Hyperinsulinemia and Cardiovascular Disease in Elderly Men
The Honolulu Heart Program
Cecil M. Burchfiel, Dan S. Sharp, J. David Curb, Beatriz L. Rodriguez, Robert D. Abbott, Richard Arakaki, Katsuhiko Yano

Abstract—Hyperinsulinemia has been associated with cardiovascular disease (CVD), but whether this relation is independent of other CVD risk factors is uncertain. Most studies have focused on coronary heart disease (CHD), but few have included peripheral vascular disease (PVD) and stroke. Moreover, evidence in elderly and minority populations is limited. Between 1991 and 1993, 3562 elderly (71 to 93 years) Japanese-American men from the Honolulu Heart Program were examined and had fasting insulin levels measured. Hyperinsulinemia, defined as a fasting insulin ≥95th percentile among nonobese men with normal glucose tolerance and no diabetic history or medication use, was observed in 22% of the population. Subjects with hyperinsulinemia had a more adverse CVD risk factor profile and had higher age-adjusted prevalences of CHD, angina, PVD, thromboembolic stroke, and hemorrhagic stroke compared with those without hyperinsulinemia. Age-adjusted fasting insulin levels but not 2-hour levels were also significantly elevated (P<.01) in those with prevalent CVD compared with those without. In logistic regression analyses, adjustment for multiple CVD risk factors attenuated the relations of hyperinsulinemia with CHD, angina, and PVD to nonsignificant levels, whereas those involving thromboembolic and hemorrhagic stroke were strengthened and remained significant (odds ratios=2.27 and 7.53, 95% confidence intervals=1.25 to 4.13 and 1.65 to 34.25, respectively). When multivariate analyses were restricted to nondiabetic subjects, associations were slightly weaker and in general nonsignificant. Nondiabetic men with thromboembolic stroke were twice as likely to have hyperinsulinemia as those who were stroke-free, although this association was of borderline significance (odds ratio=1.99, 95% confidence interval=0.95 to 4.17, P=.069). In subjects with elevated total cholesterol levels, somewhat stronger associations were observed for PVD and stroke but not for CHD. Although further prospective studies are indicated, particularly for PVD and stroke, these cross-sectional results are consistent with an indirect role for insulin in CVD, wherein hyperinsulinemia or an underlying insulin-resistant state may adversely affect other CVD risk factors or serve as a marker for an atherogenic or thrombogenic state. (Arterioscler Thromb Vasc Biol. 1998;18:450-457.)

Key Words: Asian Americans cardiovascular diseases insulin

The role of elevated insulin levels in CVD is uncertain. More than 15 years ago, several prospective epidemiological studies demonstrated an independent association between insulin concentrations and CHD.1-3 More recent investigations,4,5 but not all,6 suggest that the association may not be independent of other known CVD risk factors. Some of the discordant findings may be due to the fact that these early studies did not take into account HDL cholesterol levels.5-9
Whether hyperinsulinemia is associated with CVD has not been widely studied in the elderly nor in subsets of the population who might be at increased risk. For example, relatively low levels of total and LDL cholesterol could account for the paradoxically low rates of CHD despite a high prevalence of glucose intolerance in some populations.10-12 Moreover, although associations of insulin with CHD have been examined in a number of studies, those involving stroke13 and PVD14-16 have been assessed infrequently.

The purpose of this investigation was to assess the association of hyperinsulinemia with several clinical and subclinical manifestations of CVD in elderly subjects. A recent examination of the entire Honolulu Heart Program cohort between 1991 and 1993 provided the opportunity to examine these relations in >3500 elderly Japanese-American men by using a cross-sectional design. Adjustment for other CVD risk factors was performed to determine whether these associations were independent or whether they might be mediated through an effect
of insulin on other risk factors. Associations were also examined in nondiabetic subjects and in subsets of the population with elevated total cholesterol who might be at increased CVD risk.

Methods

Study Population

The Honolulu Heart Program is a prospective epidemiological study initiated in 1965 to determine risk factors for heart disease and stroke in a well-defined population of middle-aged Japanese-American men. Potential subjects identified from selective service records were born between 1900 and 1919 and were living on the island of Oahu in 1965.17,18 A total of 8006 men between 45 and 68 years of age completed the baseline examination (1965 to 1968). Subsequent examinations were completed an average of 2 years (1968 to 1970), 6 years (1971 to 1974), and 25 years (1991 to 1993) after the baseline examination.

