Insulin Resistance and Prevalence of Prehypertension and Hypertension Among Community-Dwelling Persons

Ryuichi Kawamoto¹, Katsuhiko Kohara², Yasuharu Tabara², Masanori Abe¹, Tomo Kusunoki¹, and Tetsuro Miki²

¹Department of Community Medicine, Ehime University Graduate School of Medicine, Ehime, Japan
²Department of Geriatric Medicine, Ehime University Graduate School of Medicine, Ehime, Japan

Aim: There are few data focusing on the effect of insulin resistance on a new risk category of prehypertension (120–139 mmHg systolic and/or 80–89 mmHg diastolic blood pressure) recently established by The Seventh Report of the Joint National Committee on High Blood Pressure (JNC-7). We aimed to determine whether insulin resistance was associated with a risk for prehypertension and hypertension.

Methods: Of 3,164 (34.6% of 9,133 adults aged 19 to 90 years) adults at the community-based annual medical check-up, study participants without a clinical history of stroke, transient ischemic attack, myocardial infarction, angina, or renal failure (567 men aged 57±14 [mean±standard deviation]; range, 20–84) years and 702 women aged 59±12; 21–88 years) were recruited. We examined the cross-sectional relationship between insulin resistance, which was evaluated by homeostasis of minimal assessment of insulin resistance (HOMA-IR) and normotension, prehypertension, or hypertension using the JNC-7 criteria.

Results: The HOMA-IR correlated significantly with systolic (r=0.171) and diastolic (r=0.170) blood pressures. Triglycerides ≥150 mg/dL, HDL-C <40 mg/dL, metabolic syndrome, serum uric acid ≥7.0 mg/dL, and HOMA-IR ≥2.5 showed the highest crude odds ratio (OR) for progression from normotension to prehypertension, and ≥65 years, FBG ≥110 mg/dL, metabolic syndrome, and HOMA-IR ≥2.5 showed the highest crude OR for progression from normotension to hypertension. Multivariate logistic regression analysis showed that HOMA-IR was independently associated with the presence of prehypertension and hypertension.

Conclusions: Insulin resistance was significantly associated with prehypertension as well as hypertension in the general population.


Key words; Insulin resistance, HOMA-IR, Metabolic syndrome, Risk factor, Prehypertension
thus lifestyle modification or even medical treatment is recommended for individuals with prehypertension\(^1\).

Metabolic syndrome is prevalent in the hypertensive stage in the Japanese population\(^6,7\) and insulin resistance relates to the underlying mechanisms of these abnormalities\(^6\); however, little is known about insulin resistance in subjects with prehypertension. The aim of this study was to assess whether insulin resistance was associated with a risk for prehypertension as well as hypertension; we examined cross-sectional data from community-dwelling participants.

**Materials and Methods**

**Subjects**

Participants were recruited at the time of their annual health examination in a rural town, Nomura-cho, Seiyo-city, which has total population of 11,136 (as of April 2002) and is located in Ehime prefecture, Japan, in 2002. Among 9,133 adults aged 19 to 90 years in this population, 3,164 (34.6\%) were recruited at the community-based annual medical check-up and agreed to join the study. Information on medical history, present conditions, and drug usage was obtained by interview. Other characteristics, such as smoking and alcohol drinking, were investigated by individual interviews using a structured questionnaire. Daily alcohol consumption was measured using the Japanese liquor unit in which 1 unit corresponds to 22.9 g ethanol. Subjects taking medications for hypertension, diabetes, or dyslipidemia and with a clinical history of stroke, transient ischemic attack, myocardial infarction, or angina were excluded. The final study sample included 1,269 eligible persons. This study was approved by the ethics committee of Ehime University School of Medicine, and written informed consent was obtained from each subject.

