Close Relationship of Abnormal Glucose Tolerance With Endothelial Dysfunction in Hypertension

Hirofumi Tomiyama, Yutaka Kimura, Ryo Okazaki, Toshio Kushiro, Masayuki Abe, Yoichi Kuwabara, Hideo Yoshida, Shoji Kuwata, Takashi Kinouchi, Nobutaka Doba

Abstract—Hypertension is frequently accompanied by left ventricular hypertrophy, endothelial dysfunction, and abnormal glucose metabolism. However, no study has examined the relative pathological significance of left ventricular hypertrophy and abnormal glucose metabolism on endothelial dysfunction in hypertension. This study was conducted to evaluate whether abnormal glucose tolerance assessed by 75-g oral glucose tolerance test or left ventricular hypertrophy is more closely associated with endothelial dysfunction in never-treated hypertensive patients without elevated fasting blood glucose. We studied 107 unmedicated hypertensive patients (mean age, 54±10 years) whose fasting blood glucose was <7.0 mmol/L. Endothelial function was assessed by change in brachial artery diameter in response to reactive hyperemia, and left ventricular mass index was determined by ultrasonography. Simple linear regression analysis demonstrated that endothelial function significantly correlated with left ventricular mass index and 2-hour blood glucose in 75-g oral glucose tolerance test, but not with fasting blood glucose. Multiple linear regression analysis revealed that endothelial function significantly correlated with 2-hour blood glucose (β = -2.68, P<0.05) after we controlled for other clinical variables. Patients were divided into 3 groups according to 2-hour blood glucose levels. Endothelial function was more impaired in patients with diabetes (n=12; 4.7±1.8%) and in those with impaired glucose tolerance (n=31; 6.3±2.9%) than in those with normal glucose tolerance (n=64; 8.4±4.5%) (P<0.05), but left ventricular mass index was similar in these 3 groups. Abnormal glucose tolerance assessed by 75-g oral glucose tolerance test, rather than left ventricular hypertrophy, may have direct pathophysiological relevance to endothelial dysfunction in borderline to moderate hypertensive patients. (Hypertension. 2000;36:245-249.)

Key Words: hyperglycemia ■ hypertension, left ventricular ■ endothelium ■ glucose

Endothelial dysfunction is a feature of early stage atherosclerosis1 and is associated with cardiovascular risk.2 Recently, the probability of this abnormality as a risk marker or surrogate end point in the management of cardiovascular disease has been discussed.3 In hypertension, an association between left ventricular hypertrophy, which is an independent predictor of cardiovascular morbidity and mortality,4 and endothelial dysfunction has been reported in patients with hypertension.5 On the other hand, abnormal glucose metabolism (especially the early stage of abnormal glucose metabolism) frequently accompanies hypertension, and this association is well documented as the insulin resistance syndrome.6 Endothelial dysfunction is recognized even in the early stage of abnormal glucose metabolism.7 Except in cases of overt hyperglycemia, the 75-g oral glucose tolerance test (OGTT) is a standard method to assess abnormalities of glucose metabolism, and recent reports reinforced the clinical importance of the 75-g OGTT for detecting the attributable risks for cardiovascular events.8 While hypertension is linked pathophysiologically with left ventricular hypertrophy and abnormal glucose metabolism in different manners,4,9 no study has ever examined the clinical significance of hypertension-associated early-stage abnormal glucose tolerance assessed by 75-g OGTT on endothelial dysfunction.

We evaluated endothelial function, left ventricular mass, and glucose metabolism in patients with borderline to moderate hypertension without diabetic fasting plasma glucose and determined the relationships of abnormal glucose tolerance assessed by 75-g OGTT and left ventricular hypertrophy with endothelial dysfunction.

Methods

Patients

We studied 107 consecutive ambulatory Japanese patients with borderline to mild hypertension (59 men, 48 women; mean age, 54±10 years) who visited Teikyo University School of Medicine, Ichihara Hospital, between April 1997 and June 1999. Inclusion
criteria were as follows: no history of treatment with antihypertensive medications; evaluable ultrasonographic recordings of the heart, carotid artery, and brachial artery; and an average systolic blood pressure between 140 and 180 mm Hg and an average diastolic pressure between 90 and 105 mm Hg during 3 consecutive visits before the study. Patients with secondary hypertension, other serious medical problems requiring specific treatments, or fasting plasma glucose ≥7.0 mmol/L were excluded from the study.

Study Protocol
The study protocol was approved by the Ethics Committee of Teikyo University School of Medicine, Ichihara Hospital. Written informed consent was obtained from all patients. Each patient underwent echocardiography, ultrasonographic examination of the carotid arteries, assessment of brachial endothelial function, and 75-g OGTT. The procedures were in accordance with institutional guidelines.

