Non-Insulin-Dependent Diabetes and Its Metabolic Control Are Important Predictors of Stroke in Elderly Subjects

Johanna Kuusisto, MD; Leena Mykkänen, MD; Kalevi Pyörälä, MD; Markku Laakso, MD

Background and Purpose Non-insulin-dependent diabetes mellitus (NIDDM) is a major risk factor for stroke in the middle-aged population, but few prospective population-based studies are available in the elderly. Moreover, the importance of metabolic control and the duration of diabetes in diabetic subjects has remained controversial. There are no previous studies on association of insulin with the risk of stroke. The present study examined whether NIDDM, its metabolic control and duration, and insulin level predict stroke.

Methods We measured cardiovascular risk factors including glucose tolerance, plasma insulin, and glycosylated hemoglobin A1c in a Finnish cohort of 1298 subjects aged 65 to 74 years and investigated the impact of these risk factors on the incidence of both fatal and nonfatal stroke during 3.5 years of follow-up.

Results Of 1298 subjects participating in the baseline study, 1069 did not have diabetes and 229 had NIDDM. During the 3.5-year follow-up, 3.4% (n=36) of nondiabetic subjects and 6.1% (n=14) of NIDDM subjects had a nonfatal or fatal stroke. The incidence of stroke was significantly higher in diabetic women compared with nondiabetic women (odds ratio [OR], 2.25; 95% confidence interval [CI], 1.65 to 3.06). In contrast, the risk of stroke was not significantly higher in diabetic men than in nondiabetic men (OR, 1.36; 95% CI, 0.44 to 4.18). In multivariate logistic regression analyses including all study subjects, fasting and 2-hour glucose (P<.01 and P<.05, respectively), glycosylated hemoglobin A1c (P<.01), atrial fibrillation (P<.05), hypertension (P<.05), and previous stroke (P<.01) predicted stroke events. In diabetic subjects, fasting and 2-hour glucose (P<.01 and P<.05, respectively), glycosylated hemoglobin A1c (P<.05), the duration of diabetes (P<.05), and atrial fibrillation (P<.05) were the baseline variables predicting stroke events. Finally, fasting insulin (P<.05), hypertension (P<.05), and previous stroke (P<.01) were associated with stroke incidence in nondiabetic subjects.

Conclusions Our 3.5-year follow-up study provides evidence that NIDDM, its metabolic control, and the duration of diabetes are important predictors of stroke in elderly subjects, particularly in women. Moreover, fasting insulin level appears to be a risk factor for stroke in elderly nondiabetic subjects.


Key Words • cerebrovascular disorders • diabetes • glucose • hemoglobin • insulin

Non-insulin-dependent diabetes (NIDDM) is a major risk factor for atherosclerotic vascular disease, including stroke. In the Framingham Study the risk of nonfatal and fatal stroke was 2.6-fold higher in men with NIDDM and 3.8-fold higher in women with NIDDM than in nondiabetic subjects of the corresponding sex. However, there are few prospective studies on the effect of NIDDM on the risk of stroke in elderly population. Hypertension is as strong a predictor of stroke in nondiabetic subjects as in patients with NIDDM. However, NIDDM may confer excess risk of stroke independently of hypertension. In diabetic subjects, factors relating to hyperglycemia might be important with respect to increased risk for manifestations of atherosclerotic vascular disease including stroke, but previous epidemiological studies have failed to prove association between the metabolic control of diabetes and the risk of stroke. Moreover, there are no prospective population-based studies evaluating metabolic control and duration of diabetes as predictors of stroke in elderly diabetic subjects. Disturbances in glucose metabolism are characterized not only by hyperglycemia but also by hyperinsulinemia, which has been found to be a risk factor for coronary heart disease in some but not all studies. The importance of insulin as a risk factor for stroke has not been evaluated in previous studies.

In this study we measured cardiovascular risk factors including glucose tolerance, plasma insulin, and glycosylated hemoglobin A1c in a Finnish cohort of 1298 subjects aged 65 to 74 years and investigated the impact of these risk factors on the incidence of both fatal and nonfatal stroke during 3.5 years of follow-up.