**Evaluation of Risk Factors**

Information on demographic characteristics and risk factors was collected from the clinical records. Body mass index was calculated by dividing weight (in kilograms) by the square of the height (in meters). We measured blood pressure once in the right upper arm of participants in a sedentary position using an automatic oscillometric blood pressure recorder (BP-103i; Colin, Aichi, Japan) while they were seated after having rested for at least 5 min. Appropriate cuff bladder size was determined at each visit based on arm circumference. Normotension was defined as not being on antihypertensive medication and having a SBP of \(< 120 \text{ mmHg}\) and DBP of \(< 80 \text{ mmHg}\). Prehypertension was defined as not being on antihypertensive med-
were analyzed by the Mann-Whitney U test or chi-square ($\chi^2$) test. Correlations between various characteristics and log HOMA-IR were determined using Spearman's correlation. Logistic regression analyses were used to test significant factors of prehypertension (versus normotension) and hypertension status (versus normotension), with prehypertension and hypertension serving as the dichotomous outcome variables. A value of $p<0.05$ was considered significant.

### Results

The subjects comprised 567 men aged $57 \pm 14$ (mean $\pm$ standard deviation; range, 20–84) years and 702 women aged $59 \pm 12$ (21–88) years. Table 1 shows the characteristics of the study participants with and without metabolic syndrome. The number of male participants with MetS was significantly higher than without. Also, participants with MetS had significantly higher values for BMI, smoking status, SBP, DBP, TG, LDL-C, FBG, IRI, serum creatinine, and serum uric acid. Age and HDL-C levels were significantly lower in participants with MetS. There were no inter-group differences in drinking status, T-C, LDL-C and eGFR. Overall, 25.1%, 56.4%, 15.7%, 5.1% and 11.7% of the study sample had obesity, hypertension, hypertriglyceridemia, low HDL-cholesterol, and impaired fasting glucose, respectively.

**Table 2** shows the characteristics of the three categories of blood pressure. Subjects with hypertension represented the highest percentage of the sample. The highest prevalence of MetS was found among hypertension subjects (13.0%), followed by prehypertension subjects (11.1%). The metabolic score increased significantly in the three categories of blood pressure. Subjects with prehypertension showed intermediate levels of age, BMI, smoking status, daily drinking status, T-C, TG, LDL-C, FBG, IRI, and HOMA-R, and these values significantly increased in parallel to blood pressure. Of note is that HDL-C was significantly lower in prehypertension as compared with the other groups, as normotension and hypertension had similar mean values. Subjects with normotension had slightly lower mean creatinine and uric acid values, and higher HOMA-IR.

The HOMA-IR significantly correlated with
systolic \((r=0.171)\) and diastolic blood pressure \((r=0.170)\) (Fig. 1). The presence of hypertriglycerides, MetS, serum uric acid ≥ 7.0 mg/dL, HDL-C < 40 mg/dL, and HOMA-IR ≥ 2.5 showed the highest crude OR for progression from normotension to prehypertension, and age ≥ 65 years, HOMA-IR ≥ 2.5, FBG ≥ 110 mg/dL, and MetS showed the highest
hypertension, as shown in Table 3.

After adjustments for age (≥65 years), gender, smoking status (≥20 pack years), daily drinking status, and serum uric acid (≥7.0 mg/dL), multivariate logistic regression analysis showed that TG ≥150 mg/dL, HOMA-IR ≥2.5, MetS, HDL-C <40 mg/dL, HOMA-IR ≥1.6, and BMI ≥25 kg/m² were independently associated with prehypertension, and HOMA-IR ≥2.5, MetS, BMI ≥25 kg/m², HOMA-IR ≥1.6, FBG ≥110 mg/dL, and TG ≥150 mg/dL were associated with the presence of hypertension (Table 4). In addition, when we analyzed the data by sex, HOMA-IR ≥2.5 was also significantly associated with prehypertension or hypertension in both genders (Table 5).

### Discussion

In this cross-sectional, population-based study, we determined the prevalence of prehypertension and hypertension, as defined by JNC-7 criteria (Chobanian 2003), and their relationship to serum insulin, HOMA-IR levels, and MetS. This study showed that prehypertension and hypertension are extremely common, affecting more than 30% of subjects (34.1% and 38.8, respectively), and both SBP and DBP significantly increased with increasing HOMA-IR levels. Furthermore, higher HOMA-IR levels and MetS were significantly associated with the risk for prehypertension or hypertension, even after adjusting for age, gender, smoking status, drinking status, and uric acid. We further suggest that HOMA-IR levels are related to clinical prehypertension, a disease state where primary prevention is possible.

