Impaired Glucose Tolerance and Risk Factors for Atherosclerosis

Olga Vaccaro, Angela Rivellese, Gabriele Riccardi, Brunella Capaldo, Loredana Tutino, Giovanni Annuzzi, and Mario Mancini

This study attempts to evaluate whether the putative excess risk of cardiovascular disease in individuals with impaired glucose tolerance (IGT) can be explained by the clustering of other major cardiovascular risk factors after controlling for obesity. The study population was 1376 male and female employees of a Naples telephone company who had participated in a health survey in which an oral glucose tolerance test (OGTT) was given. After excluding treated hypertensives, we recruited all 65 individuals with IGT and 125 euglycemic controls matched for gender, age, and weight. Systolic and diastolic blood pressure was significantly higher in individuals with IGT (134 ± 16 vs 127 ± 15 mm Hg, p < 0.001; 87 ± 10 vs 84 ± 8 mm Hg, p < 0.05 (M ± SD). Blood lipids were similar in the two groups (total cholesterol was 214 ± 34 vs 218 ± 40 mg/dl; HDL cholesterol was 39 ± 9 vs 40 ± 10 mg/dl; total triglyceride was 145 ± 58 vs 135 ± 63 mg/dl). Serum insulin values (fasting or at 1 or 2 hours after 75 g of oral glucose) were also similar. The number of persons currently smoking was significantly lower among individuals with IGT (30% vs 47%, p < 0.025) but the percentage of ex-smokers was identical in the two groups. We conclude that, among the possible cardiovascular risk factors investigated, blood pressure is the only one significantly associated with IGT independent of matched variables and antihypertensive treatment. (Arteriosclerosis 4:592–597, November/December 1984)

There is some evidence, although not conclusive, that impaired glucose tolerance (IGT) is associated with an increased risk for cardiovascular disease.1–5 It has also been suggested6–9 that in diabetic individuals this increased risk could be partly explained by an increase in other arteriosclerosis risk factors such as obesity, hyperlipidemia, and hypertension. However, although a clustering of cardiovascular risk factors has been clearly recognized in diabetics,10 the association of IGT and various cardiovascular risk factors is weak and inconsistent.11

The lack of agreement on the definition of IGT12,13 as well as the differences in methodology have limited the value of intersurvey comparisons. This probably accounts for the inconsistency of the results in the past.11 Furthermore, obesity, which is often found in individuals with IGT, may cause researchers to overlook the association of IGT with other cardiovascular risk factors.14,15

Our study was undertaken to verify whether, after controlling for obesity, there are increased cardiovascular risk factors associated with IGT as defined by the new diagnostic criteria.16

Methods

Subjects

A population of 1376 individuals, both men and women, aged 40 to 59 years, who were employed in a Naples telephone company participated in a health survey. The examination included, among other things, an oral glucose tolerance test (OGTT), fasting samples for total serum cholesterol and triglyceride evaluation, blood pressure, and weight and height measurements.

The OGTT results, evaluated according to the EASD suggestions,16 formed the basis for classifying the participants as having normoglycemia (n = 1251) or impaired glucose tolerance (n = 69). Hypertensives undergoing treatment and recently diagnosed diabetics were excluded from the study.
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Procedures

All the individuals with IGT and twice this number of euglycemic controls [matched for gender, age (± 4 years) and body mass index (BMI ± 2)] were invited to participate in the study. All were free of clinically significant diseases. Three individuals (4.6%) in the IGT group and 5 (4.0%) of the controls were taking hypolipidemic drugs; two females in the IGT group (3.0%) and three (2.4%) controls were on oral contraceptives. No one was aware of the screening results. Informed consent was given by 65 (94%) of the IGT group and 125 (91%) of the normal controls. These underwent a second examination which included an OGTT and fasting specimens for determination of total glycosylated hemoglobin (HbAI), total cholesterol, total triglycerides, and HDL cholesterol. Blood pressure and body weight and height were reassessed under the same conditions as in the first examination.

All procedures were approved by the local public health authorities and by the workers' trade unions.