Ultrasonographic Examinations of the Heart and the Carotid Arteries
Guided by 2-dimensional echocardiography, M-mode echocardiograms were obtained with the use of a Sonolayer system (SSH-160A, Toshiba Co) equipped with a 2.5-MHz or a 3.75-MHz transducer. Data were printed on a strip-chart recorder at a speed of 50 mm/s. The mean of 2 M-mode measurements determined by 2 investigators (H.T. and Y. Kimura) was used. The left ventricular mass index (LVMI) was calculated by the method of Devereux and Reichek, which is the left ventricular mass divided by the body surface area.

After the echocardiographic examination, imaging of both carotid arteries was performed with the use of an ultrasonographic system (SSH-160A, Toshiba) equipped with a 7.5-MHz transducer. Guided by 2-dimensional ultrasonography, end-diastolic far wall thickness and end-diastolic and peak-systolic internal dimensions were obtained on the basis of the means from 3 cardiac cycles of measurements from M-mode images of the right and the left common carotid arteries. Carotid arterial distensibility was calculated as previously described. Plaque was measured in B-mode images, and the plaque score was determined.

Brachial Endothelial Function Test
The brachial endothelial function test, a modified version of the method of Celermajer et al, has been described previously. Briefly, an ultrasonographic system (SSH-160A, Toshiba) equipped with a 7.5-MHz transducer was used to image the brachial artery of the dominant arm. In the long-axis view, a straight segment ($\geq$1 cm) of the brachial artery immediately above the antecubital fossa was used in the study. M-mode tracings were obtained together with simultaneous electrocardiographic recordings with the use of a strip-chart recorder. After baseline recordings were obtained, the percent change in the diameter of the brachial artery in response to reactive hyperemia (the cuff was inflated at the upper arm to 20 mm Hg above systolic blood pressure for 5 minutes) or to the administration of glyceryl trinitrate was determined. For each patient, the internal diameter of the brachial artery was measured by 2 observers (H.T. and Y. Kimura).

Oral Glucose Tolerance Test
An OGTT was performed in the morning after a 12-hour overnight fast. Blood samples were drawn before and 30, 60, and 120 minutes after ingestion of a solution containing 75 g of glucose, and blood glucose and plasma insulin levels were determined.

Laboratory Measurements
Blood glucose levels were determined with the use of a Glucoroder SX Analyzer (A & T). Plasma triglycerides, total cholesterol, and HDL cholesterol levels were measured enzymatically with a Hitachi 731 Analyzer. Plasma insulin level was determined by radioimmunoassay (SRL).

Table 1. Clinical Characteristics of Hypertensive Patients Studied

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>54±10</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>59/48</td>
</tr>
<tr>
<td>Smokers, No.</td>
<td>35</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24±4</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>159±20</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>94±9</td>
</tr>
<tr>
<td>LVM, g/m²</td>
<td>124±29</td>
</tr>
<tr>
<td>IMT, mm</td>
<td>0.75±0.13</td>
</tr>
<tr>
<td>Plaque score</td>
<td>0.5±1.1</td>
</tr>
<tr>
<td>CAD, %kPa</td>
<td>1.75±0.74</td>
</tr>
<tr>
<td>FBG, mmol/L</td>
<td>5.5±0.5</td>
</tr>
<tr>
<td>FINS, pmol/L</td>
<td>73±42</td>
</tr>
<tr>
<td>2-hour BG, mmol/L</td>
<td>8.1±2.5</td>
</tr>
<tr>
<td>2-hour INS, pmol/L</td>
<td>317±183</td>
</tr>
<tr>
<td>TC, mmol/L</td>
<td>5.3±0.9</td>
</tr>
<tr>
<td>TG, mmol/L</td>
<td>15.9±9.1</td>
</tr>
<tr>
<td>HDL, mmol/L</td>
<td>1.6±0.6</td>
</tr>
<tr>
<td>HYP, %</td>
<td>7.4±4.1</td>
</tr>
<tr>
<td>GTN, %</td>
<td>10.5±4.2</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; IMT, thickness of the intimal-media complex of the common carotid artery; CAD, carotid arterial distensibility; FBG, fasting blood glucose; FINS, fasting plasma insulin concentration; 2-hour BG, blood glucose at 2 hours in 75-g OGTT; 2-hour INS, plasma insulin concentration at 2 hours in 75-g OGTT; TC, total cholesterol; TG, triglyceride; HYP, change of diameter of brachial artery in response to reactive hyperemia; and GTN, change in the diameter of the brachial artery in response to the administration of glyceryl trinitrate.

