Hyperinsulinemia and the Risk of Stroke in Healthy Middle-Aged Men

The 22-Year Follow-Up Results of the Helsinki Policemen Study

Marja Pyörälä, MD; Heikki Miettinen, MD; Markku Laakso, MD; Kalevi Pyörälä, MD

Background and Purpose—Several studies have shown that hyperinsulinemia is associated with the risk of coronary heart disease, but information on the association of hyperinsulinemia with the risk of stroke is limited. We investigated the association of hyperinsulinemia with the risk of stroke during a 22-year follow-up of the Helsinki Policemen Study population.

Methods—The study was based on a cohort of 970 men aged 34 to 64 years who were free of cerebrovascular disease, other cardiovascular disease, or diabetes. Risk factor measurements at baseline examination included an oral glucose tolerance test with blood glucose and plasma insulin measurements at 0, 1, and 2 hours. Area under the insulin response curve during oral glucose tolerance test was used as a composite variable reflecting plasma insulin levels.

Results—During the 22-year follow-up, 70 men had a fatal or nonfatal stroke. Hyperinsulinemia (highest area under the insulin response curve quintile compared with the combined 4 lower quintiles) was associated with the risk of stroke (age-adjusted hazard ratio, 2.12; 95% CI, 1.28 to 3.49), but not independently of other risk factors (multiple-adjusted hazard ratio, 1.54; 95% CI, 0.90 to 2.62), which was mainly due to the impact of obesity, particularly upper body obesity, with subscapular skinfold thickness used as an index. Of other risk factors, upper body obesity, blood pressure, and smoking were independent predictors of the risk of stroke.

Conclusions—Hyperinsulinemia was associated with the risk of stroke in Helsinki policemen during the 22-year follow-up, but not independently of other risk factors, particularly upper body obesity. (Stroke. 1998;29:1860-1866.)

Key Words: epidemiology ■ insulin ■ risk factors ■ stroke onset

The association of insulin with atherosclerosis has been a subject of research for more than 3 decades.1 The main focus of this research has been the association of insulin with coronary heart disease (CHD). Several prospective epidemiological studies have shown that hyperinsulinemia predicts the risk of CHD,2,3 but there is still controversy regarding the importance of insulin as a risk factor.4 Hyperinsulinemia and the underlying insulin resistance are physiologically linked with other cardiovascular risk factors, such as obesity, impaired glucose tolerance, dyslipidemia, and elevated blood pressure.5 Therefore, the interpretation of the results of multivariate analyses of data from prospective epidemiological studies is complex with regard to the role of insulin as an independent risk factor.

Only 2 prospective epidemiological studies have thus far examined the association between plasma insulin and the risk of cerebrovascular disease. The Kuopio study on elderly men and women showed a positive association between fasting insulin and the risk of stroke during a 3.5-year follow-up.6 In a 15-year follow-up of Japanese-American men from the Honolulu Heart Program, a U-shaped association was observed between fasting insulin and the risk of stroke.7 Recent cross-sectional studies have shown that hyperinsulinemia or insulin resistance is associated with ultrasonographically assessed atherosclerosis in carotid arteries.8–11

The Helsinki Policemen Study was one of the first prospective studies demonstrating the association between hyperinsulinemia and CHD.12,13 The follow-up of the Helsinki Policemen Study has now been extended to 22 years, and we have demonstrated that the association between hyperinsulinemia and the risk of CHD, independent of other cardiovascular risk factors, persisted over this long follow-up period, although it became weaker with lengthening follow-up time.14 The aim of the present study was to examine the association between hyperinsulinemia and the risk of stroke in the Helsinki Policemen Study population during the 22-year follow-up.

Subjects and Methods

Study Population

This study is based on a cohort of 970 men aged 34 to 64 years (median, 48 years) who were free of cerebrovascular disease, other cardiovascular disease, and diabetes when they participated in the second examination of the Helsinki Policemen Study in 1971–1972. The initial examination of the Helsinki Policemen Study was performed in 1966–1967 and comprised a total of 1326 men aged

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The blood glucose response curve (AUC glucose) was calculated from pedaled at a workload of 150 W for 4 minutes.