The prevalence of prehypertension and hypertension has been increasing in Japan, and the high prevalence of both conditions in the current study was similar to that reported from the US, China, and Korea. Elevated blood pressure is a serious problem in the United States, and approximately 60% of American adults have prehypertension or hypertension. In Northeast China, the prevalence of prehypertension and hypertension in Mongolian people is 43.6% and 36.7%, respectively, and for Han people is 44.3% and 36.7%, respectively. In the Korean population, the estimated age-adjusted prevalence of hypertension and prehypertension was 22.9% and 31.6%, respectively. The prevalence of prehypertension and hypertension is very high in Asian as well as US adults, and they are associated with many risk factors.

### Table 3. Crude odds ratio and corresponding 95% confidence intervals for the presence of prehypertension and hypertension

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Unadjusted odds ratio (95% CI)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Prehypertension</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.85 (1.39–2.48)</td>
</tr>
<tr>
<td>Age ≥65 years</td>
<td>1.60 (1.15–2.21)</td>
</tr>
<tr>
<td>Body mass index' ≥25 kg/m²</td>
<td>1.78 (1.24–2.57)</td>
</tr>
<tr>
<td>Smoking status' ≥20 pack year</td>
<td>1.63 (1.13–2.36)</td>
</tr>
<tr>
<td>Daily drinking status</td>
<td>1.75 (1.26–2.43)</td>
</tr>
<tr>
<td>Triglycerides ≥150 mg/dL</td>
<td>3.16 (1.98–5.06)</td>
</tr>
<tr>
<td>HDL cholesterol &lt;40 mg/dL</td>
<td>2.51 (1.29–4.90)</td>
</tr>
<tr>
<td>LDL cholesterol ≥130 mg/dL</td>
<td>1.20 (0.88–1.62)</td>
</tr>
<tr>
<td>Fasting blood glucose ≥110 mg/dL</td>
<td>1.79 (1.03–3.10)</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>2.74 (1.50–4.97)</td>
</tr>
<tr>
<td>HOMA-IR' ≥1.6</td>
<td>1.75 (1.26–2.45)</td>
</tr>
<tr>
<td>HOMA-IR' ≥2.5</td>
<td>2.46 (1.39–4.35)</td>
</tr>
<tr>
<td>Serum uric acid ≥7.0 mg/dL</td>
<td>2.59 (1.51–4.45)</td>
</tr>
<tr>
<td>Estimated GFR 60–90 mL/min/1.73 m²</td>
<td>1.33 (0.99–1.78)</td>
</tr>
<tr>
<td>Estimated GFR &lt;60 mL/min/1.73 m²</td>
<td>1.09 (0.49–2.40)</td>
</tr>
</tbody>
</table>

CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; GFR, Glomerular Filtration Rate. 'Body mass index was calculated using weight in kilograms divided by the square of the height in meters. Smoking status: daily consumption (packs) × duration of smoking (years). Smoking status was examined for sex, age, daily drinking status, and serum uric acid as independent factors. Smoking status was defined as follows: 0 (nonsmokers), 1 (current smokers), and 2 (former smokers). Smoking status was defined as follows: 0 (nonsmokers), 1 (current smokers), and 2 (former smokers). Smoking status was defined as follows: 0 (nonsmokers), 1 (current smokers), and 2 (former smokers). Smoking status was defined as follows: 0 (nonsmokers), 1 (current smokers), and 2 (former smokers).
In our study, 10.0% of participants had MetS, and those with prehypertension or hypertension had more notable MetS than those with normotension (12.8% and 9.2%, respectively); however, the global prevalence of MetS in our population was lower than in other studies. It was difficult to compare our study with other studies because the response rate was low and standardized methods differed among studies. In addition, in the current study, subjects with a clinical history of CVD and taking medications for hypertension, diabetes, or dyslipidemia were excluded, and participants were strictly restricted to community-dwelling persons without overt daily-life-limiting diseases, although the prevalence of classical CVD risk factors was similar to other studies. Our most important findings are not the absolute prevalence of MetS but rather the differences in background characteristics among the three categories of blood pressure; therefore, we believe that our findings are highly representative. Indeed, MetS, its components, and HOMA-IR were significantly associated with both prehypertension and hypertension.