Measurements

On both occasions the OGTT was performed in the morning with a 75 g glucose load. The time interval between the two tests was 2 to 4 months. There were no weight changes during this interval. All the participants were instructed to fast and to abstain from tobacco for at least 10 hours before the examination. Blood glucose (BG) was evaluated in the fasting state and 2 hours after the glucose load by a glucose oxidase method\(^ \text{17} \) using venous whole blood. Normoglycemia was defined as a blood glucose level (fasting and after glucose load) of less than 120 mg/dl. IGT was diagnosed if one of the following conditions was met: 1) fasting BG was less than 120 mg/dl and BG 2 hours postload was 120 mg/dl or greater (n = 62); or 2) fasting BG was 120 mg/dl or greater and BG 2 hours postload was between 120 and 180 mg/dl (n = 3). We used the EASD diagnostic criteria\(^ \text{16} \) which are similar to those recommended by WHO.\(^ \text{18} \)

The oral glucose tolerance test has been shown to have poor reproducibility as a diagnostic test.\(^ \text{19,20} \) To minimize this problem, the study subjects were reclassified using both the OGTTs performed. This identified a subgroup of 45 individuals with IGT and another subgroup of 114 who were normoglycemic at both tests.

At the second OGTT only, circulating serum insulin was assayed after fasting and at 1 hour and 2 hours post-glucose load by a double antibody radioimmunoassay method.\(^ \text{21} \)

Total serum cholesterol and triglycerides were measured by enzymatic automated methods,\(^ \text{22} \) and HDL cholesterol was evaluated by a precipitation technique.\(^ \text{23} \) In our laboratory, these methods are controlled by the WHO European program for quality control of lipid methods.

Glycosylated hemoglobin was assayed on micro-columns with a chromatographic method.\(^ \text{24} \)

Trained observers measured blood pressure with the participants in a supine position after a 5-minute rest. Three readings were taken at 2-minute intervals, and the systolic and fifth phase diastolic values were recorded. The average value was used for calculations.

Body weight and height were measured with participants in light clothes with shoes off. BMI was calculated according to the following formula: weight (kg)/height (m)\(^2 \).

Statistical Methods

Unless otherwise stated, values given in the text are expressed as mean ± standard deviation (M ± SD). The values for blood pressure, blood lipids, and BMI represent the average of the two measurements taken at the first and second examinations. Between-group comparisons were performed using unpaired Student's t test and \( \chi^2 \) analysis. The null hypothesis was rejected when \( 2p < 0.05. \) The data were checked for normality; logarithmic transformation was used for serum insulin and triglycerides.

Results

Table 1 gives the pertinent clinical data on the participants, classified according to the results of the first OGTT. Age, BMI, and male/female ratio were almost identical in the two groups, due to the close matching on these variables. Conversely, blood glucose, both fasting and after load, and HbA1 were

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Age (yrs)</th>
<th>BMI (kg/m²)</th>
<th>Sex M/F</th>
<th>Blood glucose (mg/dl)</th>
<th>HbA1 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGT</td>
<td>47.9 ± 5.1</td>
<td>28.8 ± 3.5</td>
<td>38/27</td>
<td>93.0 ± 18.1</td>
<td>7.4 ± 1.0</td>
</tr>
<tr>
<td>(n = 65)</td>
<td></td>
<td></td>
<td></td>
<td>150.5 ± 32.2</td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>47.3 ± 5.3</td>
<td>28.4 ± 3.1</td>
<td>75/50</td>
<td>75.9 ± 12.4</td>
<td>6.9 ± 1.0</td>
</tr>
<tr>
<td>(n = 125)</td>
<td></td>
<td></td>
<td></td>
<td>74.8 ± 16.8</td>
<td></td>
</tr>
</tbody>
</table>

\( *p < 0.002. \)
\( t p < 0.001. \)

Values are means ± so. IGT = impaired glucose tolerance; BMI = body mass index; HbA1 = total glycosylated hemoglobin.
significantly higher in individuals with IGT. Figure 1 shows the major, well established, risk factors for atherosclerosis that were investigated in this study. Total cholesterol, HDL cholesterol, and total triglyceride values were very similar in the two groups and the exclusion of treated hyperlipidemics did not significantly change the findings in the mean values. Individuals with IGT had significantly higher blood pressure values than controls, in both systolic (134 ± 16 vs 127 ± 15 mm Hg, p < 0.01) and diastolic (87 ± 10 vs 84 ± 8 mm Hg, p < 0.05) blood pressure.

The analyses of those in the IGT group who did not have fasting hyperglycemia and of their controls gave similar results: 133 ± 16 vs 127 ± 15 mm Hg, p < 0.02 for systolic blood pressure, and 87 ± 11 vs 84 ± 8 mm Hg, p = 0.05 for diastolic blood pressure.

Circulating serum insulin levels were not significantly different in the two groups at any time (0, 60, or 120 minutes). In Figure 1 the sum of all the insulin values is reported for IGT subjects and controls. A more detailed analysis of the serum insulin results will be published elsewhere.

