td>
<td>0.188‡</td>
<td>0.029</td>
<td>0.087*</td>
<td>-0.077*</td>
<td>-0.143‡</td>
</tr>
<tr>
<td>Log total triglycerides</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>0.231</td>
<td>-0.109†</td>
<td>0.110†</td>
<td>0.100†</td>
<td>-0.042</td>
<td>0.077*</td>
<td>-0.119‡</td>
<td>0.097†</td>
<td>0.302‡</td>
</tr>
<tr>
<td>Women</td>
<td>0.214</td>
<td>-0.035</td>
<td>0.166‡</td>
<td>0.178‡</td>
<td>-0.075*</td>
<td>0.010</td>
<td>0.010</td>
<td>0.167‡</td>
<td>0.194‡</td>
</tr>
</tbody>
</table>

*p<0.05, †p<0.01, ‡p<0.001.

BMI = body mass index, W/H ratio = waist/hip ratio, insulin = fasting insulin, NIDDM = noninsulin-dependent diabetes, LDL = low density lipoprotein, HDL = high density lipoprotein.

Discussion

In this study of 994 men and 1246 women with varying degrees of glucose tolerance, significantly elevated levels of total triglycerides and low levels of HDL cholesterol were seen in both men and women with asymptomatic hyperglycemia.

Dyslipidemia was particularly common in persons with known diabetes. The highest total triglyceride values and the lowest HDL cholesterol levels were seen in those with previously diagnosed NIDDM. Women, but not men, with previously undiagnosed NIDDM had higher total and LDL cholesterol levels than did women with normal glucose tolerance, but these differences disappeared when antihypertensive medication was taken into account. The abnormalities in lipids and lipoproteins in subjects with abnormal glucose tolerance persisted after adjustment for age, obesity, alcohol intake, smoking, and exercise level. The lipid and lipoprotein abnormalities in patients with NIDDM are in accordance with previously published studies.14-20 These differences are not likely to be due to a diabetic diet or drugs. Our results demonstrate that the lipid and lipoprotein abnormalities in undiagnosed patients with NIDDM were intermediate between those in subjects with IGT and those with previously diagnosed diabetes. Similar results have been reported in patients with newly diagnosed NIDDM.30
Subjects with IGT also had higher levels of total triglycerides and lower levels of HDL cholesterol than did adults with normal glucose tolerance. Previous studies on lipid and lipoprotein abnormalities in adults with IGT have been conflicting. Some of the inconsistencies may be due to different criteria for IGT, the small number of subjects studied, and the variations in populations studied. Howard et al. showed that IGT in Pima Indians ages 17 to 58 years was associated with high total triglycerides and low HDL cholesterol concentrations in both men and women and with high total and LDL cholesterol levels in women. Ganda et al. reported an elevated level of total triglycerides and lower level of HDL cholesterol level in 65 subjects with IGT compared to corresponding controls. Zavaroni et al. studied an elevated total cholesterol and triglyceride level in 50 subjects with IGT compared to controls matched for gender, age, and the degree of obesity, but no difference in HDL cholesterol. In the study of Falko et al., the only lipid or lipoprotein abnormality was elevated LDL cholesterol level in men with IGT compared to corresponding controls. Their study, however, included only clinic subjects and no adjustment was made for confounding factors. The lipid and lipoprotein abnormalities associated with IGT, lipid and lipoprotein changes that favor the progression of atherosclerosis are seen in both men and women, even after adjustment for factors known to affect lipids and lipoproteins. These findings confirm the results of Howard et al. and extend these observations to older age groups and to a Caucasian population not genetically isolated.

Because of the older age of our cohort, the associations between asymptomatic hyperglycemia and abnormal lipid and lipoprotein changes were demonstrated in a survival population; survival bias tends to underestimate factors that favor mortality. Furthermore, IGT is not a homogeneous category, but consists of subjects who, on retesting, are either normal, are in transition from normal to diabetic, or are genuine diabetics. Therefore, misclassification of IGT of those who are in fact normal may underestimate the strength of association between IGT and abnormalities in lipid and lipoprotein levels. We conclude that these biases are conservative and underestimate the true association of unfavorable lipids and lipoproteins with abnormal glucose tolerance.

The lipid and lipoprotein abnormalities associated with asymptomatic hyperglycemia appear to be an early manifestation of abnormal glucose tolerance. No differences in lipid and lipoprotein levels were observed between subjects with IGT and manifest diabetes, although this observation was based on a relatively small number of cases in the latter group. The etiology of these abnormalities is likely to be related to one or more factors that are present in manifest diabetes but that are also present in asymptomatic hyperglycemia. One such factor could be insulin resistance or hyperinsulinemia. As expected, fasting and 2-hour insulin levels tended to be higher in subjects with abnormal glucose tolerance than in subjects with normal glucose tolerance, compatible with a greater degree of insulin resistance. Multiple linear-regression analyses (including subjects with normal glucose tolerance, IGT, and undiagnosed NIDDM) showed that fasting insulin was positively associated with high total triglycerides and inversely associated with low HDL cholesterol, independent of age, BMI, waist/hip ratio, alcohol intake, smoking, physical exercise, and 2-hour glucose in both men and women. When regression analyses were carried out separately in each glucose tolerance status group, fasting insulin was positively associated with total triglycerides and inversely associated with HDL cholesterol in men with normal glucose tolerance, IGT, or newly diagnosed NIDDM. In women, these associations were weaker or absent. This interesting gender difference is reminiscent of the prospective population studies of endogenous insulin as a cardiovascular risk factor. Thus, in previously diagnosed diabetics, the fasting insulin level is not an indication of insulin resistance alone. Although in subjects with abnormal glucose tolerance, fasting insulin levels, and probably insulin resistance, are related to abnormal lipid and lipoprotein changes, this association does not necessarily mean a causal relationship. The alternative possibility is that abnormal lipoproteins, especially VLDL triglycerides, which form the major part of total triglyceride concentration, could induce insulin resistance and elevate fasting insulin level by impairing insulin-mediated glucose uptake.

Several previous epidemiological studies have shown that, in addition to diabetes, a mild abnormality in glucose metabolism is also associated with an increased risk of mortality and morbidity from cardiovascular diseases. Our results indicate that lipid and lipoprotein abnormalities could, at least in part, explain this excess. Insulin resistance and accompanying hyperinsulinemia may be determinants of the lipid and lipoprotein abnormalities or independent risk factors for the atherosclerotic complications in these patients.

References
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