Subjects and Methods

Research Design and Methods at Baseline Study

Study Population at Baseline

The baseline examination of this study was conducted in Kuopio, eastern Finland, between February 1986 and April 1988. The formation and representativeness of the study population have been described in detail previously. Briefly, 1910 subjects born between 1912 and 1921 were randomly selected from the population register, including all inhabitants of Kuopio. A postal questionnaire containing questions about diagnosis of diabetes, ability to move, and willingness to participate in the study was sent to each subject. Eighty-three subjects from this sample were excluded because they were too ill to participate. Eventually, 1299 of 1827 eligible subjects...
Atrial fibrillation was considered to be present if atrial fibrillation or flutter was found on the standard ECG recording (Minnesota code 8.3).10 Left ventricular hypertrophy (LVH) was evaluated from the standard ECG recording and was considered to be present if the height of the R wave was ≥26 mm in lead V5 or V6; if the height of the R wave was ≥20 mm in any of leads I, II, III or aVF; if the R wave was ≥12 mm in lead aVL (Minnesota code 3.1); if the height of the R wave was ≥15 mm but ≤20 mm in lead I; or if the sum of the height of the R wave in lead V5 or V6 and the S wave in lead V1 was ≥35 mm (Minnesota code 3.3).16

Diagnosis of Previous Stroke

All medical records of subjects who reported that they had been admitted to the hospital because of symptoms suggestive of stroke before the baseline examination were reviewed by one of the authors (L.M.). WHO criteria for definite and possible stroke were used in the ascertainment of the previous stroke, which was defined as a clinical syndrome consisting of neurological deficits persisting more than 24 hours and observed by a neurologist, without other diseases explaining the symptoms.18 Thromboembolic and hemorrhagic strokes, but not subarachnoid hemorrhage, were included in the diagnosis of stroke.

Glucose Tolerance

WHO diagnostic criteria for diabetes mellitus were used in the classification of subjects without previously known diabetes.14 The criteria are as follows: (1) diabetes mellitus: fasting venous plasma glucose ≥7.8 mmol/L or 2-hour venous plasma glucose ≥11.1 mmol/L in a 75-g oral glucose tolerance test; (2) impaired glucose tolerance (IGT): fasting venous plasma glucose <7.8 mmol/L and 2-hour venous plasma glucose 7.8 to 11.0 mmol/L; and (3) normal glucose tolerance (NGT): fasting and 2-hour venous plasma glucose <7.8 mmol/L. Previously known diabetes was considered to be present if the diagnosis of diabetes had been made by a physician.15 NIDDM was defined according to the WHO criteria.18 Insulin-treated diabetic subjects whose C peptide level 6 minutes after intravenous glucagon (1 mg) stimulation was <0.20 nmol/L were regarded as having insulin-dependent diabetes.

Laboratory Methods

Blood samples were taken between 7:30 and 9:30 AM after a 12-hour fast. All subjects, except those receiving insulin, underwent a 75-g oral glucose tolerance test. Venous blood samples for glucose and insulin determinations were taken before and 2 hours after the glucose load. Plasma glucose was determined by the glucose oxidase method (Glucose Auto & Stat HGA-1120 analyzer, Daiichi). Plasma insulin was determined from samples stored at −70°C by a double-antibody solid-phase radioimmunoassay (Phadehus Insulin RIA 100, Pharmacia Diagnostica AB).20 Diabetic patients who were receiving insulin had C peptide levels measured at fasting and 6 minutes after intravenous glucagon administration.21 Plasma C peptide was determined from samples stored at −70°C by a commercial radioimmunoassay (C peptide of insulin kit, Incstar) with a detection limit of 0.07 nmol/L and an intra-assay variation <5%.22 Hba1c was determined by a commercial liquid-chromatographic assay (Fast Protein Liquid Chromatography, Pharmacia).23 Serum high-density lipoprotein (HDL) cholesterol was determined after precipitation of low-density and very-low-density lipoproteins with dextran sulfate and MgCl2.24 Commercial enzymatic methods were used in the determination of cholesterol (Monostet, Boehringer Mannheim)25,26 and triglycerides (Peridocrome, Boehringer Mannheim).26 Commercial control sera were used to standardize the measurements of cholesterol and triglycerides (Seronorm, Seronorm Lipid, Nycomed).