Saltin and Grimby into 4 classes: 1, inactive; 2, slightly active; 3, combined) versus current smokers. Leisure time physical activity was graded with the use of a questionnaire modified from that described by Rose cardiovascular questionnaire on the basis of the heart rate (milliliters per minute per kilogram of body weight) was used as an objective estimate of physical fitness. It was determined with the use of the nomogram of Åstrand and Ryhming on the basis of the heart rate achieved in a bicycle ergometer exercise test in which the subject pedaled at a workload of 150 W for 4 minutes.

The OGTT and collection of blood samples for other biochemical laboratory examinations were performed between 8 and 10 AM after a minimum of a 12-hour fast. The glucose dose used in the OGTT was 75 or 90 g according to body surface area (847 men received 75 g and 123 men received 90 g of glucose). Venous blood samples for blood glucose and plasma insulin were taken before the glucose load and 1 and 2 hours after it. Blood glucose was determined by o-toluidine method and plasma insulin by the “coated charcoal” radioimmunological assay described by Herbert et al. Area under the blood glucose response curve (AUC glucose) was calculated from fasting, 1-hour, and 2-hour blood glucose concentrations with the trapezoidal rule. Similarly, area under the plasma insulin response curve (AUC insulin) was calculated from fasting, 1-hour, and 2-hour insulin concentrations. Plasma total cholesterol was determined by the method of Abell et al and plasma total triglycerides by the method of Björkström.

History of hospital-verified stroke was based on checking the hospital records of those men who either at the 1966–1967 or 1971–1972 examination a history of hospitalization due to symptoms suggestive of stroke. The diagnosis of stroke was ascertained following the World Health Organization criteria, which define stroke as a neurological deficit observed by a physician and persisting for >24 hours, without other diseases explaining the symptoms.

Definite or possible CHD was diagnosed if the subject had the following at either the 1966–1967 or 1971–1972 examination: (1) a history of hospital-verified myocardial infarction (hospital records of those men with a suggestive history were checked); or (2) major QQS waves in the resting ECG (Minnesota code 1.1 to 1.2); or (3) angina pectoris or chest pain attack by the Rose cardiovascular questionnaire.

Clinically significant heart disease other than CHD was diagnosed on the basis of medical history, clinical examination, radiological examination of the chest, and resting ECG. The diagnosis was confirmed by a cardiologist.

Diabetes was considered to be present if the study subject had (1) previously diagnosed diabetes or (2) fasting blood glucose ≥6.7 mmol/L or 2-hour blood glucose in the OGTT ≥10.0 mmol/L at either the 1966–1967 or 1971–1972 examination.

The study program included a questionnaire concerning previously diagnosed diseases, drug therapy, smoking habits, and physical activity; Rose cardiovascular questionnaire; measurement of height, weight, and other anthropometric measurements, including triceps and subcapsular skinfold thicknesses; clinical examination, including measurement of blood pressure; resting and exercise ECG; assessment of physical fitness by a bicycle ergometer exercise test; radiological examination of the chest; and laboratory examinations, including determination of plasma total cholesterol and triglycerides, as well as an oral glucose tolerance test (OGTT) with plasma insulin determinations.

Clinical examination was performed by the same physician throughout the 1971–1972 examination. Body mass index (BMI), weight (kilograms)/height (meters) squared, was used as an index of the degree of overall obesity, and subcapsular skinfold thickness was used as an index of upper body obesity. Seated blood pressure on the right arm was measured twice (interval of 5 minutes) with a mercury sphygmomanometer; the average of 2 measurements was used in data analyses.

Hypertension was considered to be present when systolic blood pressure was ≥160 mm Hg and/or diastolic blood pressure ≥95 mm Hg or if the subject was using antihypertensive drugs. Resting ECGs were interpreted according to the Minnesota Code. A dichotomous classification of smoking history was used in the data analyses: current nonsmokers (those who never smoked and ex-smokers combined) versus current smokers.

A minimum of a 12-hour fast. The glucose dose used in the OGTT ≥10.0 mmol/L at either the 1966–1967 or 1971–1972 examination. The follow-up lasted until January 1, 1994, from the date of the 1971–1972 examination for each study subject. The median follow-up time for those surviving over the whole follow-up period was 22.3 years (range, 21.9 to 22.9 years). Information on the vital status of all men and copies of death certificates of all deceased men were obtained from the Statistical Office of Finland. In the final classification of the causes of death, in addition to the review of death certificates, hospital records and autopsy reports were also used, if available. Autopsy had been made in 142 of 276 cases of death (51.4%). Underlying cause of death was coded by one of the authors (M.P.) using the International Classification of Diseases, Ninth Revision (ICD-9). Subarachnoid hemorrhage was not included as an end point, and therefore death from stroke included ICD-9 codes 431 to 434.

