Hyperinsulinemia and the Risk of Cardiovascular Death and Acute Coronary and Cerebrovascular Events in Men

The Kuopio Ischaemic Heart Disease Risk Factor Study

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Background: The role of hyperinsulinemia as a cardiovascular risk factor is controversial. We studied whether hyperinsulinemia is independently associated with increased cardiovascular morbidity and mortality.

Methods: Fasting serum insulin level and other cardiovascular risk factors were determined in 1521 men in eastern Finland aged 42 to 60 years with neither cardiovascular disease nor diabetes at baseline. Forty-five cardiovascular deaths, 110 acute coronary events, 48 strokes, and 163 any cardiovascular events occurred during an average follow-up of 9.5 years. A total of 163 cardiovascular events (45 cardiovascular deaths, 110 acute coronary events, and 48 strokes) occurred during an average follow-up of 9.5 years.

Results: In Cox regression analysis adjusting for age and examination years, fasting serum insulin level as a continuous variable was directly associated with the risk of cardiovascular death ($P = .006$), acute coronary events ($P = .04$), and stroke ($P = .02$). Men with insulin levels of 52 to 66 pmol/L, 67 to 89 pmol/L, and 90 pmol/L or more (3 highest quartiles) had 1.4-fold (95% confidence interval, 0.5-3.7), 1.4-fold (95% confidence interval, 0.5-3.7), and 2.5-fold (95% confidence interval, 1.0-5.9; $P = .05$) cardiovascular mortality, respectively, compared with men with insulin levels of less than 52 pmol/L (lowest quartile) ($P = .04$ for linear trend). Adjustment for serum lipid levels, blood pressure, and obesity reduced the excess cardiovascular mortality in the highest insulin quartile by 7%, 33%, and 67%, respectively. There were no statistically significant differences in the incidence of acute coronary events and stroke between the insulin quartiles.

Conclusions: Hyperinsulinemia had a modest association with increased cardiovascular mortality in middle-aged men. This relationship was largely explained by obesity, hypertension, and dyslipidemia. Hyperinsulinemia had even weaker associations with the risk of acute coronary event and stroke.

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SUBJECTS AND METHODS

SUBJECTS

The Kuopio Ischaemic Heart Disease Risk Factor Study is a prospective, population-based study designed to investigate risk factors for CVD, carotid atherosclerosis, and other outcomes in middle-aged men in eastern Finland, an area with a high occurrence of CVD. The study was approved by the Research Ethics Committee of the University of Kuopio. All study subjects gave their written informed consent. The study population was a random sample of men, who lived in the town of Kuopio or neighboring rural communities, stratified and balanced for age, who were 42, 48, 54, or 60 years old at baseline examination. The baseline examinations were conducted between March 20, 1984, and December 7, 1989. Of 3235 eligible men, 2682 (82.9%) participated. Men who had prevalent CVD (1015 subjects), cancer (46 subjects), or diabetes (131 subjects) at baseline were excluded from the present analyses. However, men with hypertension were not excluded. Diabetes was defined as either fasting blood glucose level of 6.7 mmol/L (121 mg/dL) or more, or a clinical diagnosis of diabetes with dietary, oral, or insulin treatment. Complete data on fasting serum insulin were available for all 1521 remaining men.

Data on the following factors were missing for some men: serum HDL cholesterol level, 8 men; serum triglyceride level, 17 men; serum apolipoprotein B level, 28 men; plasma fibrinogen level, 90 men; systolic blood pressure, 10 men; diastolic blood pressure, 11 men; body mass index (BMI), 6 men; waist circumference, 275 men; alcohol consumption, 3 men; maximal oxygen uptake ($V_\text{O2}\text{max}$), 152 men; and the intensity of conditioning physical activity, 108 men. If a value was missing, the mean value for all men was used as a substitute.

