Original Article

Insulin Resistance and Hypertension: Seven-Year Follow-Up Study in Middle-Aged Japanese Men (the KEIO Study)

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Only a few longitudinal studies in Asians have shown a close association between hyperinsulinemia and the incidence of hypertension. In the present study, we used the insulin resistance index, HOMA-IR [fasting plasma glucose (FPG) (mmol/l) $\times$ insulin (μ U/ml) / 22.5], and tried to elucidate longitudinally the relationship among insulin resistance, blood pressure, body mass index (BMI), FPG, and lipid profile in middle-aged Japanese men. Three hundred and ten male non-hypertensive subjects aged 30 to 58 years in 1993 (44.5 ± 7.8 (SD) years; BMI, 22.6 ± 2.5 kg/m²) were divided into three groups according to HOMA-IR (A: lowest; B: middle; and C: highest). Their BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, FPG and lipid profile were followed up for 7 years. The percentage of high normal blood pressure in 1993 and 2000 did not differ among the three groups. However, in 2000 hypertensive subjects made up 11.7% of group A (12/103), 15.4% of group B (16/104), and 29.1% of group C (30/103) ($\chi^2 = 11.50$, $p = 0.003$). SBP, DBP, and many other metabolic parameters in 2000 were significantly higher in group C than in the other groups. Furthermore, both SBP and DBP in 2000 were positively correlated with HOMA-IR in 1993 ($r = 0.17$ and $p < 0.01$ for both). The correlation between HOMA-IR in 1993 and DBP in 2000 was significant, even after adjustment for age and BMI in 1993. These findings suggest an important role of insulin resistance in predicting the future incidence of hypertension in middle-aged Japanese men. (*Hypertens Res* 2003; 26: 795–800)

Key Words: hypertension, insulin resistance, longitudinal study

Introduction

Obesity, diabetes mellitus, hypertension, and hyperlipidemia are all risk factors for atherosclerotic diseases, based on insulin resistance and/or the resultant hyperinsulinemia (1–4). Numerous cross-sectional studies have shown a close association between insulin resistance and hypertension (1–6). Although animal and human studies have suggested that activation of the sympathetic nervous system is associated with obesity- and/or insulin resistance-related hypertension (7), the detailed mechanism(s) are not yet clear (8).

There have been several longitudinal studies in Caucasians on the impact of hyperinsulinemia or insulin resistance in predicting the future development of hypertension in non-diabetic (9, 10), impaired glucose tolerance (IGT) (11), and type-2 diabetic subjects (12). To our knowledge, however, there have been only a few studies investigating the relationship between hyperinsulinemia and the incidence of hypertension in Asians—*i.e.*, a study on obese Japanese women (13), a study on Japanese-Americans (14), and a study on the Japanese general population (15). In diabetic subjects, Kashiwabara *et al.* (16) have suggested that the insulin resistance index calculated by homeostasis model assessment

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(17, 18) (HOMA-IR), and fasting and sigma insulin during oral glucose (75 g) tolerance test (OGTT) may be useful predictors of the subsequent development of hypertension.

In the present study, we used HOMA-IR as an index of insulin resistance, and tried to elucidate the relationship among insulin resistance, blood pressure, body mass index (BMI), fasting plasma glucose (FPG), and lipid profile in a 7-year follow-up study in Japanese men aged 30 to 65 years.

Methods

Subjects

The present study was performed as a part of the Keio Epidemiological Insulin resistance Observation (KEIO) Study. The subjects of this study consisted of 379 Japanese male teachers and employees at Keio University, aged 30 to 58 years in 1993, who underwent annual medical check-ups in both 1993 and 2000. Sixty-nine subjects with hypertension, cancer, or significant renal or hepatic disease, and those taking medication for diabetes mellitus or systemic corticosteroids were excluded. Family history of hypertension, obesity, or diabetes mellitus was not taken into account in this study. The present study was carried out in accordance with the Declaration of Helsinki (1981) of the World Medical Association, and the study protocol was approved by the research review committees of the Health Center and the Department of Internal Medicine, School of Medicine, Keio University, Tokyo. Written informed consent was obtained from each subject after full explanation of the purpose, nature, and risk of all procedures used.

Measurements

Systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate were measured twice each using an automatic electronic sphygmomanometer (BP-103i II; Nippon Colin, Komaki, Japan) with the subject seated after a rest of at least 5 min, as described previously (19–21). The subjects were divided into three blood pressure categories (normal, high normal, and hypertensive) according to the criteria in the Sixth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (22).