Research Design and Methods at Follow-up Study

Study Population and Follow-up Period

The follow-up study was conducted between March 1990 and June 1991. Of 1298 subjects in the baseline study, 108 died during the follow-up. Of 1190 eligible subjects, 137 were not willing or were too ill to participate. Finally, 1054 subjects participated, giving an overall participation rate of 89%. For each study subject, the follow-up study was conducted during

Diagnosis of Previous Coronary Heart Disease Events

Chest pain symptoms suggestive of coronary heart disease (CHD) were recorded by specially trained nurses with the Rose Cardiovascular Questionnaire.15 Angina pectoris was registered if a subject had typical effort angina regardless of severity. A conventional 12-lead resting electrocardiogram (ECG) was recorded, and all ECGs were classified according to the Minnesota code.16 The coding of ECGs was performed without knowledge of the glucose tolerance status and other characteristics of the study subjects.

All medical records of subjects who reported that they had been admitted to the hospital because of chest pain or symptoms suggestive of myocardial infarction (MI) before the baseline examination were reviewed by one of the authors (L.M.). World Health Organization (WHO) criteria for verified definite and possible MI based on chest pain symptoms, ECG changes, and enzyme determinations were used in the ascertainment of previous MI.17 Previous MI was defined to be present if a subject had had a possible or definite MI according to chest pain symptoms suggestive of myocardial infarction (MI) before the baseline examination or if there was a major Q wave (Minnesota code 1.1 or 1.2) in the ECG at baseline.

Diagnosis of Atrial Fibrillation and Left Ventricular Hypertrophy

Atrial fibrillation was considered to be present if atrial fibrillation or flutter was found on the standard ECG recording (Minnesota code 8.3).10 Left ventricular hypertrophy (LVH) was evaluated from the standard ECG recording and was considered to be present if the height of the R wave was ≥26 mm in lead V5 or V6; if the height of the R wave was ≥20 mm in any of leads I, II, III or aVF; if the R wave was ≥12 mm in lead aVL (Minnesota code 3.1); if the height of the R wave was ≥15 mm but ≤20 mm in lead I; or if the sum of the height of the R wave in lead V5 or V6 and the S wave in lead V1 was ≥35 mm (Minnesota code 3.3).16

Diagnosis of Alcohol Consumption and Smoking

Alcohol consumption was determined according to the subject’s estimate of the average number of glasses of alcohol drinks ingested per week. In statistical analyses, subjects were classified as alcohol users or nonusers. Smoking habits were defined as current smoking.
one half-day visit to the Clinical Research Unit of the University of Kuopio.

The follow-up period was defined as the time period between the baseline and follow-up study for those who participated. The mean follow-up period for the participants was 3.5 years (range, 2.7 to 5.2 years). Subjects were invited to the follow-up visit in the same order as they had participated in the baseline study. For nonparticipants the follow-up period was defined as the time period between baseline study and June 30, 1991 (the day when the last subject participated in the follow-up study), and deaths and cardiovascular events during this period were recorded.

**Diagnosis of New Stroke Events**

Medical records of all nonparticipants and those who died during the follow-up, as well as medical records of those participants who reported hospitalization due to symptoms suggestive of stroke during the follow-up, were reviewed by one of the authors (J.K.). In addition, all death certificates of those who died during the follow-up were reviewed (J.K.). Hospital records and autopsy records were used in the final classification of the causes of death. All deaths were coded according to the ninth revision of the International Classification of Diseases (ICD9).27

WHO criteria for verified and possible stroke were used in the ascertainment of a new stroke; the definition was similar to that for stroke at baseline, ie, a clinical syndrome consisting of a neurological deficit observed by a neurologist and persisting more than 24 hours in the same area as without other diseases explaining the symptoms.18 Death from stroke included ICD9 codes 431 through 434. Thromboembolic and hemorrhagic strokes, but not subarachnoid hemorrhage, were included in the diagnosis of stroke. Computed tomography was performed in most cases but was not required for the diagnosis of stroke. In the following analyses, both nonfatal and fatal strokes are combined because of the limited number of stroke end points. If a subject had more than one stroke during the follow-up, only one stroke was included in each of the statistical analyses.

