Glucose Homeostasis in Hypertensive Subjects

Päivi Korhonen, Pertti Aarnio, Tarja Saarensranta, Pekka Jaatinen, Ilkka Kantola

Abstract—The objective of this study was to estimate the prevalence of undiagnosed impaired glucose homeostasis in hypertensive subjects in the general population. The most reasonable screening strategy for glucose disorders was also assessed. We carried out an oral glucose tolerance test for 1106 hypertensive subjects aged 45 to 70 years without previously diagnosed diabetes or cardiovascular disease. Blood pressure, waist circumference, body mass index, and plasma lipids were also measured. Type 2 diabetes was found in 66 (6%) of the subjects, impaired glucose tolerance in 220 (20%), and impaired fasting glucose in 167 (15%). If we had carried out an oral glucose tolerance test only for those hypertensive subjects with fasting plasma glucose ≥5.6 mmol/L, we would have missed ≈40% of the patients with impaired glucose tolerance. The International Diabetes Federation criteria of metabolic syndrome identified 96% of all the cases of type 2 diabetes and 88% of all the cases of impaired glucose tolerance. The prevalence of central obesity was alarming: 90% of the women and 82% of the men had a waist circumference ≥80 cm or ≥94 cm, respectively. Impaired glucose homeostasis and central obesity are common in hypertensive subjects. An oral glucose tolerance test is reasonable to carry out at least for the hypertensive subjects with metabolic syndrome. Weight stabilization is an important goal to treat hypertensive patients. (Hypertension. 2008;51:945-949.)

Key Words: hypertension ■ oral glucose tolerance test ■ impaired fasting glucose ■ impaired glucose tolerance ■ type 2 diabetes ■ metabolic syndrome

Concomitant hypertension and diabetes increase the risk of end organ damage, incidence of cardiovascular disease (CVD), and mortality.1,2 Also, the prediabetic condition, impaired glucose tolerance (IGT), is an independent risk predictor for incident CVD, as well as premature all-cause and cardiovascular mortality.3

Oral glucose tolerance test (OGTT) is the “gold standard” for diagnosing impaired glucose homeostasis. If fasting glucose is used alone as a screening tool, a third of diabetic subjects will not be diagnosed.4 Moreover, it is impossible to diagnose IGT without an OGTT.

The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology and of the European Association for the Study of Diabetes recently presented a recommendation that an OGTT should be carried out in all high-risk patients, such as patients with CVD.5 The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension and of the European Society of Cardiology recommended in the 2007 Guidelines for the Management of Arterial Hypertension6 that an OGTT should be carried out in all hypertensive patients whose fasting plasma glucose is ≥5.6 mmol/L.

Hypertension, per se, is associated with a double risk of developing type 2 diabetes (T2D).7 In this study we tried to assess whether all hypertensive subjects should be screened for glucose disorders with OGTT or whether fasting plasma glucose is sufficient to find the subjects for OGTT on the basis of experiences from the Harmonica Project, a population survey in southwestern Finland.

Methods

Subjects
The study sample of hypertensive subjects was drawn from the participants of a population survey, the Harmonica Project, which was carried out in the rural towns of Harjavalta and Kokemäki in southwestern Finland from autumn 2005 to autumn 2007. A risk factor survey, tape for the measurement of waist circumference (WC), and T2D risk assessment form (Finnish Diabetes Risk Score,8 available at http://www.diabetes.fi/english) were mailed to all of the inhabitants aged 45 to 70 years (n=6013). In the risk factor survey, subjects were asked for WC measured at the level of the navel, latest blood pressure, use of antihypertensive medication, gestational diabetes or hypertension, and history of coronary artery disease, myocardial infarction, or stroke of their parents or siblings.

The subjects were asked to mail the risk factor survey back to the health center if they were able to participate in the project. Participation and all of the tests included were free of charge for the subjects. Participation rate was 74% (4450 of 6013).

Subjects with above-mentioned risk factors or ≥15 points (≥12 points in Harjavalta) in the Finnish Diabetes Risk Score were invited for laboratory tests (OGTT and plasma lipids) and physical examination (measurements of WC, height, weight, and blood pressure) performed by a trained nurse. A total of 1106 hypertensive subjects were identified when all of the known patients with diabetes and patients with CVD were excluded. Hypertension was diagnosed if any of the following conditions were met: the patient was already taking antihypertensive...
therapy or the mean systolic blood pressure taken by a nurse was ≥140 mm Hg or the mean diastolic blood pressure was ≥90 mm Hg and the mean of home blood pressure monitoring was ≥135 mm Hg for systolic or ≥85 mm Hg for diastolic blood pressure.