In our previous study, increasing BMI categories were positively associated with prehypertension or hypertension. Similar results were found in a community-based, cross-sectional study in Taiwanese. Obesity has been proposed as an etiology of insulin resistance, and hypertensive patients with insulin resistance were more obese than those with out insulin-resistance. The triad of obesity, hypertriglyceridemia, and low HDL-C has been identified as a surrogate maker of insulin resistance. In the current study, the metabolic risk score and prevalence of MetS increased significantly in subjects with prehypertension or hypertension. In subjects with prehypertension to hypertension, age, BMI, smoking status, daily drinking status, and serum uric acid (≥7.0 mg/dL).
blood pressure, while eGFR decreased. HOMA-IR has been reported to be significantly and independently higher in prehypertension and hypertension than in normotension\(^2\).\(^3\). Our results also demonstrated that the cluster of these risk factors with insulin resistance increases the possibility of presenting with prehypertension and hypertension.

The mechanisms that lead to prehypertension in individuals with insulin resistance are not completely understood. Several previous studies showed that insulin resistance is correlated with an important underlying status of MetS\(^0\) and increased risk factors of cardiovascular disease\(^24\). Obesity per se induces insulin resistance and plays a central role in the regulation of MetS\(^25\). Moreover, overweight, impaired fasting glucose, hypertriglyceridemia, and low HDL-C are surrogate makers of insulin resistance and, in our study, were regarded as strong risk factors for both prehypertension and hypertension. In particular, our result demonstrated that the cluster of these two risk factors with a BMI \(\geq 25\) kg/m\(^2\) increases the possibility of presenting with prehypertension. Background mechanisms include activation of the sympathoadrenal system\(^26\), the adipose renin-angiotensin-aldosterone system\(^27\), increased systemic oxidative stress, diminished concentration of nitric oxide derivatives and antioxidant vitamins, endothelial oxidative damages\(^28\), and excess intravascular volume caused by sodium reabsorption\(^29\). All these factors result in atherosclerosis, and prehypertension may be complicated by both the severity and duration of atherosclerosis, and vice versa.

In the current study, the prevalence of prehypertension and hypertension was significantly higher in men than women, and similar results have been shown in different ethnic groups\(^15\),\(^30\). Furthermore, we also found an increased risk of prehypertension and hypertension among men with insulin resistance or MetS compared with women. As men have more visceral and hepatic adipose tissue, and women have a possible protective effect of estrogen, the effect of insulin resistance might be stronger in men than women\(^11\).

Some limitations of this study must be considered. First, the response rate was as low as 35%, which is observed mostly in other conventional community studies in Japan. However, the relatively large sample size enabled assessment of an extensive array of insulin resistance in relation to prehypertension and hypertension. Second, the cross-sectional study design is limited in its ability to eliminate causal relationships between prehypertension and HOMA-IR. Third, the prevalence of various BP categories is based on a single assessment of blood pressure, which may introduce a misclassification bias. Fourth, we used BMI \(\geq 25\) kg/m\(^2\) to classify individuals with obesity, because waist circumference measurements were not available. This might have caused an underestimation of the effect of visceral obesity on MetS\(^33\); therefore, the demographics and referral source may limit generalizability.

In conclusion, this study showed that BMI \(\geq 25\) kg/m\(^2\), TG \(\geq 150\) mg/dL, presence of MetS, HOMA-IR \(\geq 1.6\), or HOMA-IR \(\geq 2.5\) were significantly associated with elevated blood pressure in the general population. The underlying mechanism behind this relationship is insulin resistance, and seems to be independent of traditional confounding factors, such as age, gender, smoking status, drinking status, and serum uric acid. Further investigation of longitudinal data from our study will provide more definitive answers to this issue.

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**References**


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