Original Article

Predictors for Prehypertension in Patients with Impaired Glucose Tolerance

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Prehypertension (PHT) is associated with increased risk of cardiovascular disease and progression to hypertension. Insulin resistance and hyperinsulinemia have been reported among patients with hypertension. In addition, impaired glucose tolerance (IGT) is a strong predictor of not only of type 2 diabetes but also of cardiovascular disease. However, little is known about the impact of insulin resistance on recently defined categories of hypertension and IGT. The aim of this study was to examine associations of surrogate makers of insulin resistance with PHT and IGT. In a total of 102 IGT patients with normotension and PHT (age: 58±5 years; mean±SD), blood pressure measurement, 75 g oral glucose tolerance testing (OGTT), metabolic analysis and echocardiography were performed. Body mass index was higher in the PHT group than in the normotension group ($p<0.05$). The fasting immnunoreactive insulin (F-IRI) ($p<0.0001$), homeostasis model assessment (HOMA) index ($p<0.0001$), 30 min postload glucose ($p<0.05$), 60 min postload glucose ($p<0.05$), 120 min postload glucose ($p<0.01$), 120 min postload insulin ($p<0.0001$) and left ventricular mass index (LVMI) ($p<0.0005$) were higher in the PHT group than in the normotension group. Multivariate logistic analysis revealed that the presence of PHT was independently predicted by F-IRI. Our findings indicate that the presence of PHT was associated with hyperinsulinemia and that the F-IRI was an independent predictor of PHT in these Japanese patients with IGT. (*Hypertens Res* 2008; 31: 1913–1920)

Key Words: **prehypertension, normotension, insulin resistance, impaired glucose tolerance**

Introduction

Hypertension has been recognized as a major risk factor for several cardiovascular diseases (*1–3*). In its seventh report, the 2003 Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) defined a new set of guidelines for the prevention and management of hypertension. According to the JNC-7, normal blood pressure (BP) is defined as systolic BP less than 120 mmHg and a diastolic BP less than 80 mmHg; a BP of 120–139/80–89 mmHg is defined as prehypertension (PHT) (*4*). PHT is not currently categorized as a disease; however, prehypertensive individuals have double the risk for developing hypertension of those with normal BP (*5*) and even slightly elevated BP is known to increase cardiovascular risk (*6–9*).

Insulin resistance and hyperinsulinemia are two metabolic disorders that have been demonstrated to be frequently associated with both human and experimental hypertension (*10, 11*). This observed association between hypertension and hyperinsulinemia is progressively assuming greater significance because of the putative atherogenic effect of hyperinsulinemia (*12*).

Impaired glucose tolerance (IGT) is a strong predictor of not only of type 2 diabetes (*13*) but also of cardiovascular disease and other complications of diabetes (*14, 15*).

There are few data on whether insulin resistance/hyperinsulinemia are involved in individuals with PHT and IGT.

We screened 452 consecutives subjects

22 patients treatment with antihypertensive agents,
8 patients treatment with lipid-lowering medication,
7 patients treatment with antidiabetic drugs,
3 patients had angina pectoris,
2 patients had symptomatic cerebrovascular disease,
2 patients had renal failure,
1 patient had liver dysfunction,
1 patients had arteriosclerotic obliterans.

