Prevalence of Changes in Undiagnosed Glucose Intolerance According to Age and Gender in Japanese Middle-Aged Working People

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Background: Undiagnosed diabetes mellitus (DM) and impaired glucose tolerance (IGT) have important health consequences.

Methods and Results: To examine the prevalence of undiagnosed glucose intolerance, oral glucose tolerance tests were administered to 1,142 consecutively enrolled middle-aged subjects (age range 40–55 years; 914 men, mean 50.7 years; 228 women, mean 49.4 years) who worked in a company and underwent a health check in 2006. No subject had a history of glucose intolerance. Fasting glucose levels increased with age in both men and women, with the levels being higher in men than women at every age. Glucose intolerance was more common in men compared with women (fasting glucose 100.1±9.7 vs 92.9±9.6, P<0.01; 1-h 170.7±52.1 vs 139.7±11.6, P<0.01; 2-h 136.0±50.1 vs 119.8±31.5 mg/dl, P<0.01). The prevalence of IGT and DM was also higher in men than in women (IGT: 24.1 vs 16.7, P<0.01; diabetes 10.7 vs 1.4%, P<0.01).

Conclusions: Fasting glucose levels increased with age in both men and women, with levels being higher in men than in women at every age. The prevalences of undiagnosed IGT and type 2 DM were also higher in men than in women. (Circ J 2009; 73: 1062–1066)

Key Words: Age; Sex; Type 2 diabetes mellitus

Diabetes mellitus (DM) is a leading cause of both mortality and disabilities such as blindness, end-stage renal disease and non-traumatic limb amputations. In addition, DM increases the risk of cardiac, cerebral and peripheral vascular diseases, and in the obstetric setting is a major contributor to neonatal morbidity and mortality. Type 2 DM, characterized by insulin resistance and relative insulin deficiency, accounts for 90% of clinical cases. Although found with increasing frequency in adolescents, type 2 DM is usually associated with advancing age. It has a high rate of genetic penetrance and is associated with a high-fat diet, obesity and/or a lack of physical activity. The clinical features of type 2 DM can be quite insidious; for example, symptoms such as fatigue, weakness and dizziness may be mild and can be tolerated for many years before a patient seeks medical attention. If the degree of hyperglycemia is insufficient to produce symptoms, the diagnosis may be made only after the development of vascular or neuropathic complications.

Undiagnosed DM and impaired fasting glucose, a condition that increases the risk for DM, have important health consequences. It has been reported that approximately one-third of DM cases remain undiagnosed and, therefore, estimates of prevalence based on self-reporting or doctor diagnosed disease underestimate the total prevalence, which includes individuals with both known and undiagnosed type 2 DM. Type 2 DM occurs most commonly in adults over the age of 40 years so in the present study, we administered oral glucose tolerance tests to adults aged 40–55 years, who worked in a large Japanese company, in order to clarify the incidence of undiagnosed impaired glucose tolerance (IGT), including type 2 DM, in Japanese working-aged people.

Methods

Study Subjects

The study group comprised 1,142 consecutively enrolled, middle-aged subjects who worked in a large Japanese company (age range 40–55 years; 914 men, mean age 50.7 years; 228 women, mean age 49.4 years) who underwent a health check between January and December in 2006. No subject had a history of atherosclerotic disease or had been diagnosed with either impaired fasting glucose, IGT, or DM. Diabetes was diagnosed according to the criteria of the World Health Organization! Written informed consent was given by each patient before the study commenced and...
the procedures used in the study were approved by the Ethics Committee at Kumamoto University.

Study Design
The study involved 75-g oral glucose tolerance tests performed after a 12–14-h fast. Blood specimens were obtained in the fasting state at 1 and 2 h after the administration of a 75-g glucose equivalent load (Trelan-G, Takeda, Osaka, Japan). The plasma glucose concentrations were determined by the glucose oxidase method in an autoanalyzer. Fasting serum total cholesterol and triglyceride concentrations were measured enzymatically, and fasting serum high-density lipoprotein cholesterol concentration by heparin-Cu^{2+}/Ni^{2+} precipitation.

Table 1. Clinical Parameters of the Study Participants

<table>
<thead>
<tr>
<th></th>
<th>Men (n=914)</th>
<th>Women (n=228)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>50.7±5.4</td>
<td>49.4±5.2</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>124.0±18.5</td>
<td>114.8±19.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>76.9±11.6</td>
<td>70.6±12.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>148.1±109.4</td>
<td>88.2±44.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Body mass index (kg/m^2)</td>
<td>23.7±2.8</td>
<td>22.8±3.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>58.8±16.0</td>
<td>72.6±17.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>206.5±30.7</td>
<td>208.8±31.9</td>
<td>NS</td>
</tr>
</tbody>
</table>

BP, blood pressure; HDL, high-density lipoprotein.

