Hyperinsulinemia for the Development of Hypertension: Data from the Hawaii-Los Angeles-Hiroshima Study

Michinori IMAZU, Hideya YAMAMOTO, Mamoru TOYOFUKU, Kotaro SUMII, Masamichi OKUBO, Genshi EGUSA, Michio YAMAKIDO, and Nobuoki KOHNO

The present study was to assess the association of metabolic factors including hyperinsulinemia, with the development of hypertension in Japanese-Americans. One hundred forty normotensive (<140/90 mmHg) subjects aged 40 to 69 years old from the Hawaii-Los Angeles-Hiroshima study were followed for 15 years. Patients with cardiovascular disease were excluded. Body mass index (BMI), blood pressure (BP), serum total cholesterol (TC), triglycerides (TG), uric acid (UA), and glucose and insulin responses at baseline, 1 h, and 2 h after a glucose load were analyzed. Seventeen subjects became hypertensive (systolic BP ≥ 160 mmHg, diastolic BP ≥ 95 mmHg, or received drug treatment) during follow-up. Age- and sex-adjusted BMI, BP, serum UA, TG, insulin, and changes in fasting glucose during follow-up were higher in subjects who later became hypertensive than in those who did not. There was no difference in the change in BMI. Age- and sex-adjusted relative risks for the development of hypertension by quartiles of BMI, serum UA, TG, and the sum of insulin values (Σinsulin) during a glucose load were highest in highest quartile of the distribution.

When age, sex, systolic BP, BMI, serum UA, TC, TG, fasting glucose, Σinsulin, and the change in BMI were used in a proportional hazard analysis, hyperinsulinemia, hyperuricemia, and systolic BP were found to be significant risk factors for hypertension. In conclusion, hyperinsulinemia, as well as obesity, hyperuricemia, and hypertriglycerideremia were associated with hypertension in Japanese-Americans. Hyperinsulinemia and hyperuricemia were independent predictors of the development of hypertension. (Hypertens Res 2001; 24: 531–536)

Key Words: hyperinsulinemia, insulin resistance, hyperuricemia, obesity, hypertension

Introduction

Hypertensive individuals have a higher prevalence of obesity, glucose intolerance, diabetes mellitus, hyperlipidemia, and hyperuricemia. Insulin resistance and/or hyperinsulinemia are present in the majority of individuals with hypertension, and may constitute a common pathophysiologic feature of obesity, glucose intolerance, hyperlipidemia, and hypertension, possibly explaining their ubiquitous association (1).

The presence of hyperinsulinemia in hypertension was demonstrated by Welborn et al. (2) in 1966. Several studies (1, 3–7) have confirmed that patients with high blood pressure are more commonly hyperinsulinemic than subjects with normal blood pressure, but others (8–10) have not. Several prospective studies (11–13) have supported the positive relationship between hyperinsulinemia and hypertension. However, it is not clear whether hyperinsulinemia is an independent risk factor for the development of hypertension.

This study was to assess the association of hyperinsulinemia with the development of hypertension during an average observation period of 15 years in Japanese-Americans in Hawaii. This study was conducted as part of the Hawaii-Los Angeles-Hiroshima Study.

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Methods

Population Samples

The Hawaii-Los Angeles-Hiroshima Study is a long-term epidemiologic study of risk factors for cardiovascular disease and diabetes initiated in 1970. The subjects of this study were pure Japanese inhabitants of the island of Hawaii who were migrants or descendants of migrants (most of them came from Hiroshima Prefect.). Voluntary cooperation was obtained with the assistance of the Hiroshima Kenjin-kai, an association of immigrants from Hiroshima Prefect. and their descendants in Hilo and Kona districts of the island. At the time of the study, Hiroshima Kenjin-kai had approximately 1,300 members. Between 1976 and 1984, 1,108 individuals were examined at baseline (survey 1) in the Hawaii-Los Angeles-Hiroshima Study. Of these, there were 341 normotensive subjects (113 men and 201 women) 40–69 years old who were available for participation in this study. Those with cardiovascular disease (coronary heart disease or stroke) were excluded.

