Serum Uric Acid Is a Strong Predictor of Stroke in Patients With Non–Insulin-Dependent Diabetes Mellitus

Seppo Lehto, MD; Leo Niskanen, MD; Tapani Rönnemaa, MD; Markku Laakso, MD

Background and Purpose—Patients with non–insulin–dependent diabetes mellitus (NIDDM) are at increased risk for stroke. Hyperuricemia is a common finding in NIDDM, but its significance as an independent risk factor for cardiovascular disease has remained uncertain. Therefore, we investigated serum urate as a predictor of stroke in NIDDM patients free of clinical nephropathy (ie, with a serum creatinine level of ≤120 μmol/L).

Methods—In this population-based study, cardiovascular risk factors were determined in 1017 patients (551 men and 466 women) with NIDDM, aged 45 to 64 years at baseline. The patients were followed up for 7 years with respect to stroke events.

Results—During the follow-up period, 31 NIDDM patients (12 men [2.2%] and 19 women [4.1%]) died from stroke and 114 NIDDM patients (55 men [10.0%] and 59 women [12.7%]) had a fatal or nonfatal stroke. The incidence of stroke increased significantly by quartiles of serum uric acid levels (P<.001). High uric acid level (above the median value of >295 μmol/L) was significantly associated with the risk of fatal and nonfatal stroke by Cox regression analysis (hazard ratio, 1.93 [1.30 to 2.86]; P=.001). This association remained statistically significant even after adjustment for all cardiovascular risk factors (hazard ratio, 1.91 [1.24 to 2.94]; P=.003).

Conclusions—Our results indicate that hyperuricemia is a strong predictor of stroke events in middle-aged patients with NIDDM independently of other cardiovascular risk factors. (Stroke. 1998;29:635–639.)

Key Words: diabetes mellitus ■ mortality ■ uric acid ■ stroke onset

Several population-based studies1–3 have shown that subjects with NIDDM have a twofold to fourfold greater risk of all manifestations of atherosclerotic vascular disease, including stroke, compared with nondiabetic subjects. The increased risk of stroke is only partly explained by the adverse effects of NIDDM on classic risk factors4,5 or risk factors clustering with hyperinsulinemia (elevated levels of total triglycerides, decreased HDL cholesterol, hypertension, and glucose intolerance).5

Serum uric acid (or more correctly, its monoanion uric acid at physiological pH values) has been thought to be in humans a metabolically inert end product of purine metabolism without physiological significance (except gouty diathesis). However, serum uric acid has been recently associated with insulin resistance.6,7 Furthermore, in nondiabetic subjects an elevated level of uric acid has been shown to be an independent predictor of coronary heart disease and total mortality.8–11 Therefore, we examined serum uric acid as a risk factor for stroke in a prospective population-based study that included a large number of patients with NIDDM.

Subjects and Methods

Research Design and Methods at the Baseline Study

All diabetic patients in Finland who need antidiabetic drug therapy receive it free of charge according to the Sickness Insurance Act. The Social Insurance Institution maintains a central register of diabetic subjects who receive drug reimbursement. Based on this register, we identified all diabetic patients aged 45 to 64 years who were born and living in the Kuopio University Hospital district (East Finland) and in the Turku University Central Hospital district (West Finland). The formation of the final patient population, consisting of 510 diabetic subjects (253 men and 257 women) who participated in this study in East Finland (participation rate, 83%) and 549 diabetic subjects (328 men and 221 women) who participated in the study in West Finland (participation rate, 79%), has been previously described in detail.12 Insulin-dependent diabetes was excluded in all insulin-treated NIDDM patients by C-peptide measurements.13 None of the patients classified as having NIDDM according to the World Health Organization (WHO) criteria14 and included in the final study population had a history of ketoacidosis. Thirty-three patients (23 men and 10 women) with elevated serum creatinine levels of >120 μmol/L and 9 patients (7 men and 2 women) for whom serum uric acid measurement was not available were excluded from statistical analyses. Of the 1017 NIDDM patients, 88 men and 54 women were treated with diet only, 393 men and 345 women with oral hypoglycemic drugs, and 70 men and 67 women with insulin. The proportion of diet-treated patients in our study was 16.5% in East Finland and 11.5% in West Finland. It is unlikely, however, that the underrepresentation of diet-treated diabetic patients in our series could influence our results concerning the main study objective (the evaluation of risk factors for stroke in patients with NIDDM), because the mode of treatment of diabetes appeared to be quite similar in both study areas. The mean±SD age of diabetic men was 57.2±0.2 years and that of diabetic women 59.0±0.2 years.