Smoking habits are reported in Figure 1 and in more detail in Table 2. Very few individuals (two in the IGT and five in the control group) smoked pipes or cigars, and these were excluded from the analy-

Table 2. Smoking Habits in Individuals with Impaired Glucose Tolerance and Controls

<table>
<thead>
<tr>
<th>Subjects</th>
<th>No. cig/day (smokers)</th>
<th>Current smokers</th>
<th>Never smoked</th>
<th>Ex-smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGT (n = 63)</td>
<td>17.4 ± 5.8</td>
<td>19* (30.2%)</td>
<td>31* (49.2%)</td>
<td>13 (20.8%)</td>
</tr>
<tr>
<td>Controls (n = 120)</td>
<td>19.1 ± 11.1</td>
<td>56 (46.7%)</td>
<td>38 (31.7%)</td>
<td>26 (21.7%)</td>
</tr>
</tbody>
</table>

Values are means ± so. IGT = impaired glucose tolerance.

*p < 0.025.

**p < 0.01.
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Figure 2. Major risk factors for atherosclerosis in individuals with impaired glucose tolerance (IGT) and normoglycemia at two oral glucose tolerance tests (SIP Survey 1980, Naples). **p < 0.01; *p < 0.05.

Discussion

The relationship between IGT and the prevalence of risk factors for atherosclerosis has not been firmly established. Major controversies have arisen because of methodological problems such as the poor reproducibility of the OGTT as a diagnostic test19, 20 and the lack of a universal diagnostic criteria.12, 13 In fact, a clear definition of IGT is of recent origin.16, 18 Furthermore, the strong direct relationship between IGT and obesity, associated with other risk factors for atherosclerosis, may have caused researchers to overlook the effect of hyperglycemia.14, 15

The participants in our study were selected according to widely accepted diagnostic criteria,16, 18 and the controls were matched closely to subjects with respect to body weight, age, and gender in an attempt to overcome the major problems experienced in the past. Moreover, we repeated all measurements to reduce random errors or misclassifications due to the poor reproducibility of the OGTT.

Among the risk factors for atherosclerosis investigated in this study, only blood pressure (systolic and diastolic) was positively and significantly associated with IGT despite the fact that treated hypertensives were excluded. This confirms previous reports1, 11 and points out that this association is independent of age and body weight, which have been suggested as possible underlying factors. Also, other possible confounding variables, such as renal function and urinary sodium excretion, were not different in IGT and controls (unpublished data).
The difference in blood pressure was also confirmed when individuals with unequivocal IGT or euglycemia (those with IGT or normoglycemia confirmed at both OGTTs) were compared.

Although it is often stated that IGT individuals are prone to hyperlipidemia, in this study we failed to detect any significant difference in blood lipid concentrations between IGT subjects and controls. Similar results were found when the comparison was extended to the major lipoprotein fractions. This finding is contrary to most other findings and could reflect the low lipid levels in these subjects, as compared, for example, with Americans.

However, the most likely explanation of this negative finding is the close matching of IGT subjects and controls with regard to BMI. In fact, blood lipid abnormalities were detected when this same group of IGT individuals was compared with sex- and age-matched, nonoverweight controls. This suggests that the higher prevalence of hyperlipidemia reported in IGT individuals is probably due to overweight, which is often associated with IGT, and not to hyperglycemia. Similar reasoning may also explain the lack of significant differences in circulating serum insulin levels found in this study. The close comparability of the serum insulin levels of the groups is noteworthy in view of the fact that hyperinsulinemia may explain the excess cardiovascular morbidity and mortality associated with hyperglycemia in some epidemiological studies.

Smoking habits were significantly different in the two groups. This finding was unexpected, but not new; previous studies have reported fewer persons currently smoking among hyperglycemics, although not much attention has been paid to this fact. It is extremely unlikely that smoking habits at the time of the study were a consequence of the glucose tolerance status since the participants were unaware of their blood glucose values; furthermore, the only significant difference between IGT persons and controls was in the proportion of those currently smoking, while the percentage of exsmokers was identical in the two groups. One possible explanation for this association is that smoking habits might be an indicator of some other factor etiologically related to glucose tolerance, e.g., diet and alcohol consumption. Daily calorie and alcohol intake have been reported differently in smokers and nonsmokers and may be risk factors for IGT.

An alternative explanation could be chance, since the finding of a low prevalence of smokers among persons with IGT has not been consistently proven. Further knowledge is needed to clarify this matter.

In conclusion, many metabolic abnormalities reported in IGT individuals are due to the excess overweight in this group. Obesity, together with hypertension, is the only cardiovascular risk factor consistently associated with hyperglycemia and should be taken into account when planning effective strategies for preventing cardiovascular disease.

References

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Index Terms: prediabetic state • obesity • hyperlipidemia • hypertension • cigarette smoking • cardiovascular disease