LABORATORY METHODS

The subjects gave blood specimens between 8 and 10 AM on Tuesday, Wednesday, or Thursday. They were instructed to fast and to abstain from smoking for 12 hours and to abstain from drinking alcohol for 3 days. After the subjects had rested in the supine position for 30 minutes, blood was drawn with vacuum tubes (Terumo Venoject; Terumo, Tokyo, Japan). No tourniquet was used.

Serum insulin level was determined with a radioimmunoassay kit (Novo Biolabs; Novo Nordisk, Bagsvaerd, Denmark). The serum samples were stored frozen at −80°C for 0.2-2.5 years. The between-batch coefficient of variation was 8.9% at 65 pmol/L and 17.9% at 222 pmol/L ($n = 10$). The assay has cross-reactivity with proinsulin, and the values thus reflect immunoreactive insulin. Blood glucose was measured by a glucose dehydrogenase method (Merck, Darmstadt, Germany) after precipitation of proteins by trichloroacetic acid. High-density lipoprotein was separated from fresh serum samples by ultracentrifugation and precipitation. The cholesterol contents of lipoprotein fractions and serum triglycerides were measured enzymatically (Boehringer Mannheim, Mannheim, Germany) on the day after the ultracentrifugal spin. Serum apolipoprotein B level was determined by an immunoturbidimetric method (KONE, Espoo, Finland). Plasma fibrinogen level was determined on the basis of clotting of diluted plasma with excess thrombin (Cologulometer KC4; Heinrich Amelung, Lemgo, Germany). Blood leukocytes were assessed by a cell counter (Coulter Counter Electronics, Luton, England).

OTHER ASSESSMENTS

Assessment of medical history and medications, family history of diseases, smoking, alcohol consumption, physical activity, and $V_\text{O2}\text{max}$ has been described previously. Resting blood pressure was measured between 8 and 10 AM by 2 trained nurses, once during 1984 to 1985 and another time during 1986 to 1989, with a random-zero mercury sphygmomanometer (Hawksley, Lancing, England). The measurement protocol included, after supine rest of 5 minutes, 3 measurements in supine, 1 in standing, and 2 in sitting position with 5-minute intervals. The mean of all 6 measurements was used as systolic and diastolic blood pressure. Body mass index was computed as the ratio of weight (in kilograms) to the square of height (in meters). Waist circumference was calculated as an average of 6 measurements taken after inspiration and 1 taken after expiration at the midpoint between the bottom of the rib cage and the top of the iliac crest.

The purpose of this study was to investigate whether hyperinsulinemia is independently associated with the risk of CVD death, acute coronary events, stroke, and any CVD event, and to what extent the CVD risk-increasing effect of hyperinsulinemia is mediated through other risk factors in a prospective population-based sample of middle-aged men from eastern Finland.

BASELINE CHARACTERISTICS

The baseline fasting serum insulin concentration (mean ± SD) was 77 ± 42 pmol/L and ranged from 7 to 487 pmol/L. The baseline characteristics of the study

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ASCERTAINMENT OF FOLLOW-UP EVENTS

CVD Deaths

Deaths were ascertained by computer linkage to the national death registry using the Finnish social security number. There were no losses to follow-up. All deaths that occurred from study entry (from March 20, 1984, to December 7, 1989) to December 31, 1996, were included. Deaths coded with the International Classification of Diseases, Ninth Revision, codes 390 through 459 were considered CVD deaths. Death codes as CHD (410-414) or stroke (430-436) were all validated according to the international criteria adopted by the World Health Organization MONICA (MONItoring of Trends and Determinants of Cardiovascular Disease) Project. The average follow-up time to death or the end of follow-up was 9.6 years (range, 0.8-12.8 years). In the present sample, there were 45 CVD deaths, 29 of which resulted from CHD, 9 from stroke, and 7 from other causes.