Blood Pressure Measurements
Blood pressure was measured by a trained nurse with a mercury sphygmomanometer with subjects in a sitting posture, after resting for ≥5 minutes with the cuff placed on the arm. In obese arms a larger cuff was used. Diastolic blood pressure was defined as the disappearance of Korotkoff sounds (phase V). In each subject the mean of 2 readings taken at intervals of ≥2 minutes was used in the study. If the mean systolic blood pressure was ≥140 mm Hg or the mean diastolic blood pressure was ≥90 mm Hg, subjects were taught to use an automatic validated blood pressure monitor (Omron M4–1), which was lent to them for home blood pressure monitoring. The subjects whose arm circumference was >32 cm used a larger cuff. The subjects were instructed to take duplicate blood pressure measurements in the seated position after 5 minutes of rest in the morning and evening for 1 week. The recorded measurements, except those from the first day, were used to calculate the mean home blood pressure.

Height, Weight, and Body Mass Index
Height and weight were measured with the subjects in standing position without shoes and outer garments. Height was recorded to the nearest 0.1 cm. Body mass index was calculated as weight (kilograms) divided by the square of height (meters squared).

WC
WC was measured at the level midway between the lower rib margin and the iliac crest, rounded to the nearest 0.1 cm. The subjects were asked to breathe out gently at the time of the measurement, and the tape was held firmly in a horizontal position.

OGTT
OGTT was performed by measuring a fasting plasma glucose and a 2-hour plasma glucose after ingestion of a glucose load of 75 g of anhydrous glucose dissolved in water. Glucose values were measured from capillary whole blood with the HemoCue Glucose 201/H11001 anhydrous glucose dissolved in water. Glucose values were measured by using this selection criteria 58 (10.6%) had T2D and 133 (24.4%) had IGT. Thus, by using this selection criteria 66 of them (6.0%) had T2D, 220 (19.9%) had IGT, and 167 (15.1%) had impaired fasting glucose. The characteristics of the patients are shown in Table 2.

Fasting plasma glucose (fP-Gluc) was ≥5.6 mmol/L in 545 subjects. Among them, 58 (10.6%) had T2D and 133 (24.4%) had IGT based on the 2-hour postload plasma glucose. Thus, the IDF criteria of MBO were fulfilled by 744 subjects. Among them, 63 (8.5%) had T2D and 193 (25.9%) had IGT. OGTT identified 63 (95.5%) of 66 patients with T2D and 193 (87.7%) of 220 patients with IGT (Figure).

Among the 636 subjects who fulfilled the ATP III criteria of MBO, 59 (9.3%) had T2D and 161 (25.3%) had IGT. Thus, with OGTT, 59 (89.4%) of 66 patients with T2D and 161 of 220 (73.2%) patients with IGT were found (Figure).

In our cohort of 1106 hypertensive subjects, 484 (43.8%) were overweight (body mass index: 25 to 29.9 kg/m²), and 463 (41.9%) were obese (body mass index: ≥30 kg/m²). Central obesity defined as WC ≥80 cm in women and ≥94 cm in men was particularly prevalent, in 538 (89.8%) of 599

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### Table 1. Diagnostic Criteria of the Metabolic Syndrome

<table>
<thead>
<tr>
<th>Clinical Measure</th>
<th>ATP III (2001), Any 3 of the Following</th>
<th>IDF (2005), WC ≥ Any 2 of the Following</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference</td>
<td>≥88 cm in women or ≥102 cm in men</td>
<td>≥80 cm in women or ≥94 cm in men</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≥130/85 mm Hg</td>
<td>≥130/85 mm Hg or hypertension Rx</td>
</tr>
<tr>
<td>Glucose</td>
<td>&gt;5.6 mmol/L or T2D*</td>
<td>≥5.6 mmol/L or T2D</td>
</tr>
<tr>
<td>TG</td>
<td>≥1.7 mmol/L</td>
<td>≥1.7 mmol/L or TG Rx</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>&lt;1.29 mmol/L in women or &lt;1.03 mmol/L in men</td>
<td>&lt;1.29 mmol/L in women, &lt;1.03 mmol/L in men, or HDL cholesterol Rx</td>
</tr>
</tbody>
</table>

TG indicates triglycerides; HDL, high-density lipoprotein; Rx, regimen.