Among the 8006 initially examined men, 3845 men were reexamined or completed an extended telephone interview between 1991 and 1993. Of 3741 men examined (80% of survivors at that time), 86% of the examinations were performed in a clinic setting, 13% at home, and 1% in nursing homes. A total of 3573 subjects provided fasting blood specimens and 3562 had fasting insulin concentrations measured. These 3562 men, aged 71 to 93 years between 1991 and 1993, constituted the study population.

Data Collection

The examination included demographic, lifestyle (smoking, alcohol, physical activity), medical history, medication use, and psychosocial information as well as physiological, anthropometric, and other laboratory measurements. The methods used in data collection were consistent with assessments made at previous examinations, were in accordance with institutional guidelines, and were approved by the Institutional Review Committee of Kuakini Medical Center.19 BMI was calculated as weight in kilograms divided by height in meters squared. An index of physical activity was based on the number of hours spent in five activity levels weighted by the estimated oxygen required.20 Hypertension was considered present when blood pressure (systolic $>200$ mm Hg or diastolic $>115$ mm Hg). A total of 2133 subjects fasted at least 12 hours and had both fasting and 2-hour glucose measurements. Glucose was measured by a glucose oxidase method (University of Vermont). Insulin was measured by a double–antibody radioimmunoassay method24 at the University of Washington (Diabetes Endocrinology Research Center Core Radioimmunoassay Laboratory) after storage at $-70^\circ$C for up to 2 years, with a lower limit of detection of 3 $\mu$U/mL and interassay coefficients of variability of 9% and 8% at low (mean, 21 $\mu$U/mL) and high (mean, 82 $\mu$U/mL) insulin concentrations, respectively.25

Hyperinsulinemia

Hyperinsulinemia was defined as a fasting insulin concentration at or above the 95th percentile of the distribution among a subset of the population who did not have several characteristics known to influence insulin levels, such as glucose intolerance, obesity, and inadequate duration of fasting. Thus, this definition was applied to subjects who met the following specific criteria: (1) normal glucose tolerance by World Health Organization definition,26 (2) negative history and medication use for diabetes, (3) nonobesity (BMI $<25.0$), and (4) an overnight fast of at least 12 hours. Among the 3562 men who had insulin measured between 1991 and 1993, 2265 men had no missing values for the variables included in these criteria (most of those excluded did not have 2-hour glucose values). Of these subjects, 1554 men had abnormal glucose tolerance (diabetes or impaired glucose tolerance by World Health Organization criteria), had a history of diabetes, or were taking diabetic medication. Of the remaining 711 men, 190 were obese by this definition and 21 had fasted $<12$ hours (4 of these men met both criteria). Thus, a total of 504 subjects of the 3562 men with fasting insulin measurements (14.1%) met these criteria. The 95th percentile of the fasting insulin concentration for this group of 504 subjects was 20 $\mu$U/mL, and an insulin level at or above this value was used to define hyperinsulinemia for the entire population.

Prevalent CVD

Assessment of prevalent manifestations of clinical and subclinical CVD was based on current as well as previously collected information. A comprehensive hospital-based surveillance system has been in existence since initiation of the study in 1965. Both fatal and nonfatal cardiovascular events are identified by a committee on the basis of information from hospital discharge summaries, autopsy reports, and death certificates. The committee uses standardized criteria to ascertain prevalent and incident clinical events, as described in detail previously.19,27

The definition for CHD included (1) myocardial infarction, (2) coronary insufficiency or angina pectoris with surgical intervention (angioplasty or bypass graft) or with angiographic evidence of coronary artery stenosis $>70\%$ identified through surveillance, and (3) reported heart attack or angina resulting in hospitalization or surgical treatment at the current examination. Criteria for infarction included a clinically apparent event based on electrocardiographic and cardiac enzyme evidence identified through surveillance, a silent event detected by electrocardiograms at any examination or through surveillance, or a temporal change in electrocardiograms diagnostic of myocardial infarction. Angina was also examined as a separate clinical manifestation and was considered present if it was identified by hospital surveillance using specific criteria27 or was diagnosed by a physician at any Honolulu Heart Program examination. Angina defined by Rose criteria was also assessed.28

Definite and probable thromboembolic and hemorrhagic strokes (excluding transient ischemic attacks) were identified by hospital surveillance and met specific criteria as described in detail previously.19,27 In general, criteria for stroke included a persistent neurological deficit and evidence from cerebrospinal fluid, nuclear brain scans, and CT.

