Study on background factors associated with impaired glucose tolerance and/or diabetes mellitus

Shigenobu Umeki¹, Nobumi Hisamoto² and Yoshito Hara²

Division of Respiratory Diseases¹, Department of Medicine, Kawasaki Medical School, and Asahigaoka Hospital², Okayama, Japan

Abstract. In a cross-sectional health screening 636 persons with negative urine glucose, a 75-g-oral glucose tolerance test was performed. We report the clinical features of the subjects with impaired glucose tolerance or diabetes mellitus. In 96 subjects with impaired glucose tolerance, the frequencies of alcohol dependency, fatty liver, and of increased levels of serum uric acid, cholesterol, triglycerides, total serum protein and γ-glutamyl transpeptidase were significantly higher than in normal subjects. In 37 subjects with diabetes mellitus, the frequencies of fatty liver, hypertension and of increased erythrocyte sedimentation rate, triglycerides and γ-glutamyl transpeptidase were significantly higher than in normal subjects. In addition, significant increases in serum γ-glutamyl transpeptidase, triglycerides, serum total cholesterol and body mass index, and a significant decrease in high density lipoprotein cholesterol were also observed in subjects with impaired glucose tolerance and diabetes mellitus. These results suggest that alcohol dependency, fatty liver, obesity and hyperlipidemia are important concomitants of impaired glucose tolerance.

The discovery of impaired glucose tolerance (IGT) in the absence of symptoms attributable to diabetes mellitus (DM) poses problems both in interpretation and management. In many people glucose tolerance normalises spontaneously, whereas some develop gross hyperglycemia with symptoms. Although several follow-up studies of subjects with IGT have been reported in the literature (O'Sullivan & Mahan 1968; Jarrett et al. 1979), there have been few investigations of the background (risk) factors in persons with IGT. Prevalence studies are effective when trying to find these or etiological factors of the development of DM.

In the present study, we investigated the background factors related to the development of IGT or DM in 636 persons with negative urine glucose who participated in a mass health screening.

Subjects and Methods

Out of a total of 641 subjects aged 33–79 years taking part in a mass health screening with a one-night stay in the Asahigaoka Hospital between January and December 1987, 636 with no symptoms consistent with DM and negative urine glucose were divided into three classes (normal, IGT and DM) according to the results of the 75-g oral glucose tolerance test (75-OGTT) proposed in a report of the WHO Study Group on Diabetes Mellitus (1985). The normal class included 503 subjects (381 males, 122 females) with a fasting plasma glucose value of less than 6.4 mmol/l and a 2-h plasma glucose value of less than 7.8 mmol/l. The IGT class was composed of 96 subjects (82 males, 14 females) with a fasting plasma glucose of less than 7.8 mmol/l and a 2-h plasma glucose of 7.8 to 11.1 mmol/l. The DM class consisted of 37 subjects (27 males, 10 females) with a fasting plasma glucose of more than 7.8 mmol/l or a 2-h plasma glucose of more than 11.1 mmol/l.

Venous blood samples were drawn from all subjects under stable (resting) and fasting conditions in the morning and were kept in ice water before refrigerated centrifugation. Sera or plasma were obtained by centrifuga-

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tion within 5 min after each blood sampling. For the 75-
OGTT, venous blood samples were taken before and 2 h
after a glucose load in the morning. Venous plasma glu-
cose was determined by a hexokinase-G-6-P-dehydroge-
nase coupling method using an autoanalyser (Neese et al.
1976). Other serum factors, including alanine aminotransferase, aspartate aminotransferase, γ-glutamyl
transpeptidase, cholesterol, triglycerides, total serum
protein, and uric acid were measured automatically (Hi-
tachi, Tokyo) by the following methods: alanine aminotransferase (normal range, <40 U/l) and aspartate aminotransferase (<40 U/l) were measured by the method of Wroblewski & LaDue (1956, 1955); γ-glutamyl transpeptidase (<40 U/l) by the method of Orlowski & Meister (1963); cholesterol (3.38–6.50 mmol/l) by the method of Haung et al. (1961); triglycerides (<1.80 mmol/l) by the method of Eggstein & Kreutz (1966); serum protein (60–80 g/l) by biuret reaction (Gornall et al. 1949) with a slight modification; and uric acid (120–390 μmol/l) by the method of Bloch & Lata (1970). High density lipoprotein cholesterol (0.91–1.43 mmol/l) levels were measured by ultracentrifugation and MnCl₂ precipitation, according to the method described in Lipid Research Center Project (Manual of Laboratory Methods 1973). In all sub-
jects measurements were made of body mass index (kg/
²m²), blood pressure, urine glucose and protein, red blood
cell counts, white blood cell counts, hematocrit and ery-
throcyte sedimentation rate; furthermore, possible underly-
ing diseases, electrocardiographic and ultrasono-
graphic changes, and abnormalities on upper gastroin-
testinal X-ray series were evaluated. Urine glucose and
protein were evaluated using multistick system III (Miles-
Sankyo Co, Ltd, Tokyo, Umeki et al. 1988).