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Study Program and Methods at Baseline Examination in 1982–1984
The study program was carried out during one outpatient visit at the Clinical Research Unit of the University of Kuopio or the Rehabilitation Research Center of the Social Insurance Institution in Turku. These methods have been previously described in detail.12 The visit included an interview on the history of chest pain symptoms suggestive of coronary heart disease, smoking, alcohol intake, physical activity, and use of drugs. All medical records of those subjects who reported on the interview that they had been admitted to the hospital on the basis of chest pain or symptoms suggestive of stroke were reviewed. Review of the medical records was performed by two of the authors (M.L. in Kuopio and T.R. in Turku) after a careful standardization of the methods between the reviewers. The WHO criteria for verified definite or possible MI, based on chest pain symptoms, electrocardiographic changes, and enzymatic determinations, were used to ascertain the diagnosis of previous MI.15 The WHO criteria for verified definite or possible stroke were used to ascertain the diagnosis of previous stroke, which was defined as a clinical syndrome consisting of neurological symptoms persisting for >24 hours.19 Thromboembolic and hemorrhagic strokes, but not subarachnoid hemorrhage, were included in the diagnosis of stroke.

Blood pressure was measured with the patients in a sitting position after a 5-minute rest with use of a mercury sphygmomanometer and read to the nearest 2 mm Hg. Subjects were classified as having hypertension if they were receiving drug treatment for hypertension or had systolic blood pressure of at least 160 mm Hg or diastolic blood pressure of at least 95 mm Hg. Body mass index was calculated by weight (kilograms) divided by height (meters) squared.

Biochemical Methods
All laboratory specimens were drawn at 8 AM, after a 12-hour fast. All analyses except that for glycated hemoglobin A1 (GHBa1c) were performed in duplicate. Fasting plasma glucose was determined by the glucose oxidase method (Boehringer). GHBa1c was determined by affinity chromatography (Isolab). The plasma C-peptide response to glucagon was assessed according to the method of Faber and Binder.17 Plasma C-peptide was determined by radioimmunooassay (antiserum M 1230, Novo).18 Serum lipids and lipoproteins were determined from fresh serum samples drawn after a 12-hour overnight fast. Serum total cholesterol and triglycerides were assayed by automated enzymatic methods (Boehringer).19 Serum HDL cholesterol was determined enzymatically after precipitation of low-density and very-low-density lipoproteins with dextran sulfate MgCl2.20 Serum uric acid was measured with use of an enzymatic calorimetric method (Amer Division, Miles Laboratories).21 The subjects were classified into two categories, according to the median value of serum uric acid at baseline in the whole study, and in cases of hospitalization for stroke the medical records were checked. Copies of death certificates for the patients who had died were obtained from the files of the Central Statistical Office of Finland. In the final classification of the causes of death, hospital records and autopsy records were used if available. Causes of deaths were coded according to the ninth revision of the International Classification of Diseases, Clinical Modification (ICD-9-CM).22

As in the baseline study, WHO criteria for verified and possible stroke were used in the ascertainment of a new stroke event (ie, a clinical syndrome consisting of a neurological deficit and persisting more than 24 hours [nonfatal stroke]), without other diseases explaining the symptoms.10 Death from stroke included ICD9 codes 431 through 434. Thus, thromboembolic and hemorrhagic strokes but not subarachnoid hemorrhage, were included in the diagnosis of stroke. If a subject had more than one stroke during the follow-up, only the first stroke event was included in statistical analyses.