The 2001 definition identified fasting plasma glucose of ≥6.1 mmol/L as elevated. This was modified in 2004 to be ≥5.6 mmol/L.

### Plasma Lipids

Total cholesterol, high-density lipoprotein cholesterol, and triglycerides were measured enzymatically (Olympus AU640). Low-density lipoprotein cholesterol was calculated according to the Friedewald’s formula.

### Metabolic Syndrome

Metabolic syndrome (MBO) was diagnosed according to the criteria of IDF10 and the US National Cholesterol Education Program Third Adult Treatment Panel11 (ATP III; Table 1).

### Informed Consent

The study protocol and consent forms were reviewed and approved by the ethics committee of Satakunta Hospital District. All of the participants provided written informed consent for the project and subsequent medical research.

### Statistical Analysis

Data were recorded to SPSS for Windows 15.0 database. Using the database, descriptive analyses were done. Statistical significances between groups were calculated using cross-tabulation and χ² test or comparing means by using t test or variance analysis.

### Results

We examined 1106 hypertensive subjects (54.2% women and 45.8% men) who had not been diagnosed previously with diabetes or CVD. According to OGTT, 66 of them (6.0%) had T2D, 220 (19.9%) had IGT, and 167 (15.1%) had impaired fasting glucose. The characteristics of the patients are shown in Table 2.

Fasting plasma glucose (fP-Gluc) was ≥5.6 mmol/L in 545 subjects. Among them, 58 (10.6%) had T2D and 133 (24.4%) had IGT based on the 2-hour postload plasma glucose. Thus, by using this selection criteria 58 (87.9%) of 66 patients with T2D and 133 (60.5%) of 220 patients with IGT were found.

The IDF criteria of MBO were fulfilled by 744 subjects. Among them, 63 (8.5%) had T2D and 193 (25.9%) had IGT. OGTT identified 63 (95.5%) of 66 patients with T2D and 193 (87.7%) of 220 patients with IGT (Figure).

Among the 636 subjects who fulfilled the ATP III criteria of MBO, 59 (9.3%) had T2D and 161 (25.3%) had IGT. Thus, with OGTT, 59 (89.4%) of 66 patients with T2D and 161 of 220 (73.2%) patients with IGT were found (Figure).

In our cohort of 1106 hypertensive subjects, 484 (43.8%) were overweight (body mass index: 25 to 29.9 kg/m²), and 463 (41.9%) were obese (body mass index: ≥30 kg/m²). Central obesity defined as WC ≥80 cm in women and ≥94 cm in men was particularly prevalent, in 538 (89.8%) of 599
women and 413 (81.5%) of 507 men. Of the women in our study, 395 (65.9%) of 599 had WC < 88 cm, and, of the men, 251 (49.5%) of 507 had WC < 102 cm.

The mean WC in subjects with IGT was 97.5 ± 14.1 cm in women and 103.3 ± 11.8 cm in men. The mean WC in women and men with T2D was 102.6 ± 15.3 cm and 107.7 ± 9.7 cm, respectively. In hypertensive subjects with normal glucose homeostasis, the mean WC was 93.1 ± 12.2 cm in women and 102.2 ± 10.9 cm in men. There was a statistically significant difference between impaired glucose homeostasis and WC only in women.

Discussion

In this study, impaired glucose homeostasis was found in 41% of hypertensive subjects aged 45 to 70 years who had no previously diagnosed diabetes or CVD. In a recent population