PVD was identified by using a ratio of blood pressures measured by a Doppler device in the ankle to that in the arm.30 The mean of two...
TABLE 1. Age-Adjusted Cardiovascular Risk Levels (Means and Percentages) by Hyperinsulinemia Status*

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>No (n=2789)</th>
<th>Yes (n=773)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index, kg/m²</td>
<td>22.9±0.1</td>
<td>25.5±0.1</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>108.3±0.5</td>
<td>130.1±1.0</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>52.8±0.2</td>
<td>44.0±0.5</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>135.0±1.7</td>
<td>199.3±3.2</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>305.1±1.2</td>
<td>313.1±2.3</td>
</tr>
<tr>
<td>Alcohol, mL/dt</td>
<td>31.5±1.2</td>
<td>34.8±2.4</td>
</tr>
<tr>
<td>Physical activity index</td>
<td>31.1±0.1</td>
<td>30.2±0.2</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>43.8±0.1</td>
<td>45.2±0.2</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>63.2±0.2</td>
<td>65.4±0.4</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>7.3</td>
<td>6.4</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>51.5</td>
<td>63.4</td>
</tr>
<tr>
<td>Diabetic medication, %</td>
<td>7.8</td>
<td>26.4</td>
</tr>
</tbody>
</table>

Values are mean±SEM for continuous variables and prevalence (%) for discrete variables.

*All comparisons were statistically significant at P<.0001 except for current smoking (P=.40) and alcohol (P=.23).
†Values are for current and past drinkers (1508 subjects who did not have and 403 who did have hyperinsulinemia, respectively).
‡Defined as ≥160/95 mm Hg or use of antihypertensive medication.

Statistical Analysis

All subjects were initially categorized by hyperinsulinemia status using the cutpoint established among nonobese subjects with normal glucose tolerance. Age-adjusted mean levels and prevalence of a number of cardiovascular risk factors were compared for subjects with and without hyperinsulinemia by using general linear models for continuous variables and logistic regression for discrete variables. For descriptive purposes, age-adjusted mean fasting and 2-hour insulin levels were also compared for subjects with and without each of the CVD manifestations. Because insulin level was the dependent variable in this instance and its distribution was skewed, a logarithmic transformation was used in statistical comparisons, and the antilogarithm of \log_{10} mean insulin was calculated to express insulin levels in their original units.

In addition, the age-adjusted prevalence of each cardiovascular manifestation was estimated for subjects with and without hyperinsulinemia by using a marginal prediction method that calculates probabilities of disease from a logistic model for each individual on the basis of their age and then averages these probabilities for the entire population. Logistic regression models were also used to assess the association of hyperinsulinemia with each CVD manifestation. ORs and their 95% CIs were calculated from a series of logistic models adjusting for the following covariates: (1) age only; (2) age and BMI; (3) age, BMI, and indicators of diabetes (diabetic medication use and glucose level); (4) previous variables plus hypertension and triglycerides; and (5) previous variables plus smoking, alcohol intake, physical activity, hematocrit, and heart rate. The same logistic analyses were repeated among nondiabetic subjects. Separate logistic analyses were conducted to determine whether or not the association of hyperinsulinemia with CVD was more pronounced at elevated total cholesterol levels (defined by two cutpoints, ≥240 mg/dL and ≥200 mg/dL) than at lower cholesterol levels. Interaction terms were also included in logistic regression models to assess effect modification by cholesterol level.

Results

An elevated fasting insulin level (≥20 μU/mL) was found in 21.7% of these 3562 men. Subjects with hyperinsulinemia were more obese and less physically active; had higher levels of glucose, triglycerides, and hematocrit; and had higher heart rates and a higher prevalence of diabetes and hypertension than did subjects who were not hyperinsulinemic (P<.001; Table 1). Mean systolic and diastolic blood pressures (data not shown), alcohol consumption, and prevalence of current smoking did not differ significantly between the two groups.

For descriptive purposes, age-adjusted mean fasting and 2-hour insulin levels are presented for subjects with and without five manifestations of CVD (Table 2). Fasting, but not 2-hour, insulin levels were significantly higher in subjects with these prevalent disease manifestations than in those without these conditions. Angina defined by Rose criteria was not associated with insulin level (data not shown). Somewhat larger absolute differences in mean fasting insulin levels were observed for both types of stroke than for other manifestations, although fewer events were observed, particularly for hemorrhagic stroke.