**Statistical Methods**

Data analyses were conducted with the SPSSX and SPSS/PC+ programs. Data are given as mean±SEM or percentages. Student's two-tailed t test for independent samples or the χ² test was used in the assessment of differences between the two groups when appropriate. Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated according to Mantel and Haenszel. Univariate and multiple logistic regression analyses based on the maximum-likelihood method were used to investigate the association of cardiovascular risk factors with the incidence of stroke. Pearson's correlation coefficient was used to show linear correlations. Because triglyceride concentration was not normally distributed, it was log transformed in all statistical analyses.

**Results**

A total of 1298 subjects participated in the baseline study. Of 470 men included in the baseline study, 396 had NGT (66.4%) or IGT (17.9%), and 74 (15.7%) had NIDDM. Of 828 women participating in the baseline study, 673 had NGT (62.2%) or IGT (19.1%), and 155 (18.7%) had NIDDM. NIDDM was a new diagnosis in 44.5% of male and in 38.1% of female diabetic subjects. The mean±SD duration of NIDDM at baseline was 8.9±5.7 years. Thirty-eight percent of previously diagnosed diabetic patients were treated with diet, 56% with oral hypoglycemic drugs, and 6% with insulin.

Table 1 shows baseline characteristics of the study population by sex and diabetes status (NIDDM versus nondiabetic subjects). In men, the mean age was 69 years in nondiabetic and NIDDM subjects. There were no significant differences in the prevalence rates of hypertension, angina pectoris, atrial fibrillation, left ventricular hypertrophy on ECG, previous stroke or MI, current smoking, systolic or diastolic blood pressure, or total cholesterol between nondiabetic men and men with NIDDM. Men with NIDDM had higher BMI and WHR than did nondiabetic men. HDL cholesterol was lower and triglycerides were higher in men with NIDDM compared with nondiabetic men. HbA₁c and fasting insulin levels were significantly higher in men with NIDDM than in nondiabetic men. Two-hour insulin level was not significantly higher in NIDDM subjects than in nondiabetic subjects.

In women, NIDDM subjects were older than nondiabetic subjects. In addition, the prevalence rates of hypertension, angina pectoris, atrial fibrillation, and LVH were higher in women with NIDDM than in nondiabetic women. The prevalence rates of a previous stroke and MI were similar in both groups. Current smoking and alcohol consumption were less prevalent among women with NIDDM than among nondiabetic women. Women with NIDDM were heavier than nondiabetic women, and their BMI and WHR were higher than those of nondiabetic women. Systolic blood pressure was higher in diabetic women than in nondiabetic women, but diastolic blood pressure was similar in nondiabetic women and in women with NIDDM. Total cholesterol was slightly lower in women with NIDDM compared with nondiabetic women, but the difference was not statistically significant. HDL cholesterol was lower and triglycerides higher in women with NIDDM compared with nondiabetic women. HbA₁c was higher in women with NIDDM than in nondiabetic women, as were fasting and 2-hour insulin levels.

A total of 108 subjects died during the 3.5-year follow-up. Of these deaths, 11 (10.2%) were due to stroke (ICD9 codes 431 through 434; 6 atherothrombotic strokes and 5 intracerebral hemorrhages), and 66 (61.1%) to all cardiovascular causes (ICD9 codes 390 to 459). Forty-one subjects had one or more nonfatal strokes during the follow-up period. When both fatal and nonfatal strokes were counted, a total of 50 subjects had one or more strokes during the follow-up, giving an overall incidence of 3.9% for stroke.