Subjects with liver damage were excluded from the eval-
uation of body mass index, alanine aminotransferase,
aspartate aminotransferase, cholesterol, high density
lipoprotein cholesterol, triglycerides and serum protein.
Subjects with hypertension (systolic blood pressure >140
mmHg or diastolic blood pressure >90 mmHg) and liver
damage were excluded from the evaluation of blood
pressure. Subjects with alcohol dependency (drinking of
more than 600 ml of Japanese sake everyday for at least
10 years) and liver damage were excluded from the eval-
uation of γ-glutamyl transpeptidase; those with anemia
(red blood cells <4100 × 10⁹/l for males, <3600 × 10⁹/l for
females) and liver damage were excluded from that of
red blood cell counts; those with leukocytosis (>8.5 ×
10⁹/l) and liver damage were excluded from that of white
blood cell counts; those with anemia (hematocrit <39%
for males and <34% for females) and liver damage were
excluded from that of hematocrit; those with increased
erthrocyte sedimentation rate (>13 mm/h) and liver
damage were excluded from that of erythrocyte sedimen-
tation rate.

Statistical differences in the prevalence of clinical ab-
normalities in the three classes were determined by the
chi-square with Yate’s correction except when expected
values of less than 5 required the use of the Fisher’s exact
test. Furthermore, a Mantel Haenszel test was applied to
the three classes and age was used as one of the variables.
Mean results were compared by the Student’s t-test. The
values presented in the table correspond to the mean ±
SD.

Results

Table 1 shows the prevalence of clinical abnor-
malities (abnormal background) in each class. In the
IGT subjects, the prevalence of alcohol de-
dependency, fatty liver, and increased levels of serum
uric acid, cholesterol, triglycerides, total serum
protein, and γ-glutamyl transpeptidase were signifi-
cantly higher than in normal subjects. In the DM
subjects, the prevalence of fatty liver, hypertension
and increased levels of erythrocyte sedimentation
rate, serum cholesterol, triglycerides and γ-gluta-
myl transpeptidase were also higher than in nor-
mal subjects.

The body mass index in both IGT (mean ± SD,
26.0 ± 2.9 kg/m², N 86, P < 0.001) and DM (25.9 ±
3.3 kg/m², N 34, P < 0.05) subjects was signifi-
cantly higher than that in normal subjects (23.8 ±
3.1 kg/m², N 47).

As shown in Table 2, serum values of γ-glutamyl
transpeptidase, triglycerides, and total cholesterol
were significantly higher in both IGT and DM sub-
jects than in normal subjects. As to serum γ-gluta-
myl transpeptidase, the values especially were sig-
nificantly higher in IGT males and DM females
than in the normal corresponding subjects. As to
triglycerides, the values were significantly higher
in both male and female DM subjects than in the
corresponding IGT subjects. On the other hand,
high density lipoprotein cholesterol values in IGT
and DM subjects were significantly lower than in
normal subjects. There were, however, no signifi-
cant differences in high density lipoprotein choles-
terol values between normal and IGT male sub-
jects (Table 2).