Statistical Analysis
Data are expressed as the mean±SD. Statistical analysis was performed with the SPSS software package (SPSS Inc). Univariate linear regression analysis and standard t test were used to evaluate the relationships between endothelial function and other clinical variables. Multiple linear regression analysis was performed to evaluate interaction and independent correlation between these variables. To test interaction effect, a product term was introduced among the independent variables. For example, if the interaction involving gender and LVMI was of interest, one model to consider was the following:

$$\text{Y} = \beta_0 + \beta_1X_1 + \beta_2X_2 + \beta_{12}X_1X_2$$

where Y is the percent change in diameter of the brachial artery in response to reactive hyperemia, $X_1$ is LVMI, and $X_2$ is gender (1: male; 0: female).

The hypothesis $\beta_{12}=0$ was tested by partial F test. If it was rejected, we considered that there was no interaction effect between LVMI and gender.

In 2-group comparisons, the independent sample t test with Levene’s test for equality of variance was used. In 3-group comparisons, 1-way ANOVA or cross-table $\chi^2$ test was performed. For multiple comparisons, Scheffe’s method or Bonferroni’s method was performed to identify the individual difference. A value for 2-tailed $P<0.05$ was accepted as statistically significant.

Results
Of the 107 patients, 43 had borderline hypertension and 64 had mild or moderate hypertension. Table 1 summarizes the
TABLE 2. Regression Coefficients of the Univariate Linear Regression Analysis Between Vascular Function and Clinical Variables

<table>
<thead>
<tr>
<th>Correlates</th>
<th>HYP</th>
<th>GTN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>−0.27 (P&lt;0.01)</td>
<td>−0.23 (P&lt;0.05)</td>
</tr>
<tr>
<td>BMI</td>
<td>−0.11 (NS)</td>
<td>−0.13 (NS)</td>
</tr>
<tr>
<td>SBP</td>
<td>−0.15 (NS)</td>
<td>−0.15 (NS)</td>
</tr>
<tr>
<td>DBP</td>
<td>−0.11 (NS)</td>
<td>−0.10 (NS)</td>
</tr>
<tr>
<td>LVMI</td>
<td>−0.21 (P&lt;0.05)</td>
<td>−0.18 (NS)</td>
</tr>
<tr>
<td>FBG</td>
<td>−0.09 (NS)</td>
<td>−0.07 (NS)</td>
</tr>
<tr>
<td>FINS</td>
<td>0.02 (NS)</td>
<td>−0.01 (NS)</td>
</tr>
<tr>
<td>2-hour BG</td>
<td>−0.31 (P&lt;0.01)</td>
<td>−0.26 (P&lt;0.01)</td>
</tr>
<tr>
<td>2-hour INS</td>
<td>−0.12 (NS)</td>
<td>−0.19 (NS)</td>
</tr>
<tr>
<td>TC</td>
<td>−0.12 (NS)</td>
<td>−0.18 (NS)</td>
</tr>
<tr>
<td>TG</td>
<td>−0.18 (NS)</td>
<td>−0.21 (P&lt;0.05)</td>
</tr>
</tbody>
</table>

Abbreviations are as defined in Table 1.

The regression coefficient between the percent change in the diameter of the brachial artery in response to reactive hyperemia in patients with abnormal glucose metabolism was −0.24 for male and −0.17 for female. The interaction effect of gender on the correlation was tested with a regression model by introducing a product term, such as gender×LVMI. The statistical test showed no interaction effect by gender. Similarly, smoking habit or gender had no significant interaction effect on the relation between the percent change in diameter of the brachial artery in response to reactive hyperemia in hypertension.

Independent association of LVMI and 2-hour BG with the percent change in diameter of the brachial artery in response to reactive hyperemia was assessed by multiple regression analysis after we controlled for age, blood pressure, total cholesterol and triglycerides, and smoking habits (Table 3). Multivariate analysis revealed that 2-hour BG independently correlated with the percent change in diameter of the brachial artery in response to reactive hyperemia. In contrast, LVMI was no more associated with the percent change in diameter of the brachial artery in response to reactive hyperemia. Furthermore, in a multiple regression analysis with a model containing both 2-hour BG and LVMI as independent variables for the percent change in diameter of the brachial artery in response to reactive hyperemia, only 2-hour BG was a significant variable (β = −0.26, P=0.03).

When the hypertensive patients were divided into a group with normal fasting blood glucose (<6.0 mmol/L; n=89) and a group with impaired fasting blood glucose (≥6.0 mmol/L) (n=18), the change in diameter of the brachial artery in response to reactive hyperemia was 7.5±3.8% in the former and 7.1±5.2% in the latter. Thus, endothelial function was similar in both groups. Then, the patients were classified by 75-g OGTT into a normal glucose tolerance group (2-hour BG <7.8 mmol/L), an impaired glucose tolerance group (7.8≤ 2-hour BG <11.1 mmol/L), and a diabetes group (2-hour BG ≥11.1 mmol/L). Table 4 shows the results of comparison of clinical variables among hypertensive subjects with normal glucose tolerance, impaired glucose tolerance, and diabetes. The percent change in diameter of the brachial artery in response to reactive hyperemia was significantly impaired in hypertensive subjects with impaired glucose tolerance compared with those with normal glucose tolerance, and this impairment was significantly more prominent in hypertensive subjects with diabetes than in those with impaired glucose tolerance. In addition, in 1-way ANOVA with Schefé’s method, plaque score was higher in patients with diabetes (1.5±1.6) than in those with impaired glucose tolerance (0.5±1.0) (P<0.05). LVMI and age were similar in the 3 hypertensive subgroups.