Table 2 shows the incidence of fatal stroke and both fatal or nonfatal stroke by sex and glucose tolerance status. Because of the small number of fatal cases, both fatal and nonfatal strokes are combined in the subsequent analyses. Since the incidence of stroke events was similar in subjects with normal glucose tolerance (3.6%) and subjects with IGT (2.5%), these two glucose tolerance categories were also combined. In men, the overall incidence of stroke in men was 4.3% (nondiabetic men, 4.0%; men with NIDDM, 5.4%), and in women, 3.6% (nondiabetic women, 3.0%; women with NIDDM, 6.5%). In men, the incidence of stroke was not significantly higher in subjects with NIDDM than in nondiabetic subjects (OR and 95% CI for stroke risk in NIDDM subjects compared with nondiabetic men, 1.36 and 0.44 to 4.18, respectively). In contrast, women with NIDDM had a significantly higher incidence of stroke than nondiabetic women (OR, 2.25; CI, 1.65 to 3.06).

The associations of baseline risk factors with the incidence of fatal and nonfatal stroke were assessed by
univariate and multivariate logistic regression analyses. Table 3 shows the results of univariate logistic regression analyses first in all study subjects and then separately in nondiabetic and NIDDM subjects. In the whole study population, previous stroke (P<.001), angina pectoris (P<.05), hypertension (P<.01), atrial fibrillation (P<.001), fasting and 2-hour plasma glucose (P<.001), HbA1c (P<.001), and fasting insulin (P<.05) were associated with the risk of stroke. In nondiabetics, previous stroke (P<.001), hypertension (P<.01), HbA1c (P<.001), and duration of diabetes (P<.05) were associated with stroke incidence. In NIDDM subjects, only fasting and 2-hour glucose (P<.01), HbA1c (P<.05), and duration of diabetes (P<.05) were predictors of stroke.

To investigate which factors were independently associated with the risk of stroke, multiple logistic regression analyses were performed, first in the whole study population and then separately for nondiabetic and NIDDM subjects (Table 4). Independent variables included were those showing a significant association with the incidence of stroke in univariate logistic regression analyses either in nondiabetic or diabetic subjects. In model 1, previous stroke, atrial fibrillation, hypertension, angina pectoris, and HbA1c were selected as independent variables. Previous stroke and hypertension predicted a new stroke in nondiabetics and in the whole study population (for previous stroke, P<.001 and P<.01, respectively; for hypertension, P<.05 for both groups). Atrial fibrillation and HbA1c predicted stroke in NIDDM subjects and in the whole study population (for atrial fibrillation, P<.05 for both groups; for HbA1c, P<.05 and P<.01, respectively). If the duration of diabetes was included in the model instead of HbA1c (data not shown), atrial fibrillation (P<.05) and duration of diabetes (P<.05) were associated with stroke in NIDDM subjects. If both HbA1c and the duration of diabetes were included in the model, neither was associated with stroke.

In multiple logistic regression model 2, HbA1c was replaced by fasting glucose and insulin as independent variables. Again, previous stroke and hypertension predicted stroke in nondiabetic subjects as well as in the whole study population (for previous stroke, P<.01 in both groups; for hypertension, P<.05 in both groups). Atrial fibrillation predicted stroke only in the whole study population (P<.05). Fasting glucose predicted stroke in NIDDM subjects and in the whole study population. If fasting glucose was included in the model instead of insulin, diabetes (P<.05) and duration of diabetes (P<.05) were associated with stroke in NIDDM subjects. If both fasting glucose and HbA1c were included in the model, neither was associated with stroke (data not shown), probably because of the high intercorrelation of these variables (r=.34, P<.001).

In multiple logistic regression model 2, HbA1c was replaced by fasting glucose and insulin as independent variables. Again, previous stroke and hypertension predicted stroke in nondiabetic subjects as well as in the whole study population (for previous stroke, P<.01 in both groups; for hypertension, P<.05 in both groups). Atrial fibrillation predicted stroke only in the whole study population (P<.05). Fasting glucose predicted stroke in NIDDM subjects and in the whole study population. If fasting glucose was included in the model instead of insulin, diabetes (P<.05) and duration of diabetes (P<.05) were associated with stroke in NIDDM subjects. If both fasting glucose and HbA1c were included in the model, neither was associated with stroke (data not shown), probably because of the high intercorrelation of these variables (r=.34, P<.001).