There were, furthermore, no significant changes
in blood pressure among normal (mean value of
mean blood pressure, 95.1 mmHg), IGT (96.2
mmHg) and DM (97.7 mmHg) subjects, nor were
there any difference as to serum alanine aminotransferase (mean values of the three classes, 17.8,
19.8, 21.0 U/l), aspartate aminotransferase (18.9,
19.6, 20.2 U/l), white blood cell countes (5.96, 6.16,
5.81 × 10⁹/l), and erythrocyte sedimentation rate
(4.5, 3.8, 5.0 mm/h). Values for serum protein, red
Table 1.
Characteristics of clinical abnormalities in normal subjects and subjects with impaired glucose tolerance (IGT) and diabetes mellitus (DM).

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Normal (%)</th>
<th>IGT (%)</th>
<th>DM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol dependency</td>
<td>76 (15.1)</td>
<td>23 (24.0)(^1)</td>
<td>6 (16.2)</td>
</tr>
<tr>
<td>Liver damage (GOT &gt; 40 or GPT &gt; 40)</td>
<td>26 (5.2)</td>
<td>10 (10.4)</td>
<td>3 (8.1)</td>
</tr>
<tr>
<td>Fatty liver</td>
<td>53 (10.5)</td>
<td>22 (22.9)(^2)</td>
<td>14 (37.8)(^2)</td>
</tr>
<tr>
<td>Chronic cholecystitis</td>
<td>30 (6.0)</td>
<td>5 (5.2)</td>
<td>6 (16.2)</td>
</tr>
<tr>
<td>Electrocardiographically ischemic changes</td>
<td>41 (8.2)</td>
<td>9 (9.4)</td>
<td>6 (16.2)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>27 (5.4)</td>
<td>7 (7.3)</td>
<td>6 (16.2)(^1)</td>
</tr>
<tr>
<td>Chronic gastritis</td>
<td>77 (15.3)</td>
<td>13 (13.5)</td>
<td>4 (10.8)</td>
</tr>
<tr>
<td>Gastric or duodenal ulcer</td>
<td>16 (3.2)</td>
<td>3 (3.1)</td>
<td>2 (5.4)</td>
</tr>
<tr>
<td>Anemia</td>
<td>17 (3.4)</td>
<td>5 (5.2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Other clinical abnormalities</td>
<td>80 (15.9)</td>
<td>40 (41.7)(^2)</td>
<td>21 (56.7)(^2)</td>
</tr>
<tr>
<td>Increased serum uric acid (&gt;7.0)</td>
<td>14 (2.8)</td>
<td>10 (10.4)</td>
<td>3 (8.1)</td>
</tr>
<tr>
<td>Increased WBC (&gt;8500)</td>
<td>51 (10.1)</td>
<td>13 (13.5)</td>
<td>5 (13.5)</td>
</tr>
<tr>
<td>Increased ESR (&gt;13)</td>
<td>42 (8.3)</td>
<td>7 (7.3)</td>
<td>11 (29.7)(^2)</td>
</tr>
<tr>
<td>Increased serum cholesterol (&gt;250)</td>
<td>19 (3.8)</td>
<td>17 (17.7)(^2)</td>
<td>3 (8.1)(^2)</td>
</tr>
<tr>
<td>Increased serum triglycerides (&gt;160)</td>
<td>33 (6.6)</td>
<td>70 (72.9)(^2)</td>
<td>16 (43.2)(^2)</td>
</tr>
<tr>
<td>Increased total serum protein (&gt;8.0)</td>
<td>5 (1.0)</td>
<td>7 (7.3)(^3)</td>
<td>2 (5.4)</td>
</tr>
<tr>
<td>Increased serum γ-glutamyl transpeptidase</td>
<td>27 (5.4)</td>
<td>49 (51.0)(^2)</td>
<td>6 (16.2)</td>
</tr>
</tbody>
</table>

\(^1\) P < 0.05, \(^2\) P < 0.005, compared with values of normal subjects. WBC: white blood cell counts; ESR: erythrocyte sedimentation rate.

Table 2.
Changes in γ-glutamyl transpeptidase, triglycerides, serum total cholesterol and high density lipoprotein cholesterol in each class of normal subjects, and subjects with impaired glucose tolerance (IGT) and diabetes mellitus (DM).