A re-investigation (survey 2) was performed in 1992 and 1995. During the follow-up period, 27 subjects died and 155 subjects did not participate, leaving 159 subjects who participated in survey 2. For individuals who participated in both 1992 and 1995, data obtained in 1995 were analyzed. In both surveys, all participants were asked to attend a physical examination after an overnight fast.

Weight and height were recorded. The blood pressure in supine subjects was measured after a 15-min rest by a physician with a mercury sphygmomanometer. Systolic and diastolic blood pressures were determined by phase 1 and phase 5 Korotkoff sounds. When initial blood pressure levels were high (i.e., diastolic blood pressure greater than 90 mmHg; systolic blood pressure greater than 140 mmHg), blood pressure was remeasured and these levels were recorded. Hypertension was defined as systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 95 mmHg, or the receipt of antihypertensive drug treatment. Normotension was defined as systolic blood pressure < 140 mmHg and diastolic blood pressure < 90 mmHg. Body mass index (BMI), calculated as weight (kg) / height (m²) was used as a measure of obesity.

Blood samples were drawn for the determination of serum glucose, insulin, and lipids from fasting subjects in the seated position. Blood samples also were drawn for serum glucose and insulin determinations at 1 and 2 h after the administration of 50 g of oral glucose. The sum of the insulin levels during fasting, and at 1 and 2 h after the glucose load was calculated as a marker of hyperinsulinemia. Glucose levels were determined by the glucose oxidase method (14). Diabetes mellitus was defined as a fasting serum glucose level of ≥140 mg/dL, 2 h postload serum glucose level of ≥180 mg/dL, or the taking of medication for diabetes. Serum levels of insulin were measured by a commercial radioimmunoas-

say. Serum levels of total cholesterol and triglycerides were determined enzymatically with an Autoanalyzer 736-60E (Hitachi, Japan). All assays for serum lipids were standardized using Q-PAK Chemistry Control Serum 1 and 2 (Technicon Instrument Corp., New York, USA) (15).

This study was approved by the ethics committee of the Hiroshima University School of Medicine and all subjects gave their informed consent for participation.

Statistical Methods

Analysis of covariance was used to compare the mean values of BMI, serum uric acid, glucose, and insulin and the development of hypertension adjusted for age and sex. Logarithmic transformations of triglycerides and insulin were performed because these variables showed a skewed distribution in all statistical analyses. They were reconverted to their original form before presentation in the tables (Tables 1, 2). The Cox proportional hazards model was used to calculate the relative risk and 95% confidence intervals for the association between the development of hypertension and the risk factors shown in Fig. 1 and Table 3. These were adjusted for potential confounders, including age, sex, BMI, serum uric acid, glucose, insulin, lipids, and baseline systolic blood pressure in Table 3 and adjusted for age and sex in Fig. 1.

Statistical analyses were carried out using the SAS program (JMP 3.0). A level of p < 0.05 was considered to indicate statistical significance.

Results

Table 1 shows the baseline characteristics of the 159 subjects who participated in survey 2 and the 155 subjects who did not participate. There were no differences in baseline characteristics between the two groups. After excluding those heart-disease subjects in survey 2 who had received antihypertensive drugs, 140 subjects (mean, 54.8 years old; 50 men and 90 women) remained. Of these, 17 (12%) had hypertension.

Table 2 shows the differences in characteristics between subjects who later became hypertensive and those did not. BMI, blood pressure, serum uric acid, triglycerides, and insulin at baseline were higher in the former group. Moreover, the development of hypertension was associated with fasting glucose levels at follow-up as well as the change in fasting glucose during the follow-up period, but not with the change in BMI (data not shown).

Age- and sex-adjusted relative risks for the development of hypertension by quartiles of BMI, serum uric acid, triglycerides, and Δ insulin were highest in the highest quartile (Fig. 1). Fasting and 2 h serum insulin concentrations also were associated with hypertension (data not shown).