Plasma glucose, serum lipids, and other parameters were assayed in all subjects using peripheral blood samples obtained after an overnight fast. Plasma glucose was determined by the glucose oxidase method. Total cholesterol, triglycerides (TG), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, uric acid, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were measured by enzymatic assays (Hitachi autoanalyzer; Hitachi, Tokyo, Japan). Serum insulin concentration was measured with a commercially available kit (Shionogi Co., Tokyo, Japan) based on a radioimmunoassay, as described previously (19–21).

Homeostasis Model Assessment Insulin Resistance Index

HOMA-IR is calculated as follows: FPG (mmol/l) $\times$ insulin (μ U/ml) / 22.5 (17, 18). This index is considered to be a useful marker for simple assessment of insulin resistance, because the more accurate euglycemic hyperinsulinemic glucose clamp technique is not suitable for use in epidemiological studies.

Statistical Analysis

All statistical analyses were performed using the StatView® program for Macintosh (version 5.0J; SAS Inst., Cary, USA). The χ^2 test was used for comparison of proportions. The significance of the differences among the three groups was assessed by analysis of variance (ANOVA) followed by Scheffe's multiple comparison test.

Relationships between variables were analyzed by simple correlation and by multiple linear regression. Because serum insulin, TG, AST, and ALT levels and HOMA-IR were normally distributed after log-transformation, we used the logarithms of these parameters for regression analyses. The significance of simple correlation coefficients was assessed using Fisher's Z transformation. The significance of independent relationships in multiple regression was assessed by applying Student's *t*-test to the regression coefficients. All data were expressed as the mean $\pm$ SD, and a *p* value of less than 0.05 was considered statistically significant.

Results

The 310 non-hypertensive subjects in 1993 were divided into three groups by HOMA-IR, and the baseline profiles in 1993 are shown in Table 1. As shown in Fig. 1, the percentage of high normal (HN) subjects in both 1993 and 2000 did not differ among the three groups. However, hypertensive (HT) subjects in 2000 made up 11.7% of group A (12/103), 15.4% of group B (16/104), and 29.1% of group C (30/103), and this difference was statistically significant ($\chi^2 = 11.50$, $p = 0.003$). Out of the 205 normotensive subjects, 166 remained normotensive, 15 became HN, and 24 became HT after 7 years. Also, out of the 105 HN subjects, more than half (56 subjects) became normotensive, 15 remained HN, and 34 became HT.

Diabetes mellitus was newly diagnosed in only seven subjects during the 7 years. The incidence was 0.0% (A, 0/103), 1.9% (B, 2/104), and 4.9% (C, 5/103), though the difference was not statistically significant.

As shown in Table 2, SBP, DBP, and many other metabolic parameters in 2000 were significantly higher in group C (which had the highest HOMA-IR in 1993) than in the other groups. Furthermore, both SBP (Table 3) and DBP (Table 4) in 2000 were positively correlated with HOMA-IR in 1993 ($r = 0.17$ and $p < 0.01$ for both). The correlation between

Table 1. Subject Profile of 310 Non-Hypertensive Men Aged 30–58 Years in 1993, Divided into Three Groups by HOMA-IR (Baseline Data)

Group	HOMA-IR in 1993		
	A (< 1.06)	B (1.06–1.54)	C (≥ 1.54)
<i>n</i>	103	104	103
Age (years)	45.3 ± 7.9	44.8 ± 7.4	43.3 ± 7.9
BMI (kg/m ²)	21.8 ± 2.1	22.4 ± 2.2	23.7 ± 2.8 ^{**} ,##
SBP (mmHg)	121 ± 11	122 ± 11	125 ± 9 ^{**}
DBP (mmHg)	72 ± 8	73 ± 7	75 ± 6 ^{**} ,#
Heart rate (/min)	72 ± 10	73 ± 12	76 ± 10 [*]
Glucose (mg/dl)	91 ± 8	93 ± 6	100 ± 19 ^{**} ,##
HOMA-IR (—)	0.7 ± 0.2	1.30 ± 0.1 ^{**}	2.1 ± 0.7 ^{**} ,##
Total cholesterol (mg/dl)	195 ± 29	203 ± 32	208 ± 35 [*]
Triglycerides (mg/dl)	103 ± 64	123 ± 80	167 ± 98 ^{**} ,##
HDL-cholesterol (mg/dl)	60 ± 15	56 ± 13	53 ± 13 ^{**}
LDL-cholesterol (mg/dl)	114 ± 27	123 ± 30	123 ± 31
Uric acid (mg/dl)	5.9 ± 1.2	6.2 ± 1.3	6.5 ± 1.2 ^{**}
AST (IU/l)	15 ± 6	15 ± 5	18 ± 8 ^{**} ,##
ALT (IU/l)	14 ± 11	14 ± 7	21 ± 13 ^{**} ,##

Values are the mean ± SD. Analysis of variance (ANOVA) followed by Scheffe's multiple comparison test. * $p < 0.05$, ** $p < 0.01$ vs. group A, and # $p < 0.05$, ## $p < 0.01$ vs. group B. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HOMA-IR, insulin resistant index calculated by homeostasis model assessment; HDL, high density lipoprotein; LDL, low density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Fig. 1. Percentages of subjects with high normal blood pressure in 1993 and 2000, and of hypertensive subjects in 2000, when the 310 non-hypertensive subjects in 1993 were divided into three groups by HOMA-IR (A: < 1.06; B: 1.06 ≤ HOMA-IR < 1.54; C: ≥ 1.54).