↓

**We performed 75 g oral glucose tolerance test in 406 subjects
April 2005 to March 2008**

157 normal glucose	147 impaired glucose tolerance	102 type 2 diabetes mellitus

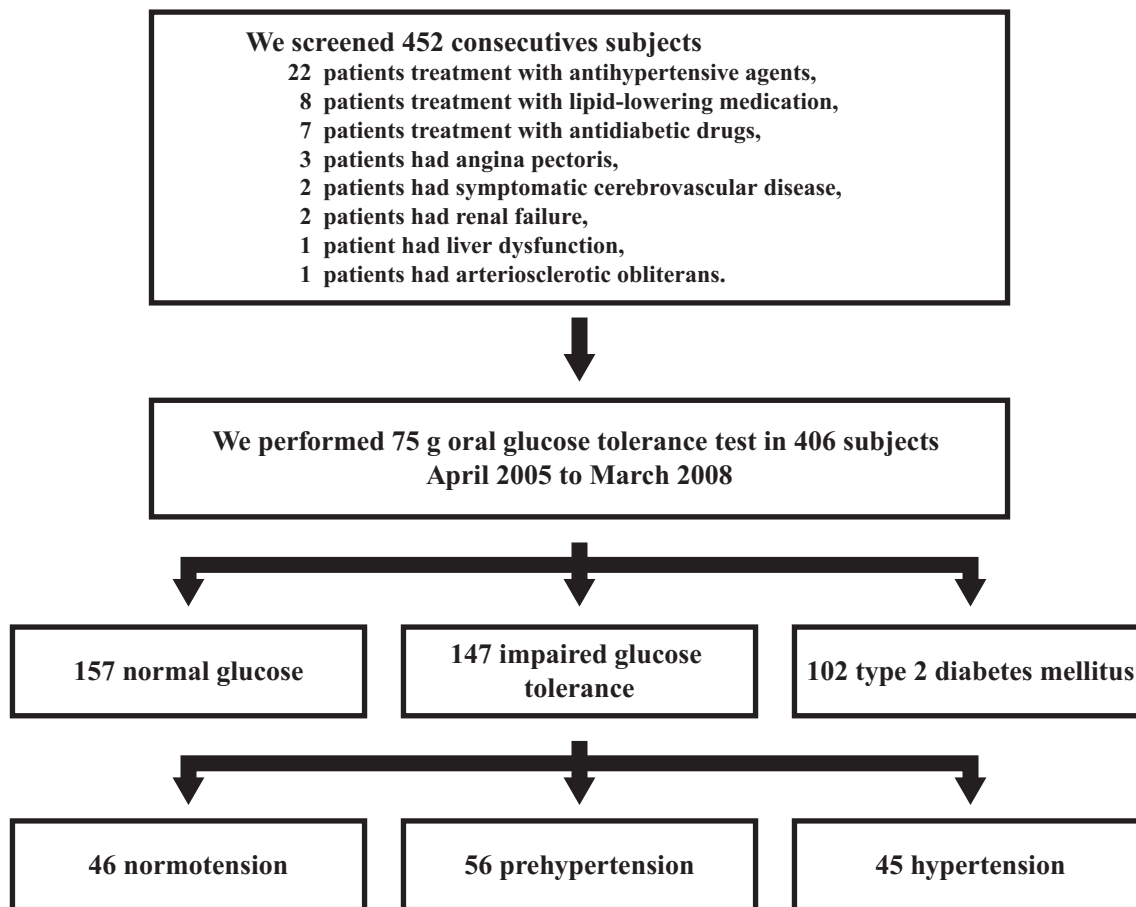| 46 normotension	56 prehypertension	45 hypertension

Fig. 1. *Study selection.*

The aim of this study was to examine associations of surrogate makers of insulin resistance with PHT and IGT. We hypothesized that the presence of PHT was associated with insulin resistance/hyperinsulinemia in IGT subjects. To test our hypothesis, we compared the 75 g oral glucose tolerance test (OGTT) results, metabolic profiles and echocardiographic findings in Japanese IGT patients with normotension and those with PHT, followed by evaluation of the independent predictors of PHT in these patients.

Methods

Study Population

We screened 452 consecutive subjects (237 men and 215 women) who visited the outpatient's clinic of Oita Red Cross Hospital during April 2005 and March 2008 because of glucose intolerance detected on medical examination.

Among them, 406 patients fulfilled the following inclusion criteria and were enrolled in the present study. 1) Organic heart disease was not determined by treadmill exercise ECG. Treadmill exercise ECG did not show ST-T abnormal changes. 2) There was no past history of chronic disease, such as renal failure, pulmonary disease, liver dysfunction, arteriosclerotic obliterans, or symptomatic cerebrovascular disease. 3) The patient was not currently receiving treatment with antihypertensive agents, lipid-lowering medication, antidiabetic drugs, or insulin.