Coronary Events

The province of Kuopio participated in the multinational MONICA project in which detailed diagnostic information of all heart attacks between 1982 and 1992 was collected prospectively. The diagnostic classification was made by the FINMONICA coronary registry group. Data on fatal and nonfatal acute coronary events from January 1, 1993, to December 31, 1996, were obtained by computer linkage to the national computerized hospital discharge registry. Diagnostic information was collected from hospitals and classified by one internist (T.A.L.) using identical diagnostic criteria. The average follow-up time to the first coronary event was 9.3 years (range, 0.1-12.8 years). If a subject had multiple nonfatal events during the follow-up, the first event was considered the end point. Of the 110 coronary events, 57 consisted of a definite acute myocardial infarction, 36 were a possible acute myocardial infarction, and 17 were episodes of typical acute chest pain (angina pectoris) of more than 20 minutes indicating CHD.

Strokes

Data on fatal and nonfatal strokes from 1984 through 1992 were collected by the FINMONICA Stroke Registry, and those from 1993 through 1996 were obtained by computer linkage to the national computerized hospital discharge registry. Diagnostic information was collected from hospitals, and all events were classified by one neurologist (J.S.) using identical diagnostic criteria. The average follow-up time to the first stroke was 9.4 years (range, 0.3-12.8 years). There were 48 strokes during the follow-up, of which 35 were ischemic; 10, hemorrhagic; and 3, undefined strokes.

Any CVD Events

For any CVD event, either a CVD death, acute coronary event, or stroke was considered. If a subject had multiple CVD events, only the first event was taken into account as an end point.

STATISTICAL METHODS

The associations of insulin with other variables were analyzed with covariance analysis. The relationships of insulin with the risk of CVD events were analyzed with Cox proportional hazards models. Insulin was entered into the Cox models as 3 dummy variables for the upper 3 quartiles of the sample, the lowest quartile serving as the reference group. Risk factor–adjusted relative risks were estimated as the antilogarithms of coefficients from multivariate models. Their confidence intervals were estimated on the basis of the assumption of asymptotic normality of the estimates. All tests of significance were 2-sided.

A variable was entered as a confounder into the Cox models if it was statistically significantly (P<.05) associated with any of the outcomes after adjustment for age and examination years. Hypothesized mediators were entered with the confounders into the Cox models as 4 sets: (1) serum HDL cholesterol and triglyceride levels, (2) systolic and diastolic blood pressure, (3) BMI and waist circumference, and (4) all mediators. Although diabetic men were excluded, we evaluated whether adjustment for blood glucose level affects the association between insulin and the outcomes. Because this adjustment had materially no effect on the relationship, glucose level was not entered into the Cox models.

population in the insulin quartiles are shown in Table 1. Fasting serum insulin level was associated directly with serum triglyceride and apolipoprotein B levels, blood leukocyte count, plasma fibrinogen level, systolic and diastolic blood pressure, BMI, and waist circumference and inversely with serum HDL cholesterol level and the mean intensity of conditioning physical activity.

RISK FACTORS FOR CVD EVENTS

The risk factors for CVD events in the study cohort after adjustment for age and examination years are shown in Table 2. Cigarette smoking, alcohol consumption, fasting serum insulin level, blood leukocyte count, serum triglyceride level, plasma fibrinogen level, systolic and diastolic blood pressure, BMI, and waist circumference were associated directly with the risk of CVD death. Cigarette smoking, blood leukocyte count, fasting serum insulin level, serum apolipoprotein B level, plasma fibrinogen level, serum triglyceride level, systolic and diastolic blood pressure, BMI, and waist circumference were related directly and serum HDL cholesterol level and \( V_{O2max} \) inversely to the risk of acute coronary events. Cigarette smoking, fasting serum insulin level, and systolic blood pressure were associated directly with the risk of stroke. Smoking, alcohol consumption, fasting serum insulin level, serum apolipoprotein B level, blood leukocyte count, plasma fibrinogen level, systolic and diastolic blood pressure, BMI, and waist circumference were related directly and \( V_{O2max} \) inversely to the risk of any CVD event.
HYPERINSULINEMIA AND THE RISK OF CVD DEATH