TABLE 2. Age-Adjusted Mean Insulin Concentrations by CVD Status*

<table>
<thead>
<tr>
<th>Cardiovascular Manifestation</th>
<th>Insulin, μU/mL</th>
<th>Disease Absent</th>
<th>Disease Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Mean</td>
<td>SEM</td>
<td>n</td>
</tr>
<tr>
<td>CHD</td>
<td>Fastig</td>
<td>2970</td>
<td>12.7</td>
</tr>
<tr>
<td></td>
<td>2-Hour</td>
<td>1830</td>
<td>93.0</td>
</tr>
<tr>
<td>Angina</td>
<td>Fastig</td>
<td>3161</td>
<td>12.8</td>
</tr>
<tr>
<td></td>
<td>2-Hour</td>
<td>1920</td>
<td>92.9</td>
</tr>
<tr>
<td>ABI&lt;0.9</td>
<td>Fastig</td>
<td>2990</td>
<td>12.7</td>
</tr>
<tr>
<td></td>
<td>2-Hour</td>
<td>1946</td>
<td>93.3</td>
</tr>
<tr>
<td>Thromboembolic stroke</td>
<td>Fastig</td>
<td>3452</td>
<td>12.9</td>
</tr>
<tr>
<td></td>
<td>2-Hour</td>
<td>2121</td>
<td>93.3</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>Fastig</td>
<td>3534</td>
<td>12.9</td>
</tr>
<tr>
<td></td>
<td>2-Hour</td>
<td>2150</td>
<td>93.5</td>
</tr>
</tbody>
</table>

*Calculated as antilogarithms of the means and SEs of \log_{10} insulin, with statistical comparisons based on \log_{10} insulin.
The age-adjusted prevalence of all CVD manifestations was significantly higher in subjects with hyperinsulinemia than in those without (Table 3). As expected, CHD, angina, and subclinical evidence of PVD were more prevalent overall than were thromboembolic and hemorrhagic stroke. Compared with subjects who did not have hyperinsulinemia, those who were hyperinsulinemic had a significantly higher prevalence of CHD (15.2% versus 21.8%), angina (10.6% versus 13.7%), PVD (12.5% versus 16.9%), thromboembolic stroke (2.7% versus 4.6%), and hemorrhagic stroke (0.6% versus 1.6%).

Age-adjusted ORs indicating the association of hyperinsulinemia with prevalent CVD were significantly elevated and ranged between 1.3 and 1.6 for CHD, angina, and PVD and were somewhat higher (1.8 and 2.8) for thromboembolic and hemorrhagic stroke, respectively (Table 4). After additional adjustment for BMI, ORs for CHD and angina were slightly reduced and those for PVD and both types of stroke slightly enhanced. Associations remained significant except for angina. With further adjustment for glucose level and use of diabetic medication, ORs for CHD were further attenuated and were no longer significantly elevated, whereas ORs for PVD and stroke were attenuated slightly but remained significantly elevated. Addition of other covariates to the models further reduced associations with CHD and angina. Additional adjustment for triglycerides, HDL cholesterol, and hypertension attenuated the OR for PVD to a nonsignificant level. However, ORs for thromboembolic and hemorrhagic stroke showed independent associations with hyperinsulinemia, even after adjustment for these variables, and these associations were slightly stronger after further adjustment for smoking, alcohol, fibrinogen, hematocrit, physical activity, and heart rate.

Similar analyses are presented in Table 5 for 2801 nondiabetic subjects (ie, excluding those with diabetic history or medication use). In general, the magnitude of the ORs was smaller and not significantly elevated after adjustment for age in nondiabetic subjects than in the entire cohort. Associations of hyperinsulinemia with CHD, angina, and hemorrhagic stroke were not statistically significant after adjustment for multiple CVD risk factors; results for hemorrhagic stroke were limited by a relatively small number of events. Adjustment for age and BMI yielded ORs that were significantly elevated for PVD and nearly so for thromboembolic stroke. With additional adjustment for glucose level, associations were significant for both PVD and thromboembolic stroke. Adjustment for additional CVD risk factors attenuated the ORs for PVD but had little impact on those for thromboembolic stroke. Associations reached borderline significant levels for thromboembolic stroke in the final two models (P=0.055 and P=0.069, respectively). When all stroke events among nondiabetic men were considered together, the OR remained significantly elevated (2.05, 95% CI 1.00 to 4.19), even after adjustment for all CVD risk factors.

Age-adjusted ORs were also calculated for all subjects stratified by total cholesterol level at two different cutpoints (Table 6). ORs for CHD were similar in magnitude in men with low and high total cholesterol based on the 240 mg/dL and 200 mg/dL cutpoints. Associations involving PVD were significant for

### Table 3. Age-Adjusted Prevalence (%) of CVD by Hyperinsulinemia Status

<table>
<thead>
<tr>
<th>Cardiovascular Manifestation</th>
<th>Hyperinsulinemia</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n=2789)</td>
<td>Yes (n=773)</td>
<td>P</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD</td>
<td>15.2</td>
<td>21.8</td>
<td>&lt;.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina</td>
<td>10.6</td>
<td>13.7</td>
<td>.0148</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABI&lt;0.9</td>
<td>12.5</td>
<td>16.9</td>
<td>.0020</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thromboembolic stroke</td>
<td>2.7</td>
<td>4.6</td>
<td>.0060</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.6</td>
<td>1.6</td>
<td>.0074</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 4. Adjusted ORs for Association of Hyperinsulinemia With Prevalent CVD