In multiple logistic regression model 2, HbA1c was replaced by fasting glucose and insulin as independent variables. Again, previous stroke and hypertension predicted stroke in nondiabetic subjects as well as in the whole study population (for previous stroke, P<.01 in both groups; for hypertension, P<.05 in both groups). Atrial fibrillation predicted stroke only in the whole study population (P<.05). Fasting glucose predicted stroke in NIDDM subjects and in the whole study population. If fasting glucose was included in the model instead of insulin, diabetes (P<.05) and duration of diabetes (P<.05) were associated with stroke in NIDDM subjects. If both fasting glucose and HbA1c were included in the model, neither was associated with stroke (data not shown), probably because of the high intercorrelation of these variables (r=.34, P<.001).
population (P<.01). Fasting insulin was associated with stroke in nondiabetic subjects (P<.05). When 2-hour glucose was included in model 2 instead of fasting glucose (data not shown), it predicted stroke events in the whole population (P<.05) and in NIDDM subjects (P<.05). With respect to the predictive role of fasting insulin, similar results were obtained when hypertension in model 2 was replaced by systolic or diastolic blood pressure (data not shown).

Because HbA1c was a significant predictor of stroke in NIDDM, we studied correlations of HbA1c with other risk factors in NIDDM subjects. Pearson’s correlation coefficients of HbA1c with fasting and 2-hour plasma glucose were .79 and .78, respectively (P<.001). HbA1c also correlated significantly with the duration of diabetes (r=.34, P<.001) but not with total (r=.07) or HDL cholesterol (r=.10), triglycerides (r=.12), apolipoprotein A1 (r=.01), or apolipoprotein B (r=.10). There were also no significant correlations between HbA1c and WHR (r=.08), BMI (r=.04), or systolic (r=.06) or diastolic blood pressure (r=.08). In contrast, HbA1c correlated negatively with fasting (r=-.19, P<.01) and 2-hour insulin (r=-.36, P<.001) in NIDDM subjects and positively in nondiabetics (r=.08 and r=.10, respectively; P<.01 in both groups). In nondiabetic subjects, fasting insulin did not correlate significantly with systolic (r=.03) or diastolic (r=.01) blood pressure.

Because previous stroke was a significant predictor of a new stroke event during the follow-up, we repeated all univariate and multiple regression analyses shown in Tables 3 and 4 excluding all subjects with previous stroke (n=39, data not shown). In this subpopulation there were 43 strokes during the follow-up. The baseline risk factors associated with stroke in the univariate and multiple logistic regression analyses were similar with the exception of the following: fasting insulin was not related to stroke in nondiabetics in either univariate or multiple regression analyses, and hypertension was not significantly associated with stroke if nondiabetic and NIDDM groups were combined.

Discussion

In this elderly Finnish population, NIDDM increased the risk of stroke during the 3.5-year follow-up, particularly in women. Among NIDDM subjects, the parameters of metabolic control of diabetes at baseline study measured by fasting or 2-hour glucose or by HbA1c level were the most important risk factors for stroke. The duration of NIDDM also affected the risk of stroke, probably through long-lasting hyperglycemia. Finally, hyperinsulinemia predicted stroke in nondiabetic subjects.

In addition to parameters of glucose metabolism, the most powerful risk factors for stroke in the whole study population were hypertension and atrial fibrillation (Table 4). This finding of the present study is in accordance with previous reports.6,7 Other predictors of stroke such as prior MI, LVH, serum lipids, smoking, or WHR, which have been found to be associated with stroke in previous studies, failed to predict stroke in the present study, probably because of the short follow-up period. Furthermore, the ECG is a rather insensitive method to evaluate LVH, which may contribute to the failure of our study to demonstrate an association between LVH and stroke.