<table>
<thead>
<tr>
<th></th>
<th>Normal (N) mean ± SD</th>
<th>IGT (N) mean ± SD</th>
<th>DM (N) mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>γ-glutamyl transpeptidase (U/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>18.7 ± 8.1 (306)</td>
<td>23.3 ± 10.8 (57)(^1)</td>
<td>20.4 ± 7.7 (21)</td>
</tr>
<tr>
<td>Female</td>
<td>10.2 ± 6.0 (113)(^1)</td>
<td>12.2 ± 6.5 (13)</td>
<td>15.0 ± 5.3 (7)(^3)</td>
</tr>
<tr>
<td>Total</td>
<td>16.4 ± 7.5 (419)</td>
<td>21.2 ± 10.0 (70)(^1)</td>
<td>19.1 ± 7.1 (28)(^3)</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.20 ± 0.40 (357)</td>
<td>1.65 ± 0.59 (73)(^1)</td>
<td>2.09 ± 0.69 (25)(^1,5)</td>
</tr>
<tr>
<td>Female</td>
<td>1.01 ± 0.36 (120)(^4)</td>
<td>1.37 ± 0.40 (13)(^1)</td>
<td>2.16 ± 0.71 (9)(^2,5)</td>
</tr>
<tr>
<td>Total</td>
<td>1.15 ± 0.39 (477)</td>
<td>1.66 ± 0.56 (86)(^1)</td>
<td>2.11 ± 0.70 (34)(^1,5)</td>
</tr>
<tr>
<td>Serum total cholesterol (mmol/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4.92 ± 0.85 (357)</td>
<td>5.81 ± 0.91 (73)(^3)</td>
<td>5.14 ± 0.89 (25)(^3)</td>
</tr>
<tr>
<td>Female</td>
<td>5.24 ± 0.85 (120)(^4)</td>
<td>5.55 ± 0.69 (13)</td>
<td>5.65 ± 0.43 (9)(^3)</td>
</tr>
<tr>
<td>Total</td>
<td>5.00 ± 0.85 (477)</td>
<td>5.24 ± 0.88 (86)(^2)</td>
<td>5.28 ± 0.77 (34)(^3)</td>
</tr>
<tr>
<td>High density lipoprotein cholesterol (mmol/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.29 ± 0.33 (357)</td>
<td>1.22 ± 0.28 (73)</td>
<td>1.15 ± 0.21 (25)(^3)</td>
</tr>
<tr>
<td>Female</td>
<td>1.51 ± 0.35 (120)(^4)</td>
<td>1.26 ± 0.13 (13)(^2)</td>
<td>1.19 ± 0.12 (9)(^1)</td>
</tr>
<tr>
<td>Total</td>
<td>1.35 ± 0.34 (477)</td>
<td>1.23 ± 0.26 (86)(^2)</td>
<td>1.16 ± 0.19 (34)(^2)</td>
</tr>
</tbody>
</table>

\(^1\) P < 0.001, \(^2\) P < 0.01, and \(^3\) P < 0.05, compared with values of normal subjects.
\(^4\) P < 0.001, compared with values of male normal subjects.
\(^5\) P < 0.001, compared with values of IGT subjects.
blood cell counts and hematocrit tended to be slightly higher in the IGT subjects than in normal subjects (data not shown), although there were no significant differences in these factors among normal, IGT and DM subjects.

Discussion

The present study indicated that alcohol dependency, fatty liver (ultrasonographically diagnosed), obesity, high values of serum factors (γ-glutamyl transpeptidase, triglycerides and cholesterol), low value of serum high density lipoprotein cholesterol, and the prevalence of increased levels in serum uric acid, cholesterol, triglycerides, serum protein and γ-glutamyl transpeptidase may be important concomitants of IGT.

Although the IGT subjects are not considered to be diabetic, they are at higher risk than normals for the development of DM. In some cases, IGT represents a stage in the natural history of non-insulin-dependent diabetes, and less frequently of insulin-dependent diabetes, and it can be expected that 1–5% of IGT subjects will proceed to overt clinical DM per year (National Diabetes Data Group 1979). However, many will return to normal glucose tolerance spontaneously, and a proportion will remain in this class for many years. Improvement in glucose tolerance in IGT subjects can be induced over the short-term by caloric restriction or weight loss (O’Sullivan & Mahan 1968; Jackson 1974). Several studies, however, have shown an increased prevalence of arterial diseases, electrocardiographic abnormalities, and increased susceptibility to atherosclerotic disease in these subjects in association with other known risk factors, including hypertension, hyperlipidemia and obesity (Keen et al. 1973; Mattock et al. 1988; Kelleher et al. 1988).