Forty-six of the 452 enrolled patients were excluded from further evaluation due to extenuating circumstances: 22 patients were treated with antihypertensive agents, eight patients were treated with lipid-lowering medication, seven patients were treated with antidiabetic drugs, three patients had angina pectoris, two patients had symptomatic cerebrovascular disease, two patients had renal failure, one patient had liver dysfunction and one patient had arteriosclerotic obliterans were excluded from the study.

Second, 304 of the 406 enrolled patients were excluded from further evaluation due to extenuating circumstances: 157 patients had normal glucose and 102 patients had type 2 diabetes mellitus. Of 147 patients with IGT, 45 were excluded because of hypertension (systolic BP≥140 mmHg and/or diastolic BP≥90 mmHg).

The remaining 102 patients were selected for the study

Table 1. Clinical Characteristics

	Normal	Prehypertension	*p* value
Age (years)	57±5	58±4	n.s.
Gender (men/women)	25/21	27/29	n.s.
Body mass index (kg/m^2)	24.4±1.0	25.2±2.2	0.0353
Waist circumference (cm)	78.5±8.9	82.5±7.0	0.0129
Metabolic syndrome (%)	13	32	0.0237
Current smokers (%)	26	48	0.0171
Current alcohol drinkers (%)	28	52	0.0089
Systolic BP (mmHg)	108±8	131±6	<0.0001
Diastolic BP (mmHg)	70±5	82±4	<0.0001
Heart rate (bpm)	68±5	70±6	n.s.
Total cholesterol (mg/dL)	189±36	199±25	n.s.
Triglycerides (mg/dL)	116±26	142±54	0.0039
HDL-C (mg/dL)	47±8	42±6	0.0007
FPG (mg/dL)	92±11	96±9	n.s.
F-IRI (μU/mL)	5.9±1.2	9.3±2.6	<0.0001
HOMA index	1.3±0.5	2.2±0.7	<0.0001
Uric acid (mg/dL)	6.1±0.9	6.7±1.1	0.0052
Creatinine (mg/dL)	0.7±0.2	0.8±0.2	n.s.
Hemoglobin A1c (%)	5.7±0.4	5.8±0.3	n.s.

Data are mean±SD. BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; FPG, fasting plasma glucose; F-IRI, fasting immunoreactive insulin; HOMA, homeostasis model assessment; n.s., not significant.

(mean age 58±6 years; 52 men and 50 women) (Fig. 1).

All subjects gave their written informed consent to participate in the study, and the study protocol was approved by the ethics committee of the Oita Red Cross Hospital.

BP Categories

The BP of each patient was registered as the average of the three measurements obtained with mercury-column sphygmomanometer after 10 min of physical rest, Based on the results, the patients were divided into normotension and PHT group. According to the JNC-7 (*4*), subjects were considered to be normotensive when systolic BP was <120 mmHg and diastolic BP was <80 mmHg and as prehypertensive when the systolic BP was 120–139 mmHg or the diastolic BP was 80–89 mmHg.

Seventy-Five Gram OGTT

Blood samples were obtained in the morning after an overnight (≥12 h) fast. The diagnosis of IGT was based on the results of the 75 g OGTT (*16*). Blood samples were taken at 0, 30, 60 and 120 min after load to determine the plasma glucose level. With respect to the immunoreactive insulin (IRI) parameters, we examined the insulin levels of at 0 min, and fasting immunoreactive insulin (F-IRI) at 30, 60, and 120 min after load of glucose. Patients with fasting plasma glucose (FPG)≥126 mg/dL and/or 120 min postload glucose <140

mg/dL or ≥200 mg/dL were excluded from the study. Therefore, all patients included in this study had IGT.

Lipids Measurements

Blood samples were obtained in the morning after an overnight (≥12 h) fast. Using standard laboratory techniques, we determined levels of total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), hemoglobin A1c (HbA1c), uric acid, and creatinine.