Table 2. Characteristics of the Subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal Glucose Homeostasis (n = 653)</th>
<th>Impaired Glucose Homeostasis (n = 453)</th>
<th>Mean Difference</th>
<th>t Test 95% Confidence Interval</th>
<th>χ² Test P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, mean, %</td>
<td>56.8</td>
<td>50.3</td>
<td>NA</td>
<td>NA</td>
<td>0.033</td>
</tr>
<tr>
<td>Current smoker, mean, %</td>
<td>14.9</td>
<td>14.8</td>
<td>NA</td>
<td>NA</td>
<td>0.976</td>
</tr>
<tr>
<td>Treated for hypertension, mean, %</td>
<td>61.4</td>
<td>70.8</td>
<td>NA</td>
<td>NA</td>
<td>0.001</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>58.72 (6.66)</td>
<td>60.37 (6.62)</td>
<td>−1.65</td>
<td>−2.44 to −0.85</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, mean (SD), kg/m²</td>
<td>29.20 (4.68)</td>
<td>30.50 (5.46)</td>
<td>−1.30</td>
<td>−1.92 to −0.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WC, men, mean (SD), cm</td>
<td>102.23 (10.94)</td>
<td>103.89 (11.36)</td>
<td>−0.67</td>
<td>−3.62 to 0.30</td>
<td>0.095</td>
</tr>
<tr>
<td>WC, women, mean (SD), cm</td>
<td>93.1 (12.2)</td>
<td>98.0 (13.9)</td>
<td>−4.89</td>
<td>−7.02 to −2.77</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clinic systolic BP, mean (SD), mm Hg</td>
<td>150.76 (17.79)</td>
<td>153.76 (17.07)</td>
<td>−3.00</td>
<td>−5.10 to −0.90</td>
<td>0.005</td>
</tr>
<tr>
<td>Clinic diastolic BP, mean (SD), mm Hg</td>
<td>90.08 (8.42)</td>
<td>90.25 (9.05)</td>
<td>−0.17</td>
<td>−1.21 to 0.86</td>
<td>0.753</td>
</tr>
<tr>
<td>Pulse pressure, mean (SD), mm Hg</td>
<td>60.67 (14.52)</td>
<td>63.51 (14.49)</td>
<td>−2.83</td>
<td>−4.57 to −1.09</td>
<td>0.001</td>
</tr>
<tr>
<td>Total cholesterol, mean (SD), mmol/L</td>
<td>5.35 (0.89)</td>
<td>5.23 (0.98)</td>
<td>0.13</td>
<td>0.02 to 0.24</td>
<td>0.025</td>
</tr>
<tr>
<td>LDL cholesterol, mean (SD), mmol/L</td>
<td>3.22 (0.78)</td>
<td>3.12 (0.85)</td>
<td>0.09</td>
<td>−0.01 to 0.19</td>
<td>0.064</td>
</tr>
<tr>
<td>HDL cholesterol, mean (SD), mmol/L</td>
<td>1.53 (0.41)</td>
<td>1.43 (0.40)</td>
<td>0.10</td>
<td>0.05 to 0.15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides, mean (SD), mmol/L</td>
<td>1.36 (0.67)</td>
<td>1.50 (0.78)</td>
<td>−0.15</td>
<td>−0.24 to −0.06</td>
<td>0.001</td>
</tr>
<tr>
<td>Fasting glucose, mean (SD), mmol/L</td>
<td>5.24 (0.47)</td>
<td>6.30 (1.28)</td>
<td>−1.06</td>
<td>−1.18 to −0.94</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2-h postload glucose, mean (SD), mmol/L</td>
<td>6.61 (1.20)</td>
<td>9.51 (2.70)</td>
<td>−2.89</td>
<td>−3.16 to −2.63</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; NA, not applicable.

Figure. Categories of glucose tolerance in subjects with or without MBO according to the IDF criteria and the ATP III criteria. IFG indicates impaired fasting glucose.
survey among 4500 randomly selected Finns aged 45 to 74 years, the prevalence of newly diagnosed impaired glucose homeostasis was 28% in women and 32% in men.\textsuperscript{12} Thus, hypertensive subjects seem to have more glucose disorders than the general population.

In our study, IGT was found in every fifth hypertensive subject highlighting the importance of OGTT in the diagnosis of glucose disorders in hypertensive patients and in estimating the total cardiovascular risk of the patient. In the DECODE (Diabetes Epidemiology: COLlaborative analysis of Diagnostic criteria in Europe) study, people with IGT and a normal fasting glucose (≤6.0 mmol/L) formed the group with the largest number of excess deaths.\textsuperscript{13} In our cohort, 67% of the IGT patients had IP-Gluc ≤6.0 mmol/L, and 40% had IP-Gluc <5.6 mmol/L.