Table 2. Glycemic Status of the Study Participants

<table>
<thead>
<tr>
<th></th>
<th>Men (n=914)</th>
<th>Women (n=228)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting blood glucose (mg/dl)</td>
<td>100.1±19.7</td>
<td>92.9±9.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>OGTT 1-h (mg/dl)</td>
<td>170.7±52.1</td>
<td>139.7±11.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>OGTT 2-h (mg/dl)</td>
<td>136.0±50.1</td>
<td>119.8±31.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Normal glucose tolerance</td>
<td>65.1%</td>
<td>81.9%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Impaired glucose tolerance</td>
<td>24.1%</td>
<td>16.7%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>10.7%</td>
<td>1.4%</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

OGTT, oral glucose tolerance test.

Table 3. Relationship Between Fasting Glucose and Glucose Tolerance

<table>
<thead>
<tr>
<th></th>
<th>NGT</th>
<th>IGT</th>
<th>Type 2 diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal fasting blood glucose (%)</td>
<td>48.5</td>
<td>8.3</td>
<td>0.8</td>
</tr>
<tr>
<td>Impaired fasting blood glucose (%)</td>
<td>21.4</td>
<td>13.0</td>
<td>8.1</td>
</tr>
</tbody>
</table>

IGT, impaired glucose tolerance; NGT, normal glucose tolerance.

Statistical Analysis
Differences in the variables between men and women were assessed by unpaired t tests. Changes in the variables were assessed by 2-way ANOVA with repeated measures, followed by post hoc testing with Scheffe’s test. Statistical significance was defined as P<0.05.

Results
Fasting glucose levels increased with age in both men and women, with the levels higher in men than women at each age (Figure 1). As shown in Table 1, blood pressure and triglyceride levels were also higher in men than in women (124.0±18.5/76.9±11.6 mmHg vs 114.8±19.4/79.6±12.5 mmHg, P<0.01; 148.1±109.4 mg/dl vs 88.2±44.0 mg/dl, P<0.01), and high-
density lipoprotein-cholesterol levels were lower in men (58.8±16.0 vs 72.6±17.4 mg/dl, P<0.01). Body mass index was also higher in men than in women (23.7±2.8 vs 22.8±3.1 kg/m², P<0.01). There was no difference between men and women in the total cholesterol levels. Glucose intolerance was more common in men than in women (fasting glucose 100.1±19.7 vs 92.9±9.6 mg/dl, P<0.01; 1-h 170.7±52.1 vs 139.7±11.6 mg/dl, P<0.01; 2-h 136.0±50.1 vs 119.8±31.5 mg/dl, P<0.01) (Table 2). The prevalence of IGT and type 2 DM was higher in men than in women (IGT: 24.1 vs 16.7%, P<0.01; type 2 DM: 10.7 vs 1.4%, P<0.01).

Subjects with normal fasting glucose (<100 mg/dl) comprised 57.6% of the study group (Table 3). Most of them showed normal glucose tolerance on the oral glucose tolerance test. However, 50% of subjects with impaired fasting glucose show normal glucose tolerance. The sensitivity and specificity of fasting glucose levels for glucose intolerance are significant (P<0.01).

The clinical parameters in subjects with glucose intolerance are shown in Tables 4 and 5. In each sex, blood pressure, body mass index, triglycerides and total cholesterol increased as glucose intolerance developed, but did not reach statistical significant.

As shown in Figure 3 the prevalence of glucose intolerance increased with age. Both blood pressure levels increased with age in men and women, with the levels higher in men.
than in women at each age (Figure 1). Total cholesterol levels were also augmented with age (Figure 2). In particular, the levels sharply increased after 50 years in women. Triglyceride levels were higher in men than in women at every age, but after 50 years of age, the levels in men tend to decrease.

Discussion

The incidence of type 2 DM increased with age in Japanese working age adults. In addition, the incidence of 2 “risk conditions”, impaired fasting glucose and IGT, also increased with age. These conditions represent the metabolic status that exists between normal glucose homeostasis and overt DM, with both significantly increasing the future risk of developing DM and in many cases forming part of the natural history of the disease. None of the subjects in this study had been diagnosed with impaired fasting glucose, IGT or atherosclerotic diseases. Our present findings support those of previous reports that showed the prevalence of type 2 DM usually increasing with advancing age.1,2

The incidence of cardiovascular disease is less in Japan than in other Western countries3 possibly because of a different lifestyle, especially in elderly Japanese, who often consume a low-calorie, low-fat diet that is high in vegetables and who also do not lead a sedentary lifestyle. In fact, we reported that hypercholesterolemia was a more important risk factor for acute myocardial infarction in patients under 65 years of age than for those older than 65 years.4 As with many other countries, Japanese dietary habits are undergoing substantial change, with younger Japanese individuals often preferring a Western lifestyle, such as high-fat meals and a lack of physical activity, which combine to lead to obesity. The incidence of DM and cardiovascular diseases can therefore be expected to increase in Japan in the near future. In fact, the International Diabetes Foundation (IDF) lists age >45 years as a major risk factor for DM and predicts that the number of affected persons will double by 2025 relative to the numbers recorded in 1995.5