Fasting serum insulin level as a continuous variable had a statistically significant direct association with the risk of CVD death after adjustment for age, examination years, and other confounders (cigarette smoking, blood leukocyte count, serum apolipoprotein B level, plasma fibrinogen level, VO\(_2\)max, and alcohol consumption) (Table 3). The association was largely explained by obesity, whereas dyslipidemia and hypertension had a weaker effect on the relationship (Table 3). The relative risks of CVD death in the insulin quartiles after adjustment for age, examination years, and other confounders and the putative effect of mediators (serum HDL cholesterol and triglyceride levels, systolic and diastolic blood pressure, BMI, and waist circumference) are shown in Table 4. The numbers of the men who died of CVD in the quartiles of insulin were 7 (15.6% of CVD deaths), 10 (22.2%), 10 (22.2%), and 18 (40.0%), respectively. Men with insulin levels of 90 pmol/L or more (highest quartile) had 2.5-fold (95% confidence interval [CI], 1.0-5.9) CVD mortality compared with men with insulin levels less than 52 pmol/L (lowest quartile) after adjustment for the confounders. The excess risk of CVD death (relative risk minus one) in the highest insulin quartile was reduced by 7% adjusting also for serum HDL cholesterol and triglyceride levels, by 33% adjusting also for systolic and diastolic blood pressure, and by 67% adjusting also for BMI and waist circumference. All of these metabolic risk fac-
tors jointly explained 73% of the excess risk associated with high fasting serum insulin level.

**HYPERINSULINEMIA AND THE CORONARY RISK**

Fasting serum insulin level as a continuous variable was also associated with the risk of an acute coronary event after adjustment for the confounders (Table 3). The number of men who had an acute coronary event in the insulin quartiles was 23 (20.9% of the events), 21 (19.1%), 34 (30.9%), and 32 (29.1%), respectively. After adjustment for the confounders, the relative risks of an acute coronary event in the 3 highest insulin quartiles were 0.9 (95% CI, 0.5-1.6), 1.4 (95% CI, 0.8-2.4), and 1.2 (95% CI, 0.7-2.1) ($P = .28$ for linear trend), respectively, compared with the men in the lowest quartile.

**HYPERINSULINEMIA AND THE RISK OF STROKE**

Fasting serum insulin level as a continuous variable also had a statistically significant direct association with the risk of a fatal or nonfatal, either ischemic or hemorrhagic stroke after adjustment for the confounders (Table 3). The relationship was partly explained by obesity and hypertension (Table 3). The number of men who had a stroke in the insulin quartiles was 9 (18.8% of the strokes), 14 (29.2%), 8 (16.7%), and 17 (35.4%), respectively. The relative risks of stroke in the 3 highest insulin quartiles were 1.6 (95% CI, 0.7-3.7), 0.9 (95% CI, 0.4-2.5), and 2.0 (95% CI, 0.9-4.4) ($P = .26$ for linear trend), respectively, compared with the men in the lowest quartile, adjusting for the confounders.

**HYPERINSULINEMIA AND THE RISK OF ANY CVD EVENT**

Fasting serum insulin level as a continuous variable had a statistically significant direct association with the risk of any first CVD event after adjustment for the confounders, and further adjustment for obesity had the strongest effect on the relationship (Table 3). The number of men who had any CVD event in the insulin quartiles was 33 (20.2% of the events), 38 (23.3%), 41 

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**Table 3. Associations of Fasting Serum Insulin (as a Continuous Variable) With the Risk of Cardiovascular Death, Acute Coronary Events, and Stroke**