<table>
<thead>
<tr>
<th>Adjustment Variables*</th>
<th>CHD</th>
<th>Angina</th>
<th>ABI &lt;0.9</th>
<th>Thromboembolic Stroke</th>
<th>Hemorrhagic Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.55 (1.27–1.90)</td>
<td>1.34 (1.06–1.71)</td>
<td>1.44 (1.14–1.82)</td>
<td>1.78 (1.18–2.68)</td>
<td>2.81 (1.32–5.98)</td>
</tr>
<tr>
<td>Age, BMI</td>
<td>1.47 (1.18–1.84)</td>
<td>1.29 (0.99–1.67)</td>
<td>1.76 (1.36–2.27)</td>
<td>2.20 (1.35–3.58)</td>
<td>4.77 (1.67–13.63)</td>
</tr>
<tr>
<td>Above glucose, diabetic medication</td>
<td>1.19 (0.94–1.50)</td>
<td>1.16 (0.88–1.53)</td>
<td>1.44 (1.09–1.91)</td>
<td>2.19 (1.29–3.70)</td>
<td>3.72 (1.19–11.65)</td>
</tr>
<tr>
<td>Above HDL, triglyceride, hypertension</td>
<td>1.13 (0.89–1.44)</td>
<td>1.10 (0.83–1.47)</td>
<td>1.33 (0.99–1.77)</td>
<td>2.09 (1.22–3.59)</td>
<td>6.01 (1.77–20.35)</td>
</tr>
<tr>
<td>Above smoking, alcohol†</td>
<td>1.05 (0.81–1.36)</td>
<td>1.11 (0.83–1.49)</td>
<td>1.34 (0.98–1.82)</td>
<td>2.27 (1.25–4.13)</td>
<td>7.53 (1.65–34.25)</td>
</tr>
</tbody>
</table>

Values in parentheses are 95% CIs.

*Separate logistic regression models with successive addition of the independent variables indicated.
†Alcohol intake (mL/d) and drinking status (never- versus ever-drinkers) variables were included.
both low- and high-cholesterol groups at the 240 mg/dL cutpoint and were somewhat stronger among subjects with elevated cholesterol levels (ORs 1.4, 95% CI 1.1 to 1.7, and 2.6, 95% CI 1.2 to 5.3, respectively) but were similar in subjects stratified by the 200 mg/dL total cholesterol level. ORs for thromboembolic stroke appeared stronger in men with elevated total cholesterol relative to men with lower levels for both cutpoints (7.5 versus 1.7 for 240 mg/dL and 2.8 versus 1.5 for the 200 mg/dL cutpoint); however, ORs in the ≥240 mg/dL group were based on only three events among 244 subjects. ORs for hemorrhagic stroke could not be estimated or were less stable in the elevated cholesterol groups, given the relatively infrequent occurrence of these outcomes (n=0 and n=4, respectively) and the low prevalence of cholesterol levels ≥240 mg/dL in this cohort. Despite the apparent stronger associations of hyperinsulinemia with PVD in subjects with cholesterol levels ≥240 mg/dL and with stroke in both elevated-cholesterol groups, there was no evidence of statistical interaction when interaction terms were included in logistic models.

### Discussion

The prevalence of CHD, angina, PVD, thromboembolic stroke, and hemorrhagic stroke was significantly higher in elderly Japanese-American men who had fasting hyperinsulinemia (defined as ≥20 μU/mL) than in those who did not. In all subjects, associations of hyperinsulinemia with CHD, angina, and, to a lesser extent, PVD were accounted for by other CVD risk factors, whereas those involving both types of stroke were independent of other CVD risk factors. When multivariate analyses were restricted to nondiabetic subjects, ORs tended to be slightly smaller and statistically significant less frequently. In general, the likelihood of having most of these CVD manifestations was not significantly elevated in nondiabetic men with hyperinsulinemia compared with men without hyperinsulinemia. However, the likelihood of having thromboembolic stroke remained twofold greater in hyperinsulinemic men compared with nonhyperinsulinemic men after adjustment for CVD risk factors, although the OR was no longer significantly elevated (1.99, 95% CI=0.95 to 4.17).