Aging invariably leads to a deterioration in insulin sensitivity in muscle and adipose tissue, and the subsequent development of fasting hyperglycemia. Over time, pancreatic β-cell dysfunction caused by “exhaustion”, in combination with free fatty acids and inflammatory adipokines, leads to the emergence of glucose intolerance in elderly people. Thus, both basal and first-phase insulin release are affected.6 Working age adults in Japan also have an increased risk of developing chronic diseases, such as hypertension, obesity, dyslipidemia and diabetes. Psychosocial factors, physical activity and daily meals, and quality of life issues are important in this age group. The majority of working age adults’ life is characterized by stressful, long hours of work, combined with a high fat diet and lack of physical activity. In addition, alcohol intake and long night meals with other people, including workers in other companies may become very important. The resulting changes in body composition, reduction in activity, and environmental stressors that impede insulin action are important factors. The combined effect may increase the risk of working adults developing impaired fasting glucose, IGT and type 2 DM.

The fasting plasma glucose level is currently recommended as a screening test for type 2 DM and impaired fasting glucose because it is quick, easy to obtain and generally acceptable to patients in the clinical setting. Most subjects with normal fasting glucose (<100 mg/dl) show normal glucose tolerance on the oral glucose tolerance test. On the other hand, 50% of subjects with IGT show glucose intolerance. The sensitivity and specificity of the fasting glucose level for glucose intolerance are significant because in the present study some subjects with normal fasting glucose showed glucose intolerance, and 50% with IGT had normal glucose tolerance. It is well established that lifestyle modification, such as weight management and increased physical activity, reduces the risk of type 2 DM.7 Therefore, early recognition and intervention would be beneficial, particularly as cardiovascular complications develop soon after the onset of DM.8 Knowledge of type 2 diabetes, especially undiagnosed diabetes, may enhance people’s awareness, thereby leading to lifestyle modification. No patient in our study had been diagnosed with impaired fasting glucose or IGT. Fasting glucose levels alone do not identify individuals at increased risk of death associated with hyperglycemia.9 The oral glucose tolerance test enables detection of individuals with undiagnosed IGT, including type 2 DM, but when screening for abnormal glucose tolerance, even in people of working age, it is important to measure postprandial glucose concentrations after the glucose challenge.

Type 2 DM is more prevalent in men than women, which may be attributable to endogenous sex hormones. We, and other previous investigators, have reported that proinflammatory cytokines and/or elevation of blood glucose generates oxidative stress in the pancreatic islets, which ultimately leads to β-cell death by apoptosis.10 In the present study, the prevalence of type 2 DM and IGT was lower in women than in men aged 40–55 years. In this age range the majority of women were premenopausal or early postmenopausal. Estrogen is a major hormone involved in female reproduction and physiology, including glucose homeostasis and insulin sensitivity.11 Estrogen receptors are present in pancreatic β-cells12 and estrogen increases the release of insulin.13 It has been shown in mice that estrogen, at least in part, protects β-cells from oxidative stress-induced apoptosis by interacting with the estrogen receptor-α.26 There is evidence that estrogen also decreases hepatic glucose production in humans.27 In fact, estrogen replacement has been reported to improve insulin sensitivity28 and has beneficial effects on glucose tolerance in postmenopausal women.29–31 Endogenous ovarian hormones may therefore have a crucial role in determining the incidence of glucose intolerance in working age women.

It is well known there is a correlation between hyperandrogenicity and insulin resistance in women with polycystic ovarian syndrome and in non-diabetic women with abdominal obesity.32 There is also evidence in men of a link between low levels of testosterone and hyperinsulinemia,32 with lower testosterone levels being associated with increased waist/hip ratio, which suggests that lower testosterone levels may promote abdominal obesity. A derangement in the sex hormone levels in men may therefore contribute to the pre-diabetic state, leading eventually to the development of type 2 DM. Men with poorly controlled diabetes have been reported to have significantly lower free testosterone levels than men with good metabolic status.33 As there is a relationship between total testosterone and insulin sensitivity, mediated by obesity and visceral adiposity in non-diabetic men,34 testosterone may also play an important role in the pathogenesis of glucose intolerance in working age men.

In conclusion, fasting glucose levels increased with age in both men and women, with levels being higher in men.
than in women at every age. The prevalence of both undiagnosed IGT and type 2 DM was also higher in men than in women. These features of undiagnosed glucose intolerance in working age people may contribute to the gender difference in the incidence of coronary artery disease.

Acknowledgments

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References