Hospitalizations for acute cerebrovascular events with ICD codes 431 to 434 as discharge diagnoses (ICD-8 until 1986; ICD-9 since 1987) were identified from the National Hospital Discharge Register over the period from January 1, 1971, until January 1, 1994. The patient records on these hospitalizations were reviewed by one of the authors (M.P.). The diagnosis of a nonfatal stroke was ascertained, as at baseline, according to the World Health Organization criteria for stroke; a neurological deficit observed by a physician and persisting for >24 hours, without other diseases explaining the symptoms. Thromboembolic or hemorrhagic subarachnoid hemorrhage were included in the diagnosis of stroke. Strokes occurring within 28 days after a hospital-verified acute myocardial infarction were interpreted as secondary complications of myocardial infarction and excluded. Because in Finland almost all stroke patients are treated in hospitals, we were able to have a rather complete ascertainment of strokes occurring in our study population, including nonfatal strokes in those men who later died from stroke or other cause.

The Finnish Social Insurance Institution maintains a central register of diabetic subjects receiving reimbursement of hypoglycemic drugs. We obtained from this register the dates of the beginning of such reimbursement for men belonging to the study cohort.

Statistical Methods

Data analyses were performed with SPSS 6.1.3 and SAS 6.10 software. Because of the skewed distribution of blood glucose and plasma insulin variables, as well as triglycerides, these variables were log-transformed for statistical analyses. Age-adjusted Pearson partial correlation coefficients were calculated to examine the associations between plasma insulin variables with other continuous variables. The Student’s 2-tailed t test for independent samples, ANCOVA, or Mantel-Haenszel test was used in comparisons between groups, as appropriate. Age-adjusted incidence and significance of their trends were calculated by general
TABLE 1. Baseline Characteristics of Men Without or With Stroke During 22-Year Follow-Up

<table>
<thead>
<tr>
<th></th>
<th>Without Stroke (n=900)</th>
<th>With Stroke (n=70)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>46.9±7.5</td>
<td>52.8±6.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height, cm</td>
<td>179±5</td>
<td>178±6</td>
<td>0.557</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>83.8±10.6</td>
<td>87.8±12.2</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.1±2.9</td>
<td>27.6±3.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triceps skinfold, mm</td>
<td>10±4</td>
<td>11±4</td>
<td>0.029</td>
</tr>
<tr>
<td>Subscapular skinfold, mm</td>
<td>18±7</td>
<td>21±7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>136±18</td>
<td>145±21</td>
<td>0.011</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>85±11</td>
<td>91±11</td>
<td>0.005</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>23.2 (209)</td>
<td>38.6 (27)</td>
<td>0.137</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>6.26±1.16</td>
<td>6.32±0.91</td>
<td>0.952</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.73±1.01</td>
<td>1.92±1.00</td>
<td>0.066</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>4.9±0.5</td>
<td>4.9±0.4</td>
<td>0.972</td>
</tr>
<tr>
<td>1-hour glucose, mmol/L</td>
<td>6.5±1.9</td>
<td>6.9±2.1</td>
<td>0.455</td>
</tr>
<tr>
<td>2-hour glucose, mmol/L</td>
<td>4.4±1.2</td>
<td>4.7±1.3</td>
<td>0.169</td>
</tr>
<tr>
<td>AUCinsulin, mmol/L - h</td>
<td>11.1±2.4</td>
<td>11.7±2.6</td>
<td>0.351</td>
</tr>
<tr>
<td>Fasting insulin, pmol/L</td>
<td>44±28</td>
<td>54±28</td>
<td>0.016</td>
</tr>
<tr>
<td>1-hour insulin, pmol/L</td>
<td>368±256</td>
<td>435±301</td>
<td>0.106</td>
</tr>
<tr>
<td>2-hour insulin, pmol/L</td>
<td>155±151</td>
<td>222±235</td>
<td>0.005</td>
</tr>
<tr>
<td>AUCinsulin, pmol/L - h</td>
<td>467±312</td>
<td>573±407</td>
<td>0.035</td>
</tr>
<tr>
<td>Current smokers, %</td>
<td>44.7 (402)</td>
<td>50.0 (35)</td>
<td>0.342</td>
</tr>
<tr>
<td>Physically active (leisure time), %</td>
<td>34.6 (311)</td>
<td>28.6 (20)</td>
<td>0.281</td>
</tr>
<tr>
<td>Maximal O₂ uptake, mL/min/kg body wt</td>
<td>35.5±8.4</td>
<td>33.1±6.8</td>
<td>0.711</td>
</tr>
</tbody>
</table>

Values are mean±SD or as percentages, with number of subjects in parentheses.