### TABLE 5. Adjusted ORs for Association of Hyperinsulinemia With Prevalent CVD in Nondiabetic* Subjects

<table>
<thead>
<tr>
<th>Adjustment Variables†</th>
<th>CHD (n=423)</th>
<th>Angina (n=298)</th>
<th>ABI&lt;0.9 (n=324)</th>
<th>Thromboembolic Stroke (n=77)</th>
<th>Hemorrhagic Stroke (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.26 (0.97–1.63)</td>
<td>1.31 (0.97–1.76)</td>
<td>1.16 (0.85–1.58)</td>
<td>1.53 (0.89–2.62)</td>
<td>1.21 (0.34–4.31)</td>
</tr>
<tr>
<td>Age, BMI</td>
<td>1.13 (0.85–1.50)</td>
<td>1.22 (0.88–1.69)</td>
<td>1.42 (1.02–2.00)</td>
<td>1.86 (0.98–3.51)</td>
<td>2.42 (0.55–10.66)</td>
</tr>
<tr>
<td>Above+glucose</td>
<td>1.05 (0.79–1.41)</td>
<td>1.14 (0.82–1.59)</td>
<td>1.42 (1.00–2.01)</td>
<td>2.00 (1.04–3.83)</td>
<td>2.57 (0.56–11.74)</td>
</tr>
<tr>
<td>Above+HDL, triglyceride, hypertension</td>
<td>0.97 (0.72–1.31)</td>
<td>1.08 (0.77–1.53)</td>
<td>1.31 (0.91–1.87)</td>
<td>1.93 (0.99–3.77)</td>
<td>4.23 (0.84–21.44)</td>
</tr>
<tr>
<td>Above+smoking, alcohol,‡ fibrinogen, hematocrit, physical activity, heart rate</td>
<td>0.94 (0.69–1.28)</td>
<td>1.08 (0.76–1.55)</td>
<td>1.22 (0.83–1.80)</td>
<td>1.99 (0.95–4.17)</td>
<td>5.20 (0.60–45.19)</td>
</tr>
</tbody>
</table>

Values in parentheses are 95% CIs.

*Without a history of diabetes or use of diabetic medication (n=2801).

†Separate logistic regression models with successive addition of the independent variables indicated. Final models included 2540 of the 2801 nondiabetic subjects who had nonmissing values for all variables. Of these subjects, 369 had CHD, 266 had angina, 265 had ABI<0.9, 50 had thromboembolic stroke, and 6 had hemorrhagic stroke.

‡Alcohol intake (mL/d) and drinking status (never- versus ever-drinkers) variables were included.

### TABLE 6. Age-Adjusted ORs for Association of Hyperinsulinemia With Prevalent CVD by Cholesterol Level*

<table>
<thead>
<tr>
<th>Cholesterol Level</th>
<th>CHD (n=3317)</th>
<th>Angina (n=244)</th>
<th>ABI&lt;0.9 (n=2213)</th>
<th>Thromboembolic Stroke (n=1348)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;240 mg/dL</td>
<td>1.54 (1.25–1.90)</td>
<td>1.66 (0.74–3.75)</td>
<td>1.56 (1.21–2.00)</td>
<td>1.54 (1.10–2.14)</td>
</tr>
<tr>
<td>≥240 mg/dL</td>
<td>1.38 (1.08–1.76)</td>
<td>0.92 (0.33–2.57)</td>
<td>1.24 (0.91–1.69)</td>
<td>1.53 (1.06–2.22)</td>
</tr>
<tr>
<td>&lt;200 mg/dL</td>
<td>1.36 (1.06–1.74)</td>
<td>2.56 (1.24–5.29)</td>
<td>1.53 (1.14–2.07)</td>
<td>1.34 (0.93–1.94)</td>
</tr>
<tr>
<td>≥200 mg/dL</td>
<td>1.71 (1.12–2.60)</td>
<td>7.45 (0.65–85.20)</td>
<td>1.49 (0.92–2.43)</td>
<td>2.75 (1.26–6.00)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>2.81 (1.32–5.98)</td>
<td>. . .</td>
<td>2.15 (0.93–4.96)</td>
<td>11.87 (1.23–114.7)</td>
</tr>
</tbody>
</table>

Values in parentheses are 95% CIs.