<table>
<thead>
<tr>
<th>Factors Adjusted for</th>
<th>Cardiovascular Death (45 Deaths)</th>
<th>Acute Coronary Event (110 Events)</th>
<th>Stroke (48 Strokes)</th>
<th>Any Cardiovascular Event† (163 Events)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR (95% CI) P</td>
<td>RR (95% CI) P</td>
<td>RR (95% CI) P</td>
<td>RR (95% CI) P</td>
</tr>
<tr>
<td>Age and examination years</td>
<td>1.006 (1.002-1.011) .006</td>
<td>1.004 (1.000-1.007) .04</td>
<td>1.006 (1.001-1.011) .02</td>
<td>1.004 (1.001-1.007) .003</td>
</tr>
<tr>
<td>Also other confounders‡</td>
<td>1.006 (1.002-1.011) .008</td>
<td>1.004 (1.000-1.007) .045</td>
<td>1.006 (1.001-1.011) .02</td>
<td>1.004 (1.001-1.007) .005</td>
</tr>
<tr>
<td>Confounders and serum HDL cholesterol and triglycerides</td>
<td>1.006 (1.001-1.011) .03</td>
<td>1.003 (0.999-1.007) .13</td>
<td>1.006 (1.001-1.012) .02</td>
<td>1.004 (1.001-1.007) .02</td>
</tr>
<tr>
<td>Confounders and systolic and diastolic blood pressure</td>
<td>1.006 (1.001-1.010) .03</td>
<td>1.003 (0.999-1.007) .14</td>
<td>1.005 (1.000-1.010) .06</td>
<td>1.003 (1.000-1.006) .04</td>
</tr>
<tr>
<td>Confounders and BMI and waist circumference</td>
<td>1.002 (0.995-1.009) .57</td>
<td>1.002 (0.997-1.006) .53</td>
<td>1.005 (0.999-1.012) .11</td>
<td>1.003 (0.999-1.007) .16</td>
</tr>
<tr>
<td>Confounders and all hypothetical mediators</td>
<td>1.002 (0.995-1.009) .59</td>
<td>1.001 (0.996-1.006) .62</td>
<td>1.006 (0.999-1.012) .09</td>
<td>1.003 (0.999-1.007) .15</td>
</tr>
</tbody>
</table>

*RR indicates relative risk; CI, confidence interval; HDL, high-density lipoprotein; and BMI, body mass index.
†Any first cardiovascular event (cardiovascular death, acute coronary event, or stroke).
‡Confounders: age, examination years, smoking, blood leukocyte count, serum apolipoprotein B level, plasma fibrinogen level, maximal oxygen uptake, and alcohol consumption.

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**Table 4. Relative Risk (RR) of Cardiovascular Death in the Quartiles of Fasting Serum Insulin**

<table>
<thead>
<tr>
<th>Quartile of Fasting Serum Insulin</th>
<th>&lt;52 pmol/L (Reference), RR</th>
<th>52-66 pmol/L</th>
<th>67-89 pmol/L</th>
<th>≥90 pmol/L</th>
<th>P for Linear Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factors Adjusted for</td>
<td>RR (95% CI) P</td>
<td>RR (95% CI) P</td>
<td>RR (95% CI) P</td>
<td>RR (95% CI) P</td>
<td></td>
</tr>
<tr>
<td>Age and examination years</td>
<td>1.0</td>
<td>1.4 (0.5-3.7) .50</td>
<td>1.4 (0.5-3.7) .52</td>
<td>2.5 (1.0-5.9) .045</td>
<td>.04</td>
</tr>
<tr>
<td>Also other confounders†</td>
<td>1.0</td>
<td>1.7 (0.6-4.5) .31</td>
<td>1.5 (0.6-4.1) .41</td>
<td>2.5 (1.0-6.2) .05</td>
<td>.06</td>
</tr>
<tr>
<td>Confounders and serum HDL cholesterol and triglycerides</td>
<td>1.0</td>
<td>1.7 (0.6-4.5) .31</td>
<td>1.5 (0.6-4.2) .41</td>
<td>2.4 (0.9-6.3) .08</td>
<td>.09</td>
</tr>
<tr>
<td>Confounders and systolic and diastolic blood pressure</td>
<td>1.0</td>
<td>1.5 (0.6-4.1) .40</td>
<td>1.3 (0.5-3.5) .63</td>
<td>2.0 (0.8-5.1) .14</td>
<td>.18</td>
</tr>
<tr>
<td>Confounders and BMI and waist circumference</td>
<td>1.0</td>
<td>1.5 (0.6-4.1) .41</td>
<td>1.1 (0.4-3.1) .80</td>
<td>1.5 (0.6-4.2) .40</td>
<td>.52</td>
</tr>
<tr>
<td>Confounders and all hypothetical mediators</td>
<td>1.0</td>
<td>1.5 (0.5-4.0) .45</td>
<td>1.1 (0.4-3.0) .89</td>
<td>1.4 (0.5-4.0) .53</td>
<td>.66</td>
</tr>
</tbody>
</table>