\* t test for age; for other variables, ANCOVA or Mantel-Haenszel test, with adjustment for age.

linear modeling of the SAS system. Kaplan-Meier survival curves for remaining free of stroke were calculated to describe the occurrence of such events by quintiles of insulin variables over the 22-year follow-up period, and differences between and over quintiles were tested by log-rank test. The Cox proportional hazards model was used to estimate the predictive value of AUCinsulin with regard to the risk of stroke, with adjustment for age and other risk factors. Three subjects became censored from the Cox models because of an early noncerebrovascular death. There was no indication of nonproportional hazards during the 22-year follow-up period. Statistical significance is expressed either as P-values for 2-tailed tests or by giving 95% CI for the estimates.

Results

During the 22-year follow-up, a total of 276 men died (36.3%). One hundred thirty (47.1%) of these deaths were caused by cardiovascular disease and 38 (3.4%) by stroke. The number of nonfatal strokes as the first stroke event during 5-, 10-, 15-, and 22-year follow-up periods was 7, 21, 33, and 70, respectively. Of these strokes, 55 (78.6%) were classified as thromboembolic, 7 (10.0%) as hemorrhagic, and 8 (11.4%) remained nonclassifiable. Table 1 shows the baseline characteristics of men without and with stroke (fatal or nonfatal) during the 22-year follow-up. Men with stroke were older than men without stroke, and they were heavier and had higher BMI and thicker triceps and subscapular skinfolds than men without stroke. Both systolic and diastolic blood pressures were higher in men with stroke than in men without stroke. Cholesterol and triglyceride concentrations did not differ significantly between men with and without stroke, and the same applied to glucose concentrations during OGTT. Fasting and 2-hour insulin and AUCinsulin were higher in men with stroke than in those without stroke. The prevalence of current smoking and the proportion of men who were physically active during leisure time, as well as estimated maximal O₂ uptake, did not differ significantly between men with and without stroke.

In the whole study cohort, BMI and triceps and subscapular skinfolds were positively correlated with all insulin variables; age-adjusted Pearson correlation coefficients for BMI ranged from 0.35 to 0.43 (P<0.001), for triceps skinfold from 0.20 to 0.24 (P<0.001), and for subscapular skinfold from 0.35 to 0.40 (P<0.001), respectively. The positive correlation between systolic and diastolic blood pressure and insulin variables was weaker but significant (for systolic blood pressure, 0.12 to 0.17 [P<0.001], and for diastolic blood pressure, 0.15 to 0.19 [P=0.049]).
Triglycerides were also positively and significantly correlated with insulin variables (0.18 to 0.24; \( P < 0.001 \)), but cholesterol was positively and significantly correlated only with 1-hour insulin (0.10; \( P < 0.01 \)) and AUC\(_{\text{insulin}}\) (0.08; \( P < 0.05 \)). All glucose variables correlated positively and significantly with corresponding insulin variables (fasting, 0.23; 1-hour, 0.47; 2-hour, 0.67; and AUC, 0.49; \( P < 0.001 \) for all correlations). Maximal O\(_2\) uptake showed a significant inverse correlation with insulin variables (from 0.29 to 0.33; \( P < 0.001 \)).

Age- and BMI-adjusted 2-hour insulin levels were slightly lower in smokers than in nonsmokers (geometric means: 100 versus 118 pmol/L; \( P < 0.002 \)), but other insulin variables did not differ between smokers and nonsmokers. Physically inactive men had significantly higher plasma insulin levels than physically active men (age- and BMI-adjusted geometric means: fasting, 38 versus 32 pmol/L; 1-hour, 330 versus 261 pmol/L; 2-hour, 121 versus 91 pmol/L; AUC\(_{\text{insulin}}\), 427 versus 337 pmol/L · h; \( P < 0.001 \) for all comparisons).

Figure 1 shows the age-adjusted incidence of stroke (fatal or nonfatal) by quintiles of fasting, 1-hour, and 2-hour insulin and AUC\(_{\text{insulin}}\) during the 22-year follow-up. The incidence of stroke tended to increase with increasing levels of all plasma insulin variables, but the trend over the quintiles reached statistical significance only for fasting insulin.