It has been shown in young men that fasting plasma glucose levels >5.0 mmol/L significantly increase the risk of T2D.\textsuperscript{14} In our study of 1106 middle-aged hypertensive subjects, 248 (22%) had IP-Gluc ≤5.0 mmol/L. Of them, 37 (15%) had IGT and 3 (1%) had T2D based on the 2-hour postload plasma glucose. Because OGTT is a time- and effort-consuming test, it would be practical to select persons for proceeding to OGTT. The joint effect of overweight and a high-normal fasting plasma glucose level might be a useful tool in this regard, as shown by Tirosh et al.\textsuperscript{14}

If we would have carried out OGTT only for the subjects with IP-Gluc ≥5.6 mmol/L, we had missed ≈40% of the patients with IGT. But if OGTT is performed for the hypertensive subjects who fulfill the IDF criteria of MBO, ≈90% of IGT can be found. In this regard, the ATP III criteria were less sensitive, because the cutoff values for WC are higher than in the IDF definition (Table 1). The IDF definition also better identified the patients with impaired fasting glucose compared with the ATP III definition (80% versus 67%). In our cohort of 599 hypertensive women, 24% had a WC 80 to 88 cm, and among them, the prevalence of T2D was 5%, and the prevalence of IGT was 22%. Of the 507 hypertensive men, 32% had a WC of 94 to 102 cm. Among them, 4% had T2D and 20% had IGT. Thus, using the ATP III criteria of MBO to select patients for proceeding to OGTT would reduce the number of investigations needed but would miss ≈30% of the patients with IGT compared with the 10% who would be missed by using the IDF criteria. The diagnosis of IGT is very important, because, as shown in the Whitehall Study, during 18 to 20 years of follow-up, cardiovascular mortality among people with IGT was about twice that among normal control subjects.\textsuperscript{15} In the Hoorn Study, risk of conversion to T2D during 6.5 years of follow-up was >10 times higher in people with IGT than in people with normal glucose homeostasis.\textsuperscript{16}

In Finland, it is estimated that the excess costs of treating T2D with complications is 24 times higher than treating T2D patients with no complications.\textsuperscript{17} This highlights the importance of OGTT in diagnosing T2D and prediabetes early before any complications have been developed.

OGTT has not been widely used in risk assessment among hypertensive patients. Salmasi et al\textsuperscript{18} studied 99 consecutive patients with unknown diabetes or cardiac history who were attending a hypertension clinic because of uncontrolled hyperglycemia. OGTT was abnormal in 58% of the patients, indicating IGT in 18% and T2D in 24%. These figure are higher than in our cohort, possibly reflecting a more serious disturbance of metabolic homeostasis in uncontrolled hypertension. Lüders et al\textsuperscript{19} performed an OGTT on 260 hypertensive patients in daily clinical practice in Germany. T2D was diagnosed in 12% and IGT in 39% of the patients. In our cohort of 1106 Finnish hypertensive subjects, T2D was found in 6% and IGT in 20%, but we excluded the patients with known T2D or CVD. Total cholesterol was surprisingly higher in the normal glucose homeostasis group, but the difference was explained by the higher high-density lipoprotein cholesterol concentration (Table 2).

The proportion of overweight and obese individuals among hypertensive subjects is alarming. In our cohort of 45- to 70-year-old hypertensive subjects, the prevalence of central obesity according to the International Diabetes Federation (IDF) criteria (WC of 80 cm for women and 94 cm for men) was 90% in women and 82% in men. In the Finnish general population aged 45 to 74 years, the corresponding figures were 76% and 69%.\textsuperscript{12} In our study, glucose homeostasis and WC had statistically significant correlation only in women and not in men, which is surprising and needs to be studied further. Nevertheless, it is well established that there is a linear relationship between reduction in weight and reduction in blood pressure.\textsuperscript{20} Because in middle-aged individuals body weight frequently shows a progressive increase, weight stabilization should be considered an important goal to treat hypertension and to prevent diabetes. For a hypertensive individual, the motivation to lose weight might be higher when she or he has the knowledge of glucose homeostasis as well.

**Perspectives**

We demonstrated that IGT and T2D are more common in hypertensive subjects than in the general population. Cardiovascular mortality among people with IGT is approximately twice that among normal people and close to patients with T2D.\textsuperscript{16} An OGTT is needed to define the total cardiovascular risk of the hypertensive patient, because it enables detection of people with IGT and T2D even when their fasting plasma glucose is normal. OGTT is a time- and effort-demanding method to be performed on all hypertensive subjects. Using the IDF criteria of MBO as the criteria for carrying out OGTT, the number of investigations can be reduced by one third and still find 96% of the patients with T2D and 88% with IGT.

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**Disclosures**

None.

**References**


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