Insulin Resistance

Insulin resistance was evaluated by the homeostasis model assessment (HOMA) index (*17*).

$$HOMA = (\text{fasting plasma insulin [μU/mL]} \times \text{fasting plasma glucose [mmol/L]})/22.5.$$

Definition of Metabolic Syndrome

According to the International Diabetes Federation (IDF), metabolic syndrome is defined by a combination of waist circumferences ≥90 cm in men and ≥80 cm in women, and 2 or more of the following 4 criteria: systolic BP≥130 mmHg and/or diastolic BP≥85 mmHg; triglycerides ≥150 mg/dL; HDL-C <40 mg/dL in men and <50 mg/dL in women; FPG>100 mg/dL (*18*).
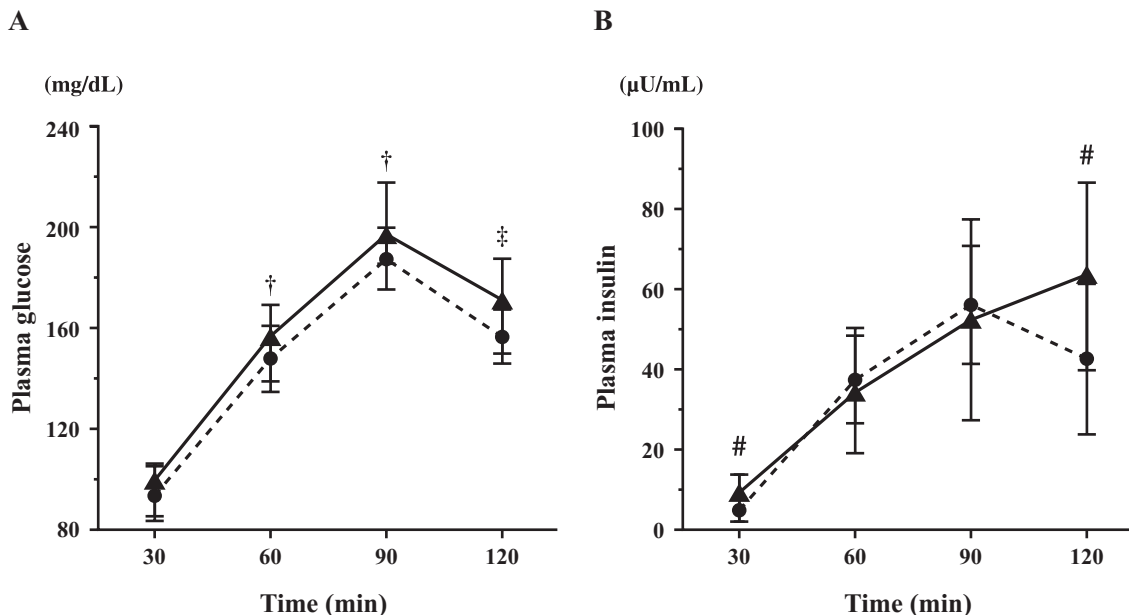
Fig. 2. *The plasma glucose (A) and IRI concentrations (B) during OGTT in IGT patients with normotension (●) and prehypertension (▲). All data are given as means±SD. $^{†}p<0.05$, $^{‡}p<0.01$, $^{#}p<0.0001$.*

Echocardiography

M-mode 2-dimensional echocardiography and cardiac Doppler recordings were obtained using a phase-array echo-Doppler system. Echocardiograms were obtained in the standard manner using standard parasternal, short axis and apical views. Left ventricular (LV) mass was calculated as described previously (*19*). The LV mass was calculated as $1.04 ([LVIDd + IVSTd + PWTd]^3 − LVIDd^3) − 14$ (g), where LVIDd, LV internal dimension at end-diastole; IVSTd, interventricular septal thickness at end-diastole; and PWTd, posterior wall thickness at end-diastole. The LV mass was divided by the body surface area to calculate the LV mass index (LVMI). Pulsed Doppler recordings were made from the standard apical 4-chamber view.