Kaplan-Meier survival curves for remaining free of stroke during the 22-year follow-up by quintiles of fasting, 1-hour, and 2-hour insulin and AUC\(_{\text{insulin}}\) are shown in Figure 2. For all the insulin variables, the proportion of men without stroke was lowest in the highest quintile; comparison of this proportion in the highest quintile with that in the lowest quintile was statistically significant for fasting insulin but did not quite reach statistical significance for 1-hour insulin, 2-hour insulin, and AUC\(_{\text{insulin}}\). Overall trend over the quintiles was statistically significant only for fasting insulin.

Since the association between insulin and the risk of stroke appeared to be rather similar for all insulin variables, in further analyses we used AUC\(_{\text{insulin}}\) as a composite variable reflecting insulin levels. To assess the predictive value of hyperinsulinemia with regard to the risk of stroke during different follow-up periods, hyperinsulinemia was defined by the cutoff point for the highest AUC\(_{\text{insulin}}\) quintile (669 pmol/L · h). Hazard ratios and their 95% CIs for the highest AUC quintile compared with the 4 lower quintiles were calculated with the Cox proportional hazards model (Table 2). In the age-adjusted model, the hazard ratio for hyperinsulinemia with regard to the risk of all strokes (fatal or nonfatal) was not markedly altered with lengthening follow-up time, but it became statistically significant only during the 22-year follow-up. For fatal stroke, the age-adjusted model gave even higher hazard ratios that were significant for the 10-year and 22-year follow-up periods. The age-adjusted hazard ratios for nonfatal stroke were lower than those for fatal stroke, and only the hazard ratio for the 22-year follow-up was statistically significant.

Multivariate Cox models including AUC\(_{\text{insulin}}\) quintile 5 versus quintiles 1 to 4, age, BMI, subscapular skinfold (as an index of upper body obesity), AUC\(_{\text{glucose}}\), cholesterol, triglycerides, systolic blood pressure, smoking, degree of physical activity, and maximal O\(_2\) uptake showed that age, subscapular skinfold, systolic blood pressure, and smoking were statistically significant independent predictors of the risk of all strokes during the 22-year follow-up. BMI was a statistically significant independent predictor only if subscapular skinfold was omitted from the model. If diastolic blood pressure was entered into the model instead of systolic blood pressure, it was also a statistically significant predictor with a predictive power similar to that of systolic blood pressure. Age, subscapular skinfold, systolic blood pressure, and smoking were chosen as variables included in multiple-adjusted Cox models examining the impact of other risk factors on the predictive value of hyperinsulinemia with regard to different manifestations of stroke (Table 2). With this adjustment all the statistically significant age-adjusted hazard ratios for hyper-
Hyperinsulinemia and the Risk of Stroke

To examine the individual impact of other risk factors on the age-adjusted 22-year hazard ratio for hyperinsulinemia with regard to the risk of all strokes, BMI, subscapular skinfold, systolic blood pressure, and smoking were entered separately into the Cox model, in addition to \( \text{AUC}_{\text{insulin}} \) (quintile 5 versus quintiles 1 to 4) and age. Adjustment for BMI or subscapular skinfold had the greatest effect, reducing the age-adjusted hazard ratio for hyperinsulinemia to nonsignificant 1.47 (95% CI, 0.84 to 2.58) and 1.53 (95% CI, 0.90 to 2.61), respectively. Adjustment for systolic blood pressure reduced the hazard ratio only slightly, to 1.97 (95% CI, 1.19 to 3.25), and adjustment for smoking had no effect, resulting in a hazard ratio of 2.26 (95% CI, 1.37 to 3.74). Because glucose levels are strongly correlated with insulin levels, we also analyzed the impact of \( \text{AUC}_{\text{glucose}} \) in a similar way, but it had virtually no effect on the hazard ratio for hyperinsulinemia, reducing it only to 2.05 (95% CI, 1.18 to 3.55). Similar analyses with regard to fatal or nonfatal stroke gave comparable results (data not shown).

We also calculated age-adjusted hazard ratios and their 95% CIs for different clinical subcategories of stroke. When insulinemia were markedly reduced and became nonsignificant.