*Cholesterol levels were measured in 3561 subjects.
In a recent review of studies assessing the association between insulin and heart disease, Wingard et al.\(^{34}\) concluded that insulin does not appear to be a major risk factor for heart disease, based primarily on evidence from prospective epidemiological studies. It was also recently reported that considerable controversy still exists over whether endogenous hyperinsulinemia is an independent risk factor for CVD.\(^{35}\) Other investigators have concluded that hyperinsulinemia and insulin resistance are related to atherosclerotic CVD but that their roles as independent CVD risk factors is less certain and that they are not major risk factors for CVD in the absence of other risk factors.\(^{36,37}\)

Results from our study are consistent with several other recent population-based studies that have reported associations between insulin level or hyperinsulinemia and CHD.\(^{7,36–39}\) In most prospective studies of nondiabetic subjects, including the present one, associations of insulin level with heart disease have not been independent in multivariate analyses.\(^{34}\) In some of these studies, no evidence of an association between insulin and heart disease was present.\(^{38,39}\) Although a recent investigation found these associations to be independent of other CVD risk factors, including HDL cholesterol,\(^{17}\) the findings from most studies are consistent with a more indirect role for hyperinsulinemia, one in which elevated insulin levels may lead to adverse changes in CVD risk factor.\(^{37}\) The insulin and insulin levels serve as an indicator of an underlying insulin-resistant state.\(^{38,36}\)

Recent results from the Quebec Cardiovascular Study have suggested that the relation of hyperinsulinemia to ischemic heart disease among nondiabetic men may be independent of body weight, blood pressure, and lipoprotein levels.\(^{3}\) The authors of this investigation suggested that hyperinsulinemia may therefore serve as a marker for other metabolic and hemostatic disturbances. Such a role for hyperinsulinemia is also consistent with earlier evidence suggesting that both CVD and non-insulin-dependent diabetes mellitus may share common etiologic factors that may have been present for a number of years prior to clinical onset of disease.\(^{40–42}\)

Although not ideal, fasting insulin level appears to be a reasonable indicator of insulin resistance, particularly in subjects with normal glucose tolerance.\(^{43}\) It has been suggested that insulin resistance or the compensatory hyperinsulinemia that follows\(^{44}\) may be the central underlying defect of “syndrome X,” or the “insulin resistance syndrome,” which is characterized by glucose intolerance, dyslipidemia, and hypertension.\(^{45,46}\) It has also been suggested that hyperinsulinemia is intimately related to the CVD risk factors that are known to cluster within individuals and that the components of this syndrome are involved, to a substantial degree, in several major chronic disease states (CHD, non–insulin-dependent diabetes mellitus, obesity, and essential hypertension).\(^{47–49}\) Because of the close associations between insulin and constituents of the insulin resistance syndrome, adjustment for glucose intolerance, dyslipidemia, and hypertension would be expected to attenuate relations with CVD outcomes. Any remaining excess risk associated with insulin could reflect mechanisms other than atherosclerosis.

Relatively few studies have examined associations of insulin with PVD and stroke. Previously, subjects with lower-extremity arterial disease were shown to have elevated insulin levels following an oral glucose challenge.\(^{15,16}\) Results from the current study were consistent with the findings from the Cardiovascular Health Study, another population-based cohort study of the elderly. In the Cardiovascular Health Study, fasting insulin level was inversely associated with the ABI index, after adjustment for age and sex, but did not exhibit an independent association in multivariate analysis wherein multiple CVD risk factors, including diabetes and HDL cholesterol, were included.\(^{14}\) Also consistent with findings from this study, insulin resistance with compensatory hyperinsulinemia was significantly related to atherothrombotic stroke in a small case-control study.\(^{13}\) In a recent investigation of the current cohort, evidence suggested that unidentified factors other than hypertension might play an increasingly important role in the etiology of stroke with advancing age.\(^{25}\) It is possible that insulin resistance or hyperinsulinemia might be one of these factors.

Indicators of asymptomatic atherosclerosis have recently been used to investigate potential associations with insulin levels. Fasting\(^{51,52}\) and postload insulin levels as well as insulin resistance\(^{46}\) have been associated with intimal wall thickness of the carotid artery. In addition, femoral atherosclerosis, defined as the presence of plaques by ultrasonography, was associated with insulin resistance in one study\(^{55}\) but not with fasting insulin level or insulin sensitivity index in another.\(^{56}\) Further studies that assess associations of insulin levels and insulin resistance with subclinical indicators of atherosclerosis are needed.