HOMA-IR in 1993 and DBP in 2000 was significant, even after adjustment for age and BMI in 1993 (Table 4).

As shown in Table 5, 7-year changes in blood pressure (Δ SBP and Δ DBP) were significantly correlated with Δ BMI and Δ body weight, but not with Δ insulin, Δ HOMA-IR, baseline glucose, insulin, or HOMA-IR. The correlations of Δ heart rate with Δ SBP and Δ DBP were both significant, even after adjustment for age and Δ BMI.

Discussion

In the present 7-year follow-up study, subjects with the highest baseline HOMA-IR were found to be more likely to become hypertensive after 7 years. Moreover, future blood pressure, both SBP and DBP, was significantly correlated with baseline HOMA-IR. These results suggest that the base-

Table 2. Subject Profile in 2000 of 310 Non-Hypertensive Men in 1993, Aged 37–65 Years, Divided into Three Groups by HOMA-IR in 1993 (Longitudinal Data)

Group	HOMA-IR in 1993		
	A (< 1.06)	B (1.06–1.54)	C (≥ 1.54)
<i>n</i>	103	104	103
Age (years)	52.3 ± 7.9	51.8 ± 7.4	50.3 ± 7.9
BMI (kg/m ²)	22.5 ± 2.2	22.9 ± 2.1	24.4 ± 3.2 ^{**} , ^{##}
SBP (mmHg)	121 ± 16	120 ± 14	129 ± 18 ^{**} , ^{##}
DBP (mmHg)	77 ± 10	77 ± 10	82 ± 11 ^{**} , [#]
Heart rate (/min)	72 ± 10	73 ± 12	77 ± 11 ^{**} , [#]
Glucose (mg/dl)	93 ± 11	94 ± 8	105 ± 26 ^{**} , ^{##}
HOMA-IR (—)	1.3 ± 0.9	1.1 ± 0.7	1.5 ± 0.9 ^{##}
Total cholesterol (mg/dl)	201 ± 30	205 ± 28	209 ± 31
Triglycerides (mg/dl)	116 ± 81	116 ± 74	155 ± 121 [*] , [#]
HDL-cholesterol (mg/dl)	59 ± 15	56 ± 12	52 ± 12 ^{**}
LDL-cholesterol (mg/dl)	122 ± 27	130 ± 26	133 ± 27 [*]
Uric acid (mg/dl)	6.0 ± 1.1	6.2 ± 1.3	6.6 ± 1.2 ^{**} , [#]
AST (IU/l)	24 ± 7	24 ± 9	30 ± 17 ^{**} , ^{##}
ALT (IU/l)	24 ± 15	25 ± 19	37 ± 29 ^{**} , ^{##}

Values are the mean ± SD. ANOVA followed by Scheffe's multiple comparison test. * $p < 0.05$, ** $p < 0.01$ vs. group A, and # $p < 0.05$, ## $p < 0.01$ vs. group B. The abbreviations are the same as Table 1.

Table 3. Correlation Coefficients between SBP in 2000 and Variables in 1993 in 310 Non-Hypertensive Japanese Men Aged 30–58 Years

vs. SBP in 2000	1993 data	Adjusted for age and BMI in 1993
Age	0.064	—
BMI	0.280 [#]	—
Glucose	0.122 [*]	0.079
Insulin (log)	0.153 ^{**}	0.083
HOMA-IR (log)	0.174 ^{**}	0.087
Total cholesterol	0.123 [*]	0.039
Triglycerides (log)	0.200 [#]	0.096
HDL-cholesterol	- 0.075	0.024
LDL-cholesterol	0.054	- 0.024
Uric acid	0.143 [*]	0.068
AST (log)	0.129 [*]	0.051
ALT (log)	0.174 ^{**}	0.067

* $p < 0.05$, ** $p < 0.01$ and # $p < 0.001$. The abbreviations are the same as Table 1.