To examine the individual impact of other risk factors on the age-adjusted 22-year hazard ratio for hyperinsulinemia with regard to the risk of all strokes, BMI, subscapular skinfold, systolic blood pressure, and smoking were entered separately into the Cox model, in addition to \( \text{AUC}_{\text{insulin}} \) (quintile 5 versus quintiles 1 to 4) and age. Adjustment for BMI or subscapular skinfold had the greatest effect, reducing the age-adjusted hazard ratio for hyperinsulinemia to nonsignificant 1.47 (95% CI, 0.84 to 2.58) and 1.53 (95% CI, 0.90 to 2.61), respectively. Adjustment for systolic blood pressure reduced the hazard ratio only slightly, to 1.97 (95% CI, 1.19 to 3.25), and adjustment for smoking had no effect, resulting in a hazard ratio of 2.26 (95% CI, 1.37 to 3.74). Because glucose levels are strongly correlated with insulin levels, we also analyzed the impact of \( \text{AUC}_{\text{glucose}} \) in a similar way, but it had virtually no effect on the hazard ratio for hyperinsulinemia, reducing it only to 2.05 (95% CI, 1.18 to 3.55). Similar analyses with regard to fatal or nonfatal stroke gave comparable results (data not shown).

We also calculated age-adjusted hazard ratios and their 95% CIs for different clinical subcategories of stroke.

Thromboembolic and nonclassifiable strokes were considered as 1 group (63 events), the age-adjusted hazard ratio for the 22-year follow-up was 2.15 (1.28 to 3.64). Considering thromboembolic strokes (55 events) and hemorrhagic strokes separately (7 events) gave age-adjusted hazard ratios of 1.60 (0.89 to 2.90) and 1.70 (0.33 to 8.76), respectively.

Because some other studies have measured only fasting insulin, we also analyzed our data by defining hyperinsulinemia by the cutoff point for the highest fasting insulin quintile (66 pmol/L). The age-adjusted hazard ratio for fasting hyperinsulinemia with regard to the 22-year risk of all strokes (fatal or nonfatal) was 1.85 (95% CI, 1.13 to 3.03), and the multiple-adjusted hazard ratio was 1.21 (95% CI, 0.70 to 2.07).

Table 3 shows the results of Cox model analysis of the predictors of stroke (fatal or nonfatal) during the 22-year follow-up with \( \text{AUC}_{\text{insulin}} \) as a continuous variable. Other continuous variables included in the model were subscapular skinfold and systolic blood pressure. Hazard ratios were calculated for 1-SD differences in these continuous variables to allow a comparison of their predictive power. Smoking was entered as a dichotomous variable. With adjustment for age alone (model 1), \( \text{AUC}_{\text{insulin}} \) was also as a continuous variable significantly associated with the risk of stroke. However, with adjustment for other risk factors (model 2), \( \text{AUC}_{\text{insulin}} \) was no more a statistically significant independent predictor of the risk of stroke, whereas subscapular skinfold, systolic blood pressure, and smoking were strong independent predictors. When BMI was entered as the only obesity index into the multivariate model, a hazard ratio of 1.46 (95% CI, 1.13 to 1.88) was obtained for it. When subscapular skinfold and BMI were simultaneously entered into the model, the hazard ratio for subscapular skinfold was 1.47 (95% CI, 1.11 to 1.96), but the hazard ratio for BMI became reduced to nonsignificant 1.16 (95% CI, 0.85 to 1.58). Corresponding analyses with regard to fatal and nonfatal strokes gave largely similar results (data not shown).

Altogether 63 men developed drug-treated diabetes during the follow-up. This occurred more frequently in the top quintile of \( \text{AUC}_{\text{insulin}} \) than in the lower \( \text{AUC}_{\text{insulin}} \) quintiles.

### Table 2. Hazard Ratios and 95% CIs for Hyperinsulinemia (AUC insulin Quintile 5 vs Quintiles 1–4) with Regard to Risk of All Strokes (Fatal or Nonfatal), Fatal Strokes, and Nonfatal Strokes During Different Follow-Up Periods