When age, sex, systolic blood pressure, BMI, serum uric acid, total cholesterol, triglycerides, fasting glucose, Δ insulin, and the change in BMI were used in a proportional
Table 1. Baseline Characteristics of the Study Cohort

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Follow-up</th>
<th>Lost to follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$n = 159$</td>
<td>$n = 155$</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>55.1 (0.6)</td>
<td>54.0 (0.7)</td>
</tr>
<tr>
<td>Men : Women</td>
<td>52 : 103</td>
<td>61 : 98</td>
</tr>
<tr>
<td>Body mass index (kg/m(^2))</td>
<td>22.6 (0.3)</td>
<td>22.7 (0.3)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>120.8 (0.8)</td>
<td>120.7 (0.9)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>74.6 (0.6)</td>
<td>74.4 (0.6)</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>5.1 (0.1)</td>
<td>5.0 (0.1)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>226.6 (3.3)</td>
<td>232.8 (3.3)</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)*</td>
<td>110.9 (102.7–111.9)</td>
<td>119.1 (109.0–130.0)</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>89.7 (1.1)</td>
<td>93.8 (1.8)</td>
</tr>
<tr>
<td>Fasting insulin (µU/ml)*</td>
<td>9.4 (8.7–10.2)</td>
<td>10.1 (9.3–11.0)</td>
</tr>
</tbody>
</table>

Values are given as the means (± SE) or (95% confidence intervals). * Values are back-transformed from log transformation.

Table 2. Anthropometric and Clinical Characteristics of Individuals with and without the Development of Hypertension Adjusted for Age and Sex by Analysis of Variance

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Development of hypertension</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(−) ($n = 123$)</td>
<td>(+) ($n = 17$)</td>
</tr>
<tr>
<td>Age (years)*</td>
<td>54.7 (0.7)</td>
<td>55.4 (1.8)</td>
</tr>
<tr>
<td>Men : Women*</td>
<td>45 : 78</td>
<td>5 : 12</td>
</tr>
<tr>
<td>Body mass index (kg/m(^2))</td>
<td>22.3 (0.3)</td>
<td>25.2 (0.7)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>119.7 (0.9)</td>
<td>126.6 (2.5)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>74.1 (0.6)</td>
<td>80.1 (1.6)</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>5.2 (0.1)</td>
<td>6.0 (0.3)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>225.2 (3.8)</td>
<td>221.9 (9.9)</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)*</td>
<td>108.9 (99.7–119.0)</td>
<td>134.3 (106.4–169.4)</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>90.6 (1.3)</td>
<td>94.7 (3.4)</td>
</tr>
<tr>
<td>2 h glucose (mg/dl)</td>
<td>104.1 (3.8)</td>
<td>115.0 (10.1)</td>
</tr>
<tr>
<td>Fasting insulin (µU/ml)*</td>
<td>8.7 (8.0–9.5)</td>
<td>13.4 (10.6–17.0)</td>
</tr>
<tr>
<td>2 h insulin (µU/ml)*</td>
<td>25.5 (22.1–29.5)</td>
<td>47.9 (32.6–70.3)</td>
</tr>
<tr>
<td>Σ insulin (µU/ml)*</td>
<td>88.7 (81.1–97.0)</td>
<td>145.2 (115.1–183.2)</td>
</tr>
</tbody>
</table>

Values are given as the means (± SE) or (95% confidence intervals). Σ insulin, sum of fasting, 1 h, and 2 h postload insulin levels during a 50 g oral glucose-tolerance test. * Values are not adjusted for age and sex. † Values are back-transformed from log transformation.

hazard analysis, Σ insulin, uric acid, and systolic blood pressure were significant risk factors for hypertension (Table 3). BMI seemed to be related to hypertension. When the change in fasting glucose was included in this analysis, the relation of Σ insulin to hypertension was not significant (data not shown).