Statistical Analysis

All data are classified into two groups—normal and the prehypertensive—and are summarized as means±SD (Table 1). For each variable in Table 1, a two-sided test with a 0.05 level of significance was performed to test the difference between the two groups. Student's *t*-test was used for continuous variables, and the χ^2 test was carried out for categorical variables. Logistic regression analysis was used to assess the influence of explanatory variables on PHT, and age, gender, body mass index (BMI), waist circumference, metabolic syndrome, current smokers, current alcohol drinkers, heart rate, ejection fraction, LVIDd, LVIDs, IVSTd, PWTd, LVMI, total cholesterol, triglycerides, HDL-C, F-IRI, FPG, HOMA index, 30 min postload glucose, 30 min postload insulin, 60 min postload glucose, 60 min postload insulin, 120 min postload glucose, 120 min postload insulin, HbA1c, uric acid, and creatinine were represented by dummy variables (1=male, 0=female; 1=presence, 0=absence). For PHT, presence was procedure represented as 1, and absence as 0.

A backward elimination procedure was employed to determine the significant factors among all the explanatory variables.

All the analyses were performed using a standard statistical package (JMP 6.0; SAS Institute, Cary, USA).

Results

As shown in Table 1, the mean age of the patients in the two groups was similar, and no significant differences were observed between the two groups with respect to gender. The BMI and waist circumferences were higher in the PHT group than in the normotension group ($p=0.0353$, $p=0.0129$, respectively). The percentage of current smokers, current alcohol drinkers, and those with metabolic syndrome were higher in the PHT group than in the normotension group ($p=0.0171$, $p=0.0089$, $p=0.0237$, respectively). The systolic BP and diastolic BP were higher in the PHT group than in the normotension group ($p<0.0001$, $p<0.0001$, respectively). However, heart rate was similar in the two groups.

When metabolic parameters were compared between the two groups, total plasma cholesterol levels were not significantly different. However, the triglyceride ($p=0.0039$) and uric acid ($p=0.0052$) levels were higher in the PHT group

Table 2. Echocardiographic Findings

	Normotension	Prehypertension	*p* value
EF (%)	68±5	69±4	n.s.
LVIDd (mm)	46±3	47±2	0.0081
LVIDs (mm)	30±2	30±3	n.s.
IVSTd (mm)	7.5±0.9	7.7±0.8	n.s.
PWTd (mm)	8.0±0.9	8.4±1.0	0.0378
LVMI (g/m²)	83±11	93±15	0.0004

Data are mean±SD. EF, ejection fraction; LVIDd, left ventricular internal dimension at end-diastole; LVIDs, left ventricular internal dimension at end-systole; IVSTd, interventricular septal thickness at end-diastole; PWTd, posterior wall thickness at end-diastole; LVMI, left ventricular mass index.

than in the normotension group, but the plasma HDL-C was lower in the PHT group than in the normotension group (*p*=0.0007). Parameters during 75 g OGTT were compared between the two groups (Fig. 2). With respect to the glucose parameters, 30 min postload glucose (*p*=0.0152), 60 min postload glucose (*p*=0.0166), 120 min postload glucose (*p*=0.0004) were higher in the PHT group than in the normotension group. F-IRI (*p*<0.0001) and 120 min postload insulin (*p*<0.0001) were higher in the PHT group than in the normotension group. However, the HbA1c and plasma creatinine were not significantly different between the two groups.

Analysis of echocardiographic findings demonstrated that the LV dimensions at end-diastole (*p*=0.0081), posterior wall thickness at end-diastole (*p*=0.0378), and the LVMI (*p*=0.0004) were greater in the PHT group than in the normotension group. However, the two groups had similar LV ejection fractions (Table 2).