Although the majority of NIDDM subjects are elderly,8 there are few prospective population-based studies on the impact of NIDDM on stroke incidence in this age group. In addition, the age range in most previous studies has been wide, including middle-aged subjects, which makes it difficult to draw conclusions on the impact of NIDDM on stroke incidence in the elderly. In this prospective study in a large elderly population with a narrow age range at baseline (from 65 to 74 years), NIDDM was a predictor of stroke (Tables 2 and 4). These findings indicate that NIDDM in old age continues to have a major effect on the risk of cerebrovascular events.

The effect of NIDDM on the risk of stroke was more marked in women than in men (Table 2), which is in accordance with previous studies. The OR for fatal and nonfatal stroke in women with NIDDM compared with nondiabetic women was 2.25, whereas in men the corresponding OR was 1.36. However, the majority of NIDDM subjects (68%) were women, and subsequently stroke cases among NIDDM men were few, giving little power to this subanalysis. On the other hand, diabetes was associated with more adverse effects in cardiovascular risk factors in women than in men (Table 1), which may suggest that NIDDM causes more serious adverse effects in women than in men in this age group. In any case, our study cannot rule out a slight increase in the risk of stroke among men with NIDDM compared with nondiabetic men, since in the Finnish population fewer men than women survive to age 65 years.

Metabolic control of diabetes measured by fasting or 2-hour glucose or HbA1c, which reflects hyperglycemia during the preceding 3 months, was the strongest baseline predictor of stroke in NIDDM subjects, outweighing all classic risk factors for stroke, although most cardiovascular risk factors were more prevalent among
TABLE 3. Association of Baseline Cardiovascular Risk Factors With Incidence of Stroke in All Subjects and Separately in Nondiabetics and Subjects With Non–Insulin-Dependent Diabetes Mellitus (Univariate Logistic Regression Analysis)

<table>
<thead>
<tr>
<th></th>
<th>All (50/1298)$/B/SE</th>
<th>Nondiabetics (36/1069)/B/SE</th>
<th>NIDDM (14/229)/B/SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>-0.57</td>
<td>-0.93</td>
<td>0.31</td>
</tr>
<tr>
<td>Age</td>
<td>1.35</td>
<td>0.94</td>
<td>0.95</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>4.09†</td>
<td>4.67‡</td>
<td>-0.24</td>
</tr>
<tr>
<td>Previous MI</td>
<td>1.78</td>
<td>1.49</td>
<td>0.88</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>2.29*</td>
<td>1.91</td>
<td>0.90</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.70†</td>
<td>2.57*</td>
<td>0.52</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>3.64†</td>
<td>2.78†</td>
<td>1.93</td>
</tr>
<tr>
<td>LVH on ECG</td>
<td>1.37</td>
<td>1.61</td>
<td>-0.16</td>
</tr>
<tr>
<td>Current smoking</td>
<td>1.29</td>
<td>1.36</td>
<td>0.63</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>1.19</td>
<td>0.73</td>
<td>1.62</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.51</td>
<td>-0.22</td>
<td>0.55</td>
</tr>
<tr>
<td>Waist-hip ratio</td>
<td>0.23</td>
<td>0.05</td>
<td>-0.10</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>1.95</td>
<td>1.39</td>
<td>0.99</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>1.48</td>
<td>1.71</td>
<td>-0.04</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>0.29</td>
<td>0.08</td>
<td>0.48</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>-1.30</td>
<td>-0.22</td>
<td>-1.51</td>
</tr>
<tr>
<td>Triglycerides(log)</td>
<td>1.55</td>
<td>0.33</td>
<td>1.20</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>3.68†</td>
<td>-0.19</td>
<td>2.92†</td>
</tr>
<tr>
<td>2-Hour plasma glucose</td>
<td>3.30†</td>
<td>-0.12</td>
<td>2.59†</td>
</tr>
<tr>
<td>Glycosylated hemoglobin A1c</td>
<td>3.32†</td>
<td>0.85</td>
<td>2.32*</td>
</tr>
<tr>
<td>Fasting insulin</td>
<td>2.19*</td>
<td>2.78†</td>
<td>-0.41</td>
</tr>
<tr>
<td>2-Hour insulin</td>
<td>-0.59</td>
<td>-0.07</td>
<td>-1.07</td>
</tr>
<tr>
<td>Duration of diabetes</td>
<td>...</td>
<td>...</td>
<td>2.00*</td>
</tr>
</tbody>
</table>