**Discussion**

In the present study, hyperinsulinemia and hyperuricemia were independent risk factors for the development of hypertension during 15 years of follow-up in Japanese-Americans in Hawaii. Many studies have shown that hyperinsulinemia and/or insulin resistance are related to obesity, hypertension, dyslipidemia, and glucose intolerance. Some epidemiologic prospective studies (11–13, 16) have shown that hyperinsulinemia plays an important role in the development of hyperinsulinemia. Data from the San Antonio Heart Study (17) have suggested that the fasting insulin concentration was associated with the incidence of hypertension, even after adjustment for BMI in lean subjects, but that this association was not present in obese subjects. Skarfors et al. (11) have reported that baseline blood pressure is the strongest predictor of the future development of hypertension. In the absence of baseline blood pressures, fasting and late insulin levels during an intravenous glucose tolerance test, and the difference in BMI between surveys were associated with hypertension. Hyperinsulinemia was not associated with the development of hypertension when adjusted for differences in BMI. Tsaruta et al. (18) have suggested that hyperinsulinemia is significantly related to the development of hypertension in nonobese (BMI < 26 kg/m\(^2\)) and non-diabetic Japanese individuals. Lissner et al. (16) have suggested that the fasting insulin concentration is associated with the incidence of hyperten-
sion in women. This association is statistically independent of baseline BMI, waist/hip ratio, and weight change. Haffner et al. (13) have reported in the San Antonio Heart Study (phase 2 cohort) that hyperinsulinemia is predictive of the development of hypertension in lean and obese subjects. In our results, hyperinsulinemia was predictive of the development of hypertension after adjustment for BMI and changes in BMI during the follow-up period. Obesity has been associated with hypertension (19). In addition, some studies (20–23) have shown that obese hypertensive subjects who lose weight can also reduce their blood pressure. The mechanism by which obesity leads to hypertension, however, remains unclear. Insulin resistance and compensatory hyperinsulinemia have been evaluated as potential links between obesity and hypertension (3, 19, 24–26). In our study, body weight change during the follow-up period was very small and was not associated with the development of hypertension. Baseline BMI was a strong predictor of hypertension. After adjustment for serum insulin and uric acid, however, obesity was not associated with the development of hypertension. These results suggest that hyperinsulinemia can explain, in part, the relationship between obesity and hypertension.

Some studies (10, 27) have reported that the relationship between hyperinsulinemia and hypertension differs among different races. Saad et al. (11) have reported that plasma insulin concentrations and insulin resistance are related to blood pressure in Caucasians but not in Pima Indians or blacks. Shetterly et al. (27) have reported that increased fasting insulin levels are associated with hypertension in lean non-Hispanic white persons, but not in Hispanic persons. The prevalence of hyperinsulinemia has been reported to be higher in Japanese-Americans than in the Japanese (28, 29). A Westernized lifestyle has been suggested as playing an important role in the increased prevalence of hyperinsulinemia. In cross-sectional studies, hyperinsulinemia has been associated with hypertension in Japanese-Americans (29, 30). And in a prospective study (18) in Japanese and Japanese-Americans in Hawaii, hyperinsulinemia was associated with the incidence of hypertension.

Hypertension is more common in patients with gout (31). And, in a study by Breckenridge, hyperuricemia was present in 27% of patients with untreated mild essential hypertension (32). Uric acid is the end product of purine metabolism and is produced by xanthine oxidase. Nakazono et al. (33) reported that oxypurinol, a potent inhibitor of xanthine oxidase (also a source of superoxide radicals), decreased the blood pressure of spontaneously hypertensive rats (SHR), and that superoxide radicals play critical roles in the pathogenesis of hypertension of SHR. Suzuki et al. (34) reported that an elevated activity of xanthine oxidase might be related to the elevation of the arterial blood pressure in SHR. Messerli et al. (35) have reported that mild asymptomatic hyperuricemia is associated with decreased renal blood flow without affecting glomerular filtration. They have suggested

![Figure 1](image-url)

**Fig. 1.** Bar graphs show the relative risks for the development of hypertension by quartiles of body mass index (BMI), serum uric acid (UA), triglycerides (TG), Σ insulin, and systolic blood pressure (SBP) adjusted for age and sex. Quartile ranges for BMI are ≤ 20.2, 20.3–21.6, 21.9–24.3, and ≥ 24.4 kg/m²; those for UA are ≤ 4.2, 4.3–4.9, 5.0–5.9, and ≥ 6.0 mg/dl; those for TG are ≤ 77, 78–104, 105–144, and ≥ 145 mg/dl; those for Σ insulin are ≤ 67, 68–94, 95–136, and ≥ 138 μU/ml; and those for SBP are ≤ 112, 114–120, 122–128, and ≥ 130 mmHg. The relative risks are evaluated in comparison with the highest quartiles.