In univariate logistic regression analysis, the risk of PHT in IGT patients was significantly associated with BMI (odds ratio [OR] 1.34, 95% confidence interval [CI]=1.04–1.75, *p*=0.0266), waist circumferences (OR 1.07, 95% CI=1.01–1.12, *p*=0.0156), the percentage of metabolic syndrome (OR 3.16, 95% CI=1.13–8.80, *p*=0.0279), the percentage of current smokers (OR 2.37, 95% CI=1.14–6.12, *p*=0.0238), the percentage of current alcohol drinkers (OR 2.73, 95% CI=1.19–6.25, *p*=0.0177), LVIDd (OR 1.29, 95% CI=1.07–1.58, *p*=0.0093), PWTd (OR 1.63, 95% CI=1.04–2.57, *p*=0.0340), LVMI (OR 1.06, 95% CI=1.03–1.10, *p*=0.0006), triglyceride (OR 1.02, 95% CI=1.00–1.03, *p*=0.0021), HDL-C (OR 0.89, 95% CI=0.84–0.95, *p*=0.0006), F-IRI (OR 2.20, 95% CI=1.62–3.01, *p*<0.0001), HOMA index (OR 7.13, 95% CI=4.11–15.2, *p*<0.0001), 30 min postload glucose (OR 1.04, 95% CI=1.01–1.07, *p*=0.0183), 60 min postload glucose (OR 1.03, 95% CI=1.01–1.06, *p*=0.0072), 120 min postload glucose (OR 1.05, 95% CI=1.02–1.08, *p*=0.0006), 120 min postload insulin (OR 1.04, 95% CI=1.02–1.07, *p*=0.0001), and uric acid (OR 1.80, 95% CI=1.18–2.75, *p*=0.0060) (Table 3).

Multivariate logistic regression analysis identified plasma

F-IRI in IGT patients as a significant indicator of PHT (OR 2.20, 95% CI=1.62–3.01, *p*<0.0001).

Discussion

In the present study, measurement of metabolic parameters revealed that serum HDL-C level was lower and F-IRI, HOMA index, 120 min postload glucose and 120 min postload insulin were higher in the PHT group than in the normotension group. Multivariate logistic analysis revealed that hyperinsulinemia was an independent risk factor for the presence of PHT in patients with IGT.

Prevalence of PHT in the 1999–2000 National Health and Nutrition Examination Survey (NHANES) was 40% for men (*20*), and the Women's Health Initiative (WHI) found it to be 39% of 161,808 postmenoposal women (*21*). This prevalence of PHT is similar to that seen in the IGT patients (56 of 147 [38%]) in this study. In addition, we showed the prevalence of the metabolic syndrome according to IDF criteria in the normotensive and prehypertensive group. Our study has demonstrated that the metabolic syndrome is more common among prehypertensives than normotensives. Subjects with metabolic syndrome face substantially increased risks for the development of diabetes (*22*) and cardiovascular disease (*23*). Therefore, the results of the present study suggest that subjects with PHT have an increased risk of cardiovascular disease.

Several reported have indicated a relationship between insulin resistance and PHT (*24*, *25*). A Metabolic Syndrome in Active Subjects in Spain (MESYAS) Registry Substudy reported that insulin resistance had an impact on recently defined PHT in 19,041 healthy active workers (*24*). Kanauchi *et al*. (*25*) reported a relationship between insulin resistance and PHT in 554 subjects aged 30–79 years, showing an association between PHT and insulin resistance in healthy Japanese subjects. Furthermore, the Strong Heart Study has shown that IGT or impaired fasting glucose are associated with greatly increased risk of cardiovascular disease risk in prehypertensive people (*26*). However, their measurement were performed only in healthy subjects and not in IGT patients (*24*, *25*), and insulin resistance was not measured (*26*).

Furthermore, IGT is a strong predictor not only of type 2 diabetes (*13*) but also of cardiovascular disease and other diabetes complications (*14*, *15*). The glucose tolerance of hypertensive patients should be determined as precisely as possible in daily clinical practice in order to identify problems at an early stage (*27*, *28*).

To the authors' knowledge, this is the first report demonstrating the association between PHT and hyperinsulinemia in Japanese patients with IGT.