<table>
<thead>
<tr>
<th>Follow-Up Time</th>
<th>5 Years</th>
<th>10 Years</th>
<th>15 Years</th>
<th>22 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>All strokes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>2.68 (0.60–11.98)</td>
<td>1.96 (0.79–4.86)</td>
<td>2.05 (0.99–4.22)</td>
<td>2.12 (1.28–3.49)</td>
</tr>
<tr>
<td>Multiple-adjusted†</td>
<td>1.80 (0.36–9.07)</td>
<td>1.85 (0.70–4.89)</td>
<td>1.66 (0.76–3.59)</td>
<td>1.54 (0.90–2.62)</td>
</tr>
<tr>
<td>Fatal stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>6.12 (1.02–36.80)</td>
<td>3.27 (0.88–12.18)</td>
<td>3.01 (1.40–6.50)</td>
<td></td>
</tr>
<tr>
<td>Multiple-adjusted†</td>
<td>5.17 (0.73–36.36)</td>
<td>2.39 (0.56–10.12)</td>
<td>1.94 (0.85–4.44)</td>
<td></td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>1.82 (0.33–9.98)</td>
<td>1.52 (0.54–4.27)</td>
<td>1.80 (0.78–4.15)</td>
<td>1.93 (1.05–3.56)</td>
</tr>
<tr>
<td>Multiple-adjusted†</td>
<td>1.56 (0.25–9.58)</td>
<td>1.43 (0.47–4.32)</td>
<td>1.48 (0.61–3.59)</td>
<td>1.48 (0.77–2.84)</td>
</tr>
</tbody>
</table>

* Number of events in quintile 5/total number of events.
† Adjusted for age, subscapular skinfold, systolic blood pressure, and smoking (yes/no).

### Table 3. Hazard Ratios and 95% CIs for AUC insulin and Other Risk Factors as Continuous Variables* With Regard to Risk of All Strokes (Fatal or Nonfatal), Fatal Strokes, and Nonfatal Strokes During 22-Year Follow-Up

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio, (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1 (adjustment for age)</td>
<td></td>
</tr>
<tr>
<td>AUC insulin</td>
<td>1.31 (1.02–1.67)</td>
</tr>
<tr>
<td>Model 2 (adjustment for age and other risk factors)</td>
<td></td>
</tr>
<tr>
<td>AUC insulin</td>
<td>1.07 (0.81–1.41)</td>
</tr>
<tr>
<td>Subscapular skinfold</td>
<td>1.59 (1.26–2.00)</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>1.36 (1.18–3.06)</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.88 (1.16–3.04)</td>
</tr>
</tbody>
</table>

* Hazard ratios calculated for 1-SD differences in continuous variables: AUC insulin (0.26 logarithm), subscapular skinfold (7 mm), and systolic blood pressure (18 mm Hg). Smoking was entered as a dichotomous variable.
(12.8% versus 4.9%; P=0.001). There was also a trend, although statistically nonsignificant, to a more frequent development of diabetes among those men who had a stroke during the follow-up than among those men who did not have a stroke (11.4% versus 6.1%; P=0.116). This trend was observed in the highest AUC_{insulin} quintile (21.7% versus 11.6%; P=0.102) but not in the combined lower AUC_{insulin} quintiles (6.4% versus 4.8%; P=0.787). We also performed age- and multiple-adjusted Cox model analyses, similar to those shown in Table 2, in which those 63 men who developed drug-treated diabetes during the follow-up were excluded. The age-adjusted and multiple-adjusted hazard ratios and their 95% CIs for hyperinsulinemia with regard to the risk of all strokes obtained from these analyses were 1.92 (1.11 to 3.32) and 1.44 (0.80 to 2.57), respectively.

Discussion

Our study, based on the 22-year follow-up of the Helsinki Policemen Study population, demonstrated a positive association between plasma insulin levels during oral glucose tolerance test, expressed as the area under the insulin response curve (AUC_{insulin}), and the risk of stroke. This association could be demonstrated for all strokes (fatal or nonfatal) but also separately for fatal and nonfatal strokes. In multivariate analyses, however, the positive association between insulin levels and the risk of stroke was not independent of other cardiovascular risk factors. This was mainly due to the impact of obesity, particularly upper body obesity, with subscapular skinfold thickness as its index.