It has been sporadically reported and experimentally demonstrated that a high proportion of nondiabetic, alcoholic patients have an intolerance for glucose loading (Phillis & Safrit 1971), although the mechanism leading to alcohol-induced glucose intolerance is not understood. In the present study, the high prevalence of fatty liver in IGT subjects may be due mainly to alcohol dependency. The increased levels of γ-glutamyl transpeptidase in IGT subjects may be due to some metabolic abnormalities other than alcohol dependency, since our results were calculated with exclusion of data in subjects with alcohol dependency or liver damage.

Cardiovascular disorders are considered to be more common in adult diabetic patients than in non-diabetic patients (Ostrander et al. 1965; Kelleher et al. 1988). Although hypertension and/or myocardial ischemic changes (ST-segment depression or inversion of T-wave) in the diabetic population are associated with the prevalence of both microvascular and macrovascular complications, information as to how blood pressure levels and ischemic changes vary with bloodsugar control is scarce (Bengtsson 1978). One possible explanation for the association of hypertension and DM is that similar genetic and/or environmental factors predispose to the two conditions (Krolewski et al. 1981). In our study, the prevalence of hypertension was higher in DM subjects than in IGT or normal subjects, whereas there were no significant differences in mean blood pressure among normal, IGT and DM subjects.

In both humans and experimental animals, obesity and IGT are associated with hyperinsulinemia, which could be due to an increased secretion rate of insulin, a decrease in its metabolic clearance rate in peripheral tissues, or a combination of the two (Olefsky & Kolterman 1981). Subsequently, hyperinsulinemia promotes triglyceride production by activation of its biosynthesis, producing hypertriglyceridemia (Saudek & Eder 1979). Regarding the serum cholesterol level in DM, a control study (Howard et al. 1978) observed an increase in low density lipoprotein cholesterol and a reduction in high lipoprotein cholesterol. However, Simpson et al. (1979) reported that plasma cholesterol levels were similar in diabetic men and normal controls, but lower in diabetic women than in controls. Serum triglyceride levels, on the other hand, were significantly higher in DM subjects than in controls (Simpson et al. 1979).

Herman & Goldbourt (1982) reported that diabetics have lower serum uric acid levels and that obese prediabetics have higher levels of serum uric acid than nondiabetics. Individuals with primary gout are likely to have increased serum triglyceride levels. As a result, they suggested that obesity may be considered the reason for raised uric acid levels in prediabetics, but they also noted that hyperuricemic subjects have higher serum triglyceride levels than normouricemic ones,
matched for relative body weight (Bondy & Rosenberg 1980). They furthermore suggested that raised triglyceride levels accompany raised uric acid values before the onset of DM. In our study, too, the prevalence of increased serum uric acid was higher only in the IGT subjects.

The decrease in glucose tolerance that occurs with advancing age has been well documented (Fink et al. 1983). Decreases in insulin secretion and the beta-cell response to glucose, as well as in the sensitivity of peripheral tissues to insulin-mediated glucose metabolism, have been suggested as factors responsible for the age decline in glucose tolerance (Fink et al. 1983; Reaven & Reaven 1980). In the present study, the prevalence of DM in men also increased with advancing age.

In summary, background (risk) factors, including alcohol dependency, fatty liver, obesity, hyperuricemia, hyperlipidemia, and an increase in serum γ-glutamyl transpeptidase, may be important concomitants of IGT. However, it is of particular interest that no significant changes in serum alanine aminotransferase and aspartate aminotransferase were observed among normal, IGT and DM subjects.

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Dr Shigenobu Umeki,
Division of Respiratory Diseases,
Department of Medicine,
Kawasaki Medical School,
577 Matsushima,
Kurashiki,
Okayama 701-01, Japan.