*CI indicates confidence interval; HDL, high-density lipoprotein; and BMI, body mass index.
†Confounders: age, examination years, smoking, blood leukocyte count, serum apolipoprotein B level, plasma fibrinogen level, maximal oxygen uptake, and alcohol consumption.
In this prospective study in a population-based sample of middle-aged men who had no CVD, cancer, or diabates at baseline, hyperinsulinemia had a modest association with increased risk of CVD death, controlling for the confounders. Men in the highest quartile of fasting serum insulin level had 2.5-fold CVD mortality compared with men in the lowest quartile. The relationship between hyperinsulinemia and CVD mortality was largely mediated through obesity, hypertension, and dyslipidemia. This study also provides some evidence for the association of hyperinsulinemia with increased risk of acute coronary events and stroke, but only when insulin level was used as a continuous variable. Furthermore, the relationship with coronary risk was almost entirely, and the association with stroke risk partly, explained by these metabolic disorders.

Epidemiological evidence for the hypothesis that hyperinsulinemia increases the risk of CVD is inconclusive.\(^2,22,25\) Initially, 3 prospective population-based studies, the Helsinki Policemen Study,\(^1\) the Paris Prospective Study,\(^4\) and the Busselton study,\(^3\) showed that high fasting or postload serum insulin level was associated with an increased risk of CHD and CVD. In their recent report of the 22-year follow-up results of the Helsinki Policemen Study, the investigators concluded that "hyperinsulinemia predicted CHD risk in Helsinki policemen over the 22-year follow-up, and to a large extent independently of other CHD risk factors, but its predictive value diminished with lengthening follow-up time."\(^9\) Further evidence for the role of hyperinsulinemia as a CVD risk factor is based on 2 recent studies. There was a non-linear association between nonfasting serum insulin level and a fatal or nonfatal myocardial infarction in the British Regional Heart Study.\(^10\) Hyperinsulinemia was an independent predictor of CHD in nondiabetic men in the Quebec Cardiovascular Study.\(^9\) However, most prospective studies in the 1990s have not found an independent association between hyperinsulinemia and the risk of CVD.\(^11-21\)

Little is known about the relationship between hyperinsulinemia and the risk of stroke. There is some cross-sectional evidence that hyperinsulinemia is associated with increased prevalence of atherothrombotic or hemorrhagic stroke.\(^43,44\) In the 22-year follow-up of the Helsinki Policemen Study, hyperinsulinemia was associated with the risk of stroke, but not independently of other risk factors, and the relationship was largely explained by obesity.\(^25\) In another study, hyperinsulinemia did not predict stroke in nondiabetic elderly subjects without a previous stroke.\(^24\) In our study, there was a weak association between hyperinsulinemia as a continuous variable and the risk of stroke. This association appeared to be partly mediated through obesity and hypertension. However, we did not observe a significant difference or linear trend between the quartiles of fasting serum insulin level with respect to stroke risk.