**Discussion**

In hypertension, an elevated blood pressure induces left ventricular hypertrophy to compensate for increased wall stress and also impairs endothelial function by increasing shear stress. In this context, an association between these 2 pathophysiological abnormalities has been reported. In subjects with abnormal glucose metabolism, hyperglycemia also impairs endothelial function. Thus, either elevation of blood pressure or impaired glucose metabolism can directly affect...
endothelial function. To our knowledge, this is the first study to examine whether left ventricular hypertrophy or abnormal glucose metabolism is more closely associated with endothelial dysfunction in hypertensive patients.

In the present study, multiple linear regression analysis demonstrated a significant relationship between endothelial dysfunction and 2-hour BG but no significant correlation between endothelial function and elevated blood pressure level or increased left ventricular mass. Hypertensive patients were divided into 3 groups according to the 75-g OGTT values. Endothelial function was significantly more impaired in patients with glucose intolerance or diabetes than in those with normal glucose metabolism. Age, blood pressure, and IMT were similar in these 3 subgroups. Therefore, in the setting of untreated borderline to moderate hypertension without elevated fasting blood glucose, the accompanying early-stage abnormal glucose metabolism assessed by 75-g OGTT, rather than left ventricular hypertrophy, may have a close pathophysiological relation with the impairment of endothelial function.

The American Diabetes Association dismissed the use of OGTT and recommended using impaired fasting glucose instead of impaired glucose tolerance as the diagnostic criterion of diabetes. However, the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study demonstrated that 75-g OGTT provides additional information for the prognosis of diabetes. The results in the present study demonstrated that 2-hour BG is a better index than fasting blood glucose for evaluating endothelial dysfunction in cases complicated with hypertension. Recently, Kawano et al demonstrated that acute postprandial hyperglycemia suppresses endothelium-dependent vaso-

dilatation, and our results support their notion that prolonged and repeated postprandial hyperglycemia may contribute to the development and progression of atherosclerosis.

In addition to the role in controlling high blood pressure, left ventricular mass is a risk marker or a surrogate end point in the management of hypertension. On the other hand, interventions to correct abnormal glucose metabolism or endothelial dysfunction have not been regarded as additional surrogate end points in the management of hypertension. Although all the patients in the present study had either normal or early-stage abnormal glucose metabolism (because patients with overt diabetes mellitus were excluded from the study), endothelial dysfunction was prominent in patients with either glucose intolerance or diabetes, and atherosclerotic plaques in carotid artery were already evident in patients with diabetes. Suzuki et al reported that insulin resistance is an independent risk factor for carotid arterial sclerosis in hypertension. In addition to confirming their results, the present study also demonstrated that vascular functional damage, which is a key factor for the progression of atherosclerosis, is evident in hypertensive patients with even early-stage abnormal glucose metabolism. Therefore, the present study proposes the importance of conducting further studies to clarify whether interventions for early-stage abnormal glucose metabolism or endothelial dysfunction are beneficial in preventing progression of cardiovascular abnormalities.

**Limitations**

The impairment of endothelial function has been demonstrated in patients with either hypertension or abnormal glucose metabolism. On the other hand, some studies have demonstrated that insulin resistance is associated with endothelial dysfunction independent of blood pressure level. These findings lead to a hypothesis that elevated blood pressure and abnormal glucose level synergistically contribute to endothelial dysfunction. According to our previous report, the percent change in diameter of the brachial artery in response to reactive hyperemia in hypertensive patients with normal glucose tolerance (8.4±4.5%) was significantly lower than that in 25 age-matched healthy volunteers (11.6±2.3%) (14 men and 11 women; mean age, 52±12 years) (P<0.01). While we did not perform 75-g OGTT for these healthy volunteers, this result agrees with a synergetic contribution of elevated blood pressure and abnormal glucose metabolism to endothelial dysfunction. Further studies are needed to determine whether elevated blood pressure and abnormal glucose metabolism synergistically contribute to endothelial dysfunction.

**Conclusion**

In patients with borderline to moderate hypertension, hypertension associated with impaired glucose tolerance assessed by 75-g OGTT is closely related to endothelial dysfunction, irrespective of the presence or absence of left ventricular hypertrophy. This close relation may play some roles in the progression of cardiovascular abnormalities in untreated hypertensive patients.
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References

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