Table 4. Correlation Coefficients between DBP in 2000 and Variables in 1993 in 310 Non-Hypertensive Japanese Men Aged 30–58 Years

vs. DBP in 2000	1993 data	Adjusted for age and BMI in 1993
Age	0.091	—
BMI	0.229 [#]	—
Glucose	0.117 [*]	0.078
Insulin (log)	0.148 ^{**}	0.102
HOMA-IR (log)	0.167 ^{**}	0.117 [*]
Total cholesterol	0.096	0.023
Triglycerides (log)	0.154 ^{**}	0.065
HDL-cholesterol	- 0.052	0.030
LDL-cholesterol	0.037	- 0.033
Uric acid	0.120 [*]	0.060
AST (log)	0.177 ^{**}	0.102
ALT (log)	0.193 [#]	0.104

* $p < 0.05$, ** $p < 0.01$ and # $p < 0.001$. The abbreviations are the same as Table 1.

line insulin resistance index could be a predictive marker of the future development of hypertension. Moreover, not a few subjects in the high normal blood pressure group became normotensive over the 7-year follow-up. It is widely accepted that BMI could be a major confounding factor when considering the relationship between HOMA-IR and blood pressure. In this study, BMI was correlated with SBP more than DBP, and Δ BMI was correlated with Δ SBP more than Δ DBP. We speculate that this could be the reason why only

DBP was significantly correlated with baseline HOMA-IR, even after adjustment for baseline age and BMI.

The mechanisms of the association of insulin resistance with the development of hypertension are not fully understood (8). Animal studies have suggested that 1) increased sodium retention due to hyperinsulinemia, 2) sympathetic nervous system activation, and 3) endothelial dysfunction (decreased production of nitric oxide, *etc.*) due to insufficient action of insulin are related. In regard to obesity-related hy-

Table 5. Correlation Coefficients between 7-Year Changes in Blood Pressure (Δ SBP and Δ DBP) and Changes (Δ) in Metabolic Variables or Baseline Parameters in 310 Non-Hypertensive Japanese Men Aged 30 to 58 Years

	Δ SBP	Adjusted for age and Δ BMI	Δ DBP	Adjusted for age and Δ BMI
Age '93	0.084	—	0.034	—
Glucose '93	0.003	0.036	- 0.041	- 0.019
Insulin '93 (log)	0.060	0.086	0.033	0.046
HOMA-IR '93 (log)	0.059	0.090	0.023	0.040
Δ BMI	0.259 [#]	—	0.174 ^{**}	—
Δ Body weight	0.247 [#]	- 0.232	0.164 ^{**}	- 0.262
Δ Heart rate	0.166 ^{**}	0.168 ^{**}	0.171 ^{**}	0.174 ^{**}
Δ Insulin (log)	0.034	0.010	- 0.013	- 0.025
Δ HOMA-IR (log)	0.067	0.041	0.013	- 0.001

* $p < 0.05$, ** $p < 0.01$ and [#] $p < 0.001$. The abbreviations are the same as Table 1.

pertension, there is a possibility that an increased serum leptin level, which is often seen in obese subjects, causes sympathetic nervous system activation, as evidenced in animal studies (23–25) and an elevation of blood pressure in obese subjects (19, 20, 26). Unfortunately, we were unable to measure serum leptin level in this study. Heart rate, however, was highest in group C both in 1993 and in 2000, and Δ heart rate was well correlated with Δ SBP and Δ DBP in groups B and C, suggesting that increased sympathetic nervous activity was involved in the increase in blood pressure in insulin-resistant subjects.

According to a cross-sectional study by Stamler *et al.* (27) in subjects aged 20 to 39 years, the prevalence of hypertension in obese subjects was 2.4 times higher than that in non-obese subjects. We also observed in university students that changes in blood pressure were correlated with changes in body weight over 3 years in all four groups of lean, normal, moderately obese, and obese subjects (28). In that study, the correlation coefficients were higher in the higher BMI group. It was also observed in the present study that both Δ SBP and Δ DBP were significantly correlated with Δ BMI. However, neither Δ SBP nor Δ DBP was correlated with Δ HOMA-IR or baseline HOMA-IR.

Furthermore, in our study on university students (28), both lifestyle modification and regular exercise had beneficial effects on blood pressure in young obese subjects whose BMI was more than 28.6 kg/m². Arima *et al.* (29) studied the general Japanese population (aged 40 to 70 years) and reported that, among nondrinkers, the age-adjusted incidence of hypertension increased significantly with higher insulin tertiles in nondrinkers; this correlation was more pronounced in female than in male nondrinkers, and no correlation was found

in drinkers of either sex. In the present study, however, were there no significant relationships between the 7-year incidence of hypertension and lifestyle in 1993 or 2000 (including alcohol intake, smoking, exercise, sleep duration, *etc.*). Further studies are needed to clarify these issues.

To summarize, the findings of this study suggest an important role of insulin resistance in predicting the future incidence of hypertension in middle-aged Japanese men.

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