It has been discussed whether the relationship between hyperinsulinemia and CVD is population specific or whether hyperinsulinemia is a risk factor only in selected population groups. For example, no association has been observed between hyperinsulinemia and the risk of CVD in the elderly.\(^13,14,17,20\) Furthermore, the few prospective studies in which data from both sexes have been analyzed separately have not shown a relationship in women\(^5,14;\) however, a recent study showed a positive association between fasting insulin level and CHD in nondiabetic women, but not in men.\(^21\) Our study comprised a representative sample of middle-aged men who had no CVD, cancer, or diabetes at baseline. It is possible that hyperinsulinemia is a risk factor for CVD death mainly in middle-aged individuals, and elderly people may represent a cohort of survivors, in whom high insulin levels are not hazardous. Indeed, extended follow-up time diminished the predictive value of hyperinsulinemia in the Helsinki Policemen Study,\(^6\) the Paris Prospective Study,\(^7\) and the Busselton study.\(^8\) Furthermore, in the populations with a very high frequency of hyperinsulinemia, such as Pima Indians and Pacific Islanders, there has been not high but relatively low CVD and CHD morbidity and mortality,\(^45\) and serum insulin levels did not correlate with electrocardiographic abnormalities suggesting CHD.\(^46\) In a prospective study among Mauritians, who have among the highest CHD mortality and prevalence of diabetes in the world at the present, hyperinsulinemia did not predict CVD mortality or the incidence of CHD.\(^18\) Also, a recent meta-analysis drew attention to the role of ethnic background as a modifier of the relationship between hyperinsulinemia and CVD, which appears to be generally stronger in white than in non-white populations.\(^22\)

Cross-sectional and prospective studies have demonstrated an association between hyperinsulinemia and a number of cardiovascular risk factors. Hyperinsulinemia has been associated with hypertriglyceridemia and low HDL cholesterol levels in both cross-sectional\(^47\) and prospective population-based studies.\(^26-28\) Hyperinsulinemia\(^26,28,48\) and insulin resistance\(^49\) have also been linked to hypertension. Initially included in this cluster of cardiovascular risk factors, referred to as the insulin resistance syndrome or the metabolic syndrome, were resistance to insulin-stimulated glucose uptake, hyperinsulinemia, hypertriglyceridemia, low HDL cholesterol level, and hypertension.\(^23\) Also, central obesity, increased levels of plasminogen activator inhibitor 1, hyperuricemia, microalbuminuria, and other metabolic disturbances have been suggested as components of the syndrome.\(^50\) In our cohort, hyperinsulinemia was associated with hypertriglyceridemia, decreased serum HDL cholesterol level, hypertension, high BMI and waist circumference, and increased plasma fibrinogen level. This provides further evidence in favor of the insulin resistance syndrome.

The time order of the associations of insulin resistance or hyperinsulinemia with other metabolic disor-
ders is important when we try to establish whether hyperinsulinemia is independently associated with an increased risk of CVD or whether its risk-increasing effect is mediated through other factors. Prospective population-based studies have indicated that hyperinsulinemia predicts dyslipidemia.\textsuperscript{20-28} The role of hyperinsulinemia in the etiology of hypertension is less clear, but at least in some populations, including the present study cohort, hyperinsulinemia seems to precede hypertension.\textsuperscript{26,28} Hyperinsulinemia has consistently been associated with obesity in cross-sectional studies, but on the basis of prospective studies, the time order of the relationship is unclear and may be population specific.\textsuperscript{29,30} The factors that have most frequently been suggested to mediate the relationship between hyperinsulinemia and the risk of CVD are hypertriglyceridemia,\textsuperscript{16} high BMI,\textsuperscript{16} upper-body fat distribution,\textsuperscript{31} and hypertension.\textsuperscript{51} In our study, obesity was the strongest and hypertension the second strongest mediator of the excess CVD risk associated with hyperinsulinemia, while dyslipidemia had a modest effect on this association. As it appears likely that obesity precedes hyperinsulinemia, hyperinsulinemia might be a mediating etiologic phenomenon in the causal chain through which obesity increases the risk of CVD. Thus, a statistical inclusion of indexes of obesity in multivariate analyses may be considered an inappropriate overadjustment in the study of the association between hyperinsulinemia and CVD risk. This is the case also for other factors that have physiological links with hyperinsulinemia, such as hypertriglyceridemia, low HDL cholesterol level, and hypertension. Therefore, it is difficult to interpret findings of multivariate analyses that include all of these variables. Although epidemiological studies are essential in determining the existence of an independent relationship between an exposure and an outcome, they cannot adequately describe the pathophysiology of the insulin resistance syndrome or prove causality between hyperinsulinemia and the risk of CVD.