In our study, obesity, blood pressure, and smoking were independent predictors of the risk of stroke. Of the 2 indexes of obesity, BMI and subscapular skinfold thickness, either one was a statistically significant predictor of stroke risk when entered alone into the multivariate model, but subscapular skinfold thickness remained an independent predictor even when BMI was included in the same multivariate model. The role of elevated blood pressure and smoking as predictors of the risk of stroke has been well established in many prospective studies.27–30 In the Framingham Study male population, abdominal obesity, assessed by the ratio of waist to hip circumference, was associated with the risk of stroke, independently of BMI, but no more after adjustment for other risk factors.35 In the Framingham Study male population, abdominal obesity, assessed by the ratio of waist to height, predicted the risk of stroke independently of BMI and other risk factors.36 Similarly, in the US Health Professionals Follow-up Study population,37 abdominal obesity, assessed by the ratio of waist to hip, but not BMI, was an independent predictor of the risk of stroke. One study from the Honolulu Heart Program38 reported that in Japanese-American men subscapular skinfold thickness was an independent predictor of stroke. In our study population subscapular skinfold thickness, as an index of upper body obesity, proved to be a predictor of the risk of stroke, independently of BMI and other risk factors, suggesting in accordance with the findings of studies mentioned above that, in addition to general adiposity, truncal accumulation of body fat is of importance in relation to the risk of stroke. With regard to the relationship between upper body obesity and insulin resistance, it is of interest that a recent study in which CT was used to measure cross-sectional abdominal subcutaneous and visceral adipose tissue showed that subcutaneous abdominal fat was as strongly associated with insulin resistance as visceral fat.39

Obesity indexes, when entered into the Cox models in addition to age, were the only variables having a substantial effect on the association between hyperinsulinemia and the risk of stroke, reducing it to a nonsignificant level. Weight gain in adult life has been shown to be associated with the development of hyperinsulinemia.40 Our results suggest that obesity, especially upper body obesity, contributes to the association between hyperinsulinemia and the risk of stroke. One possible mechanism leading to an increased risk of atherothrombotic brain infarction could be the association of obesity and hyperinsulinemia with elevated plasminogen activator inhibitor-I levels.41

It has been proposed that the association of hyperinsulinemia with the risk of cardiovascular disease could be due to common causal factors for type 2 (non–insulin-dependent) diabetes and cardiovascular disease.42 Insulin resistance and hyperinsulinemia with the associated cluster of risk factors are known to precede the development of type 2 diabetes and thus could form such a link. The information available to us on the development of diabetes in our study population during the follow-up was based on a national registry of reimbursements for hypoglycemic drugs, and thus we did not obtain information on subjects with milder forms of diabetes who did not receive drug treatment. The development of drug-treated diabetes during the follow-up was approximately 2.5 times more frequent in the top AUC_{insulin} quintile than in the lower AUC_{insulin} quintiles. On the other hand, diabetes developed approximately 2 times (although nonsignificantly) more frequently in men who had a stroke during the follow-up than in those men who did not have a stroke, and this excess appeared to be mainly confined to the highest AUC_{insulin} quintile. The relatively small number of new cases of diabetes and stroke occurring during the follow-up limits the power of these analyses, and thus we cannot draw any strong conclusions on the basis of them about hyperinsulinemia as a “common soil” for diabetes and stroke. Hyperinsulinemia was found to be an independent predictor of CHD risk during the 22-year follow-up of the Helsinki Policemen Study population, its predictive power being strongest during the first 10 years of follow-up and then attenuating with lengthening follow-up time.14 As reported in this article, the positive association between hyperinsulinemia and the risk of stroke, however, became nonsignificant when adjusted for other risk factors, and this was mainly due to the confounding effect of obesity. Caution is needed in the interpretation of these seemingly different results concerning the association of hyperinsulinemia with the risk of CHD and with the risk of stroke. Fasting and postglucose plasma insulin levels are known to be markers of insulin resistance, although the correlation between plasma insulin levels and insulin resistance measured by euglycemic
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close physiological links of hyperinsulinemia and the underlying insulin resistance with several other risk factors make the interpretation of multivariate analyses difficult because of problems related to overadjustment. The main limitation of our study is the small number of strokes occurring during the 22-year follow-up of the healthy middle-aged Helsinki policemen population. Another limitation is some uncertainty in the classification of stroke events into clinical subcategories (11.4% of strokes remained non-classifiable). Furthermore, our baseline data collection did not include information on some potentially important confounders (eg, alcohol use). No conclusions can be drawn about the generalizability of our results to other populations, eg, women and other ethnic groups.

In conclusion, hyperinsulinemia was found to be associated with the risk of stroke in Helsinki policemen during the 22-year follow-up, but this association was not independent of other cardiovascular risk factors, particularly upper body obesity.

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References

Hyperinsulinemia and the Risk of Stroke in Healthy Middle-Aged Men: The 22-Year Follow-Up Results of the Helsinki Policemen Study
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