Although the precise mechanisms underlying the interactions between PHT and hyperinsulinemia remain unclear, in our opinion there are several possible mechanisms. First, insulin resistance and/or subsequent hyperinsulinemia may chronically elevate BP by enhancing sympathetic nervous

Table 3. Univariate Logistic Regression Analysis with Prehypertension as the Dependent Variable in IGT

	Prehypertension		
	Odds ratio	95% CI	*p* value
Age	0.98	0.90–1.07	n.s.
Gender (men)	0.52	0.24–1.15	n.s.
Body mass index	1.34	1.04–1.75	0.0266
Waist circumference	1.07	1.01–1.12	0.0156
Metabolic syndrome	3.16	1.13–8.80	0.0279
Current smokers	2.37	1.14–6.12	0.0238
Current alcohol drinkers	2.73	1.19–6.25	0.0177
Heart rate	1.03	0.96–1.11	n.s.
EF	1.03	0.95–1.13	n.s.
LVIDd	1.29	1.07–1.58	0.0093
LVIDs	1.10	0.88–1.36	n.s.
IVSTd	1.31	0.80–2.14	n.s.
PWTd	1.63	1.04–2.57	0.0340
LVMI	1.06	1.03–1.10	0.0006
Total-cholesterol	1.01	0.99–1.03	n.s.
Triglycerides	1.02	1.01–1.03	0.0021
High-density lipoprotein cholesterol	0.89	0.84–0.95	0.0006
Fasting plasma glucose	1.03	0.99–1.07	n.s.
Fasting immunoreactive insulin	2.20	1.62–3.01	<0.0001
HOMA index	7.13	4.11–15.2	<0.0001
30 min postload glucose	1.04	1.01–1.07	0.0183
30 min postload insulin	0.98	0.96–1.02	n.s.
60 min postload glucose	1.03	1.01–1.06	0.0072
60 min postload insulin	0.99	0.97–1.01	n.s.
120 min postload glucose	1.05	1.02–1.08	0.0006
120 min postload insulin	1.04	1.02–1.07	0.0001
Hemoglobin A1c	1.28	0.41–3.96	n.s.
Uric acid	1.80	1.18–2.75	0.0060
Creatinine	1.72	0.20–14.5	n.s.

Significant predictors of prehypertension were explored among 3 parameters: gender (female=0, men=1), hypertension (absent=0, present=1), dyslipidemia (absent=0, present=1). CI, confidence interval; other abbreviations are the same as in Tables 1 and 2.

system activity, thus increasing renal tubular sodium reabsorption, modulating cation transport, and inducing vascular smooth muscle cell hypertrophy (*29*). Second, insulin resistance may be associated with endothelial dysfunction. Defective insulin-mediated and endothelium-dependent vasodilatation in insulin-resistant states may result in hypertension (*30*).

Compared with the normotesion group, patients in the PHT group showed LVMI. Consistent with the present results, our previous studies demonstrated that LVMI is associated with insulin resistance (*31*, *32*). It has been proposed that insulin resistance contributes to the development of LVH through multiple mechanisms, including the stimulation of sympathetic nervous system activity (*33*), disordered sodium reabsorption in the kidney (*34*), the growth of smooth muscle cells in blood vessels (*35*) and the generation of insulin growth factor-1 (*36*).

There are several limitations to this study. First, there may

be some selection bias in the subjects who underwent 75 g OGTT in a single selection. This may limit the extrapolation of the study results to the overall population in Japan. Second, as a cross-sectional design, the present analysis is limited in its ability to elucidate causal relationships between insulin resistance and PHT/IGT prevalence. Finally, in the present study, we did not compare PHT with HT. JNC-7 classified hypertension into 2 groups: stage 1, systolic BP 140–159 mmHg, diastolic BP 90–99 mmHg, and stage 2, systolic BP≥160 mmHg, diastolic BP≥100 mmHg (*4*). Our small cross-sectional study did not allow us to statistically analyze such groupings. Therefore, the relationship between HT and PHT and IGT patients requires further evaluation.

In conclusion, our findings suggest that the presence of PHT was associated with hyperinsulinemia and that the F-IRI was an independent predictor of PHT in Japanese patients with IGT.

Acknowledgements

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