Several mechanisms have been proposed for how insulin could directly alter the structure and function of the arterial wall and accelerate atherogenesis.\textsuperscript{52} Insulin can increase the formation and decrease the regression of lipid lesions and stimulate lipid and connective tissue synthesis in the arterial wall. Insulin can also induce the proliferation and migration of arterial smooth muscle cells and increase sterol synthesis and low-density lipoprotein receptor activity in arterial smooth muscle cells and monocyte macrophages. Indeed, hyperinsulinemia or insulin resistance has been associated with carotid atherosclerosis in some studies. In our study cohort, men with asymptomatic atherosclerosis, determined ultrasonographically in the carotid or femoral arteries, were more insulin resistant than those without atherosclerosis.\textsuperscript{53} Insulin resistance had the strongest association with carotid intima-media thickness in nondiabetic subjects with essential hypertension.\textsuperscript{54} Furthermore, insulin resistance has been related to increased carotid intima-media thickness in men with high and low CVD risk.\textsuperscript{55} In middle-aged men and women in the Atherosclerosis Risk in Communities study, fasting serum insulin level was directly associated with carotid intima-media thickness\textsuperscript{56} and arterial wall stiffness, even after adjustment for obesity, dyslipidemia, and hypertension.\textsuperscript{57}

The strength of this longitudinal study clearly is that we could evaluate the relationship of hyperinsulinemia with all major CVD events in the same cohort, which has not been the case in most previous studies. Also, the study population is from an area with one of the highest CHD and stroke risks in the world. Moreover, we were able to evaluate the impact of other risk factors thoroughly. One weakness of this study is that only middle-aged men, not women or the elderly, were included, which was also the case in most other studies. Also, there were limited numbers of CVD deaths and strokes, although the follow-up time was relatively long. Therefore, caution is needed in the interpretation and generalization of the results of our study.

The nonspecificity of the insulin assay is a limitation, as it inevitably is in studies with long follow-up times, because of lack of specific insulin assay methods at the time of the baseline examinations. In most prospective studies in which hyperinsulinemia has not remained an independent predictor of CVD, a nonspecific insulin assay has been used. Interestingly, recent studies with a specific insulin assay\textsuperscript{9,10} have been able to detect an association. However, serum insulin levels in these two studies were determined only after several years from baseline examinations. Furthermore, in one of these,\textsuperscript{10} the serum samples were obtained in the nonfasting state. Not only insulin but also proinsulin have been associated with CVD risk factors,\textsuperscript{58} which suggests that both of them could be important in atherogenesis. However, studies in patients with premature CHD as defined by coronary angiography or thallium stress test have indicated that insulin and proinsulin are not independent risk markers for CHD but primarily depend on obesity.\textsuperscript{59} In patients with type 2 diabetes, the level of circulating proinsulin is known to be disproportionately elevated compared with that of insulin.\textsuperscript{60,61} The problem of specificity of insulin assay methods is unlikely to be serious in normal subjects, among whom proinsulinlike molecules may account for only 10% of the immunologocal insulinlike molecules in plasma. In our nondiabetic study population, fasting serum insulin concentrations were determined by a polyclonal radioimmunoassay method. Insulin measured by this method had a correlation of 0.84 with insulin measured by a highly specific, 2-site monoclonal immunoradiometric assay in fasting patients with type 2 diabetes.\textsuperscript{62}

This prospective population-based study in healthy middle-aged men suggests that hyperinsulinemia has a modest association with increased cardiovascular mortality, and that the CVD risk–increasing effect is largely mediated through obesity, hypertension, and dyslipidemia. Hyperinsulinemia appears to have even weaker associations with the risk of acute coronary and cerebrovascular events. Thus, fasting insulin determination cannot be recommended for routine clinical care to estimate the risk of CHD or stroke. Future research will identify possible interactions between insulin and other CVD risk factors.
REFERENCES