NIDDM indicates non–insulin-dependent diabetes mellitus; B, regression coefficient; SE, standard error; MI, myocardial infarction; LVH, left ventricular hypertrophy; ECG, electrocardiogram; BP, blood pressure; and HDL, high-density lipoprotein.

*P<.05, †P<.01, ‡P<.001.
§Number of incidence cases divided by number of subjects at risk.

NIDDM subjects than among nondiabetics (Tables 1 and 4). The relation between fasting and 2-hour glucose, HbA1c, and the incidence of stroke remained essentially unchanged even if NIDDM subjects with previous stroke were excluded from statistical analyses. In the present study lipids, lipoproteins, anthropometric measurements, and systolic and diastolic blood pressure did not correlate with HbA1c level. Thus, the degree of long-lasting hyperglycemia apparently is the most important factor affecting the risk of stroke in NIDDM in our study, independent of other cardiovascular risk factors.

The duration of diabetes was also an important risk factor for stroke events in NIDDM subjects (Tables 3 and 4). However, because the duration of diabetes correlated significantly with HbA1c, it probably affects the risk of stroke through long-lasting hyperglycemia. The failure of previous studies to demonstrate the association between stroke risk and the duration of diabetes may be due to a narrow range of the duration of diabetes in these studies. In the present study the diabetic population included a significant number of patients with newly detected NIDDM at baseline, which allows a more reliable evaluation of the importance of the duration of NIDDM with respect to the risk of stroke.

Why does poor metabolic control of NIDDM predict stroke? Hyperglycemia is related to abnormalities in lipoprotein particle composition, which, in turn, are known to be atherogenic.7 Hyperglycemia also accelerates oxidation of lipoproteins and prevents transverse cholesterol transport in the arterial wall.33 Moreover, NIDDM is a procoagulant state, and hyperglycemia may directly relate to thrombosis formation, which is an important factor in the pathogenesis of stroke, as well as in other manifestations of atherosclerosis.34,35 Eventually, long-lasting hyperglycemia is known to cause irreversible glycosylation of proteins in the arterial wall and to occlude the arterial lumen.36,37

Hyperinsulinemia predicted stroke in nondiabetic subjects. In previous studies the risk of CHD has been found to be associated with hyperinsulinemia,10-12 but no study has demonstrated an association between insulin levels and stroke in either nondiabetic or NIDDM subjects. Because stroke is an atherothrom-
bolic disease and hyperinsulinemia and insulin resistance are risk factors for atherosclerosis, there is theoretical support for this association.

We conclude that NIDDM in old age is a risk factor for stroke, particularly in women. In addition, poor metabolic control increases the risk of stroke in elderly diabetic subjects. Finally, in nondiabetic subjects, fasting insulin seems to be a risk factor for stroke. Since NIDDM continues to be a major risk factor for stroke in the elderly and long-term blood glucose level also appears to be a significant factor with respect to stroke risk, it is reasonable to try to normalize the blood glucose level in diabetic patients in this age group. With respect to insulin levels as a predictor of stroke, further studies are warranted to confirm the results of the present study.

Acknowledgments

This study was supported by grants from the Academy of Finland, the Helena Vuorenmies Foundation, the Aarne and Aili Turunen Foundation, the Yrjo Jahnsson Foundation, the Finnish Heart Research Foundation, and the Finnish Society of Cardiology.

References


Non-insulin-dependent diabetes and its metabolic control are important predictors of stroke in elderly subjects.

J Kuusisto, L Mykkänen, K Pyörälä and M Laakso

*Stroke*. 1994;25:1157-1164
doi: 10.1161/01.STR.25.6.1157

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1994 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/25/6/1157