Several populations, including the Pima Indians,\(^{10}\) Hispanics,\(^{11}\) and perhaps Japanese,\(^{12}\) have paradoxically low rates of CHD despite relatively high proportions of individuals with glucose intolerance. It has been suggested that the relatively low total and LDL cholesterol levels in these populations may protect them from the adverse effects of glucose intolerance, hyperinsulinemia, or insulin resistance.\(^{57}\) Results from the present study do not support this hypothesis with regard to CHD but instead are suggestive of an enhanced risk of PVD and thromboembolic stroke in Japanese-American men with elevated cholesterol levels, although evidence of statistical interaction was not significant. In addition, other investigators have suggested that hyperinsulinemia may potentiate the risk of CVD in subgroups who have an adverse risk factor profile characterized by hypertriglyceridemia and abnormally low glucose tolerance\(^{58–60}\) or obesity.\(^{61}\)

Atherogenic and thrombogenic roles for insulin are biologically plausible because insulin may (1) promote smooth muscle cell proliferation in arterial walls,\(^{62–65}\) (2) increase intima-media arterial wall thickness,\(^{51,52}\) (3) increase arterial wall stiffness independent of its effect on wall thickness,\(^{56}\) (4) inhibit fibrinolysis,\(^{52,67}\) or (5) act indirectly through adverse effects on lipids\(^{45,48,68,69}\) and possibly blood pressure.\(^{45,48,68,70}\) It is possible that hyperinsulinemia may have an adverse influence through mechanisms other than atherosclerosis of large vessels. Evidence indicates that hyperinsulinemia may impair fibrinolysis by stimulating plasminogen activator inhibitor–1 synthesis.\(^{71}\) Consistent with this hypothesis, insulin resistance has been associated with low fibrinolytic activity.\(^{67}\) Another potential mechanism includes the association of hyperinsulinemia with cerebral small-vessel disease.\(^{72}\) Such potential influences of elevated insulin levels through nonatherosclerotic mechanisms are consistent with population-based autopsy evidence of associations between diabetes and small-vessel disease in the heart.\(^{73}\)
Hyperinsulinemia and CVD

Potential limitations of this study include its cross-sectional design, possible bias from selective survival, and a limited number of subjects who developed stroke (particularly hemorrhagic stroke) and survived to participate in the current examination. Causal inferences cannot be made from cross-sectional studies, since the temporal sequence between the presumed exposure (hyperinsulinemia) and disease (CVD) has not been elucidated. In addition, if subjects have had CVD for a number of years, it is possible that associations between risk factors and CVD may be altered by treatment of CVD. Use of medication for hypertension and diabetes was taken into account in multivariate logistic models. Exclusion of diabetic subjects may also have been useful in this regard. It is possible that this limitation was diminished in the case of PVD, since subjects identified with an abnormally low ABI could have been asymptomatic. Subjects who had CVD, survived, and participated in the examination may have had a less-severe CVD event than similar subjects who died, and if hyperinsulinemic subjects were also less likely to survive, measures of association would most likely be underestimated. Such a survival bias could account for a lack of association reported among some elderly populations. Thus, in this study of elderly men who may have a relatively advanced stage of atherosclerosis, hyperinsulinemia was significantly associated with CVD outcomes, and these associations may actually be stronger than those observed if a survival bias were present. Strengths of this study include its large sample size, its population-based design, the availability of a comprehensive surveillance system that used standardized criteria for more than three decades, and the ability to investigate the influence of multiple CVD risk factors in associations of hyperinsulinemia with these CVD manifestations.

In this population-based study of elderly Japanese-American men, hyperinsulinemia was associated with several manifestations of CVD. After adjustment for multiple CVD risk factors, hyperinsulinemia remained independently related to thromboembolic and hemorrhagic stroke. When analyses were restricted to nondiabetic subjects, hyperinsulinemia was not in general significantly associated with CVD, although individuals who had a stroke were at least twice as likely to have hyperinsulinemia as those who were stroke-free, even after adjustment for other CVD risk factors. For PVD and stroke, but not CHD, there was some evidence of enhanced risk associated with hyperinsulinemia among elderly men with elevated cholesterol levels relative to those with normal cholesterol levels. Prospective studies are clearly needed to discern whether hyperinsulinemia acts directly or indirectly to increase the risk of CVD. The relatively stronger associations of hyperinsulinemia with thromboembolic and hemorrhagic stroke may also warrant further investigation. Results from this study are in general consistent with an indirect role for insulin in CVD, wherein insulin may adversely affect other CVD risk factors or may serve as a marker for an enhanced atherogenic or thrombogenic state.

Acknowledgment

This study was supported by contract NO1-HC-05102 to the Honolulu Heart Program, Kikumi Medical Center from the National Heart, Lung, and Blood Institute, Bethesda, Md.

References


457


Hyperinsulinemia and Cardiovascular Disease in Elderly Men: The Honolulu Heart Program

Cecil M. Burchfiel, Dan S. Sharp, J. David Curb, Beatriz L. Rodriguez, Robert D. Abbott, Richard Arakaki and Katsuhiko Yano

doi: 10.1161/01.ATV.18.3.450

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1998 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/18/3/450

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/