<table>
<thead>
<tr>
<th>Table 3. Assessing the Independent Effect of Risk Factors on the Development of Hypertension with a Cox Hazard Model</th>
<th>Risk ratio</th>
<th>Quartile 4*</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index</td>
<td>1.0</td>
<td>1.84 (0.98–3.45)</td>
<td>0.06</td>
</tr>
<tr>
<td>Σ insulin</td>
<td>1.0</td>
<td>1.86 (1.05–3.62)</td>
<td>0.03</td>
</tr>
<tr>
<td>Uric acid</td>
<td>1.0</td>
<td>2.03 (1.02–3.90)</td>
<td>0.04</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.0</td>
<td>0.85 (0.44–1.61)</td>
<td>0.62</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>1.0</td>
<td>1.87 (1.06–3.33)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Values in parentheses are 95% confidence intervals. Σ insulin, fasting, 1 h, and 2 h postload insulin levels during a 50 g oral glucose-tolerance test. *Body mass index ≥ 24.4 kg/m², Σ insulin ≥ 138 μU/ml, uric acid ≥ 6.0 mg/dl, triglycerides ≥ 145 mg/dl, and systolic blood pressure ≥ 130 mmHg. †Body mass index, Σ insulin, uric acid, triglycerides, and systolic blood pressure are entered into Cox hazard models predicting the development of hypertension as dummy variables with quartiles 1–3 as the referents. Sex is entered as a dummy variable with women as the referent. Age and change in body mass index are entered as continuous variables.
that unexplained hyperuricemia in patients with essential hypertension most likely reflects early renal vascular involvement, specifically, nephrosclerosis. Modan et al. (36) have reported that elevated serum uric acid is a feature of hyperinsulinemia/insulin resistance. In the present study, hyperuricemia was an independent predictor of the development of hypertension. These results suggest that serum uric acid can be a marker in the development of hypertension.

Diabetic persons have an increased prevalence of hypertension (37), and glucose intolerance is more common in hypertensive persons (15% to 18%) (38). In previous studies (12, 39), glucose intolerance was predictive of the development of hypertension. However, other studies (13, 27) have failed to find an effect of glucose intolerance on the incidence of hypertension. In our study, glucose intolerance was not predictive of the development of hypertension in normotensive subjects. Hypertension was not developed in diabetic individuals treated with oral hypoglycemic agents; moreover, diabetes was not associated with the development of hypertension (data not shown). Even after excluding diabetic individuals, hyperinsulinemia was associated with the development of hypertension (data not shown). Hyperinsulinemia has been found to be a strong predictor of diabetes mellitus (17). We also found that hyperinsulinemia was a predictor for the development of glucose intolerance (data not shown), but it was not associated with hypertension after adjusting for the change in fasting serum glucose levels during the follow-up period (data not shown). These results suggest that hyperinsulinemia may be associated with hypertension in part via glucose intolerance-induced alterations such as sodium retention, vasculopathy, and nephropathy.

Our study may be limited because insulin was measured with an assay that cross-reacts with proinsulin. Several studies (40–42) have shown that proinsulin is elevated disproportionately in subjects with non-insulin-dependent diabetes mellitus. In subjects with impaired glucose tolerance, the ratio of proinsulin to insulin can be slightly higher than in subjects with normal glucose tolerance (40, 42) or can be unchanged (41). Moreover, because the ratio of proinsulin to insulin was very low, and most of our study populations had normal glucose tolerance, hyperinsulinemia in this study would seem to have been mainly due to the elevation of specific insulin concentration. An additional limitation was the high percentage of subjects lost to follow-up (45%). However, the baseline characteristics between the groups who were and were not followed up were similar, and we believe that the incidence of hypertension in these two groups would not have been significantly different. The third limitation was that during follow-up, the dietary and lifestyle factors were not assessed for all subjects. These factors influence the BMI. However, since there was no difference between the BMI at baseline and follow-up, the influence of the change in dietary and lifestyle factors on the development of hypertension in this study appeared to be weak.

In conclusion, hyperinsulinemia, as well as obesity, hyperuricemia, and hypertriglyceridemia, were associated with hypertension in our study. Hyperinsulinemia associated with obesity, hyperuricemia, and hypertriglyceridemia appears to be a most important predictor of the development of hypertension in Japanese-Americans in Hawaii.

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References

15. Henry RJ, Cannon DC, Winkleman JW: Clinical Chem-