Statistical Methods
Data analyses were conducted with the SPSSX and SPSS/PC+ programs (SPSS Inc). The results for continuous variables are given as mean±SEM and proportions as percentages. The differences between the groups were assessed by the χ2 test or the Student two-tailed t test for independent samples when appropriate. A univariate and multivariate Cox regression model23 was used to investigate the association of cardiovascular risk factors with the incidence of stroke events.

Approval of Ethics Committee
This study was approved by the Ethics Committees of the Kuopio University Central Hospital and the Turku University Central Hospital. All subjects gave their informed consent for participation in the study.

Results
During the 7-year follow-up (mean follow-up was 7.2 years in men and women), 31 patients (12 men [2.2%] and 19 women [4.1%]) with NIDDM died of stroke. Altogether, 114 patients (55 men [10.0%] and 59 women [12.7%]) had a fatal or nonfatal stroke event.

Table 1 presents clinical characteristics of NIDDM patients by the median value of serum uric acid at baseline in the whole study population by gender. Data from East and West Finland were combined because no significant differences existed between these areas in the levels of cardiovascular risk factors with respect to stroke. Men with high uric acid levels (≥295 μmol/L) were more obese and hypertensive and were more likely to receive treatment with diuretics and have a history of MI. Furthermore, men with high uric acid level had higher levels of serum creatinine and total triglycerides and lower levels of HDL cholesterol, plasma glucose, and GHBa1c than men with low (<295 μmol/L) levels. Women with high uric acid levels were older and more obese, more likely to have a history of MI and hypertension, and more likely to receive treatment with diuretics than those with low levels. Furthermore, women with high uric acid levels had higher serum creatinine and total triglyceride levels as well as lower LDL cholesterol, plasma glucose, and GHBa1c levels than those with low uric acid levels.

At baseline, serum uric acid level was significantly correlated with the components of the insulin resistance syndrome, body mass index (r=0.26, P<.001), total triglycerides (r=0.14, P<.001), and HDL cholesterol (−0.25, P<.001). No signifi-
cant correlation between hyperuricemia and total cholesterol levels was observed.

Fig 1 shows the incidence of stroke events (men and women combined) by quartiles of serum uric acid. Incidence of stroke increased with increased serum uric acid levels ($P<.001$), and the threshold for increased risk was close to the median value (295 μmol/L). The results were essentially similar when the data were analyzed separately for men and women (data not shown).

The role of hyperuricemia ($>295$ versus $\leq 295$ μmol/L) as a risk factor for fatal or nonfatal stroke in NIDDM patients was investigated by Cox regression analysis (Table 2). Hazard ratios were calculated for the whole study population, as the interpretation of the results was essentially similar in men and women (data not shown). Hyperuricemia increased the risk of stroke by approximately twofold. This association remained essentially unchanged, even after adjustment for age, gender, smoking, total cholesterol, hypertension, body mass index, serum total triglycerides, HDL cholesterol, plasma glucose, previous history of stroke, use of diuretics, and known duration of diabetes. Further adjustment for serum creatinine did not affect the interpretation of the findings (note that subjects with serum creatinine $>120$ μmol/L were excluded). The results remained essentially similar when only the incident strokes were included in regression analysis. Moreover, exclusion of patients who used diuretics did not abolish the statistical significance of uric acid as an independent risk factor for stroke.

**Discussion**

Our population-based 7-year follow-up study is the first to demonstrate the independent role of hyperuricemia as a predictor of fatal and nonfatal stroke events in patients with NIDDM. In univariate analysis the risk of stroke was increased twofold among NIDDM patients with high uric acid ($>295$ μmol/L) compared with those with low uric acid. The predictive value of hyperuricemia remained statistically significant even after adjustment for all major cardiovascular risk factors measured in our study.

Previous studies have indicated that hyperuricemia predicts ischemic heart disease in nondiabetic subjects, and one

**TABLE 2.** Adjusted Hazard Ratios and 95% CIs for Hyperuricemia (serum uric acid $>295$ μmol/L) to Increase the Risk of Stroke during 7-year Follow-up in Patients with NIDDM (Cox Regression Model)

<table>
<thead>
<tr>
<th>Adjustment</th>
<th>Hazard ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>1.93</td>
<td>1.30–2.86$^\dagger$</td>
</tr>
<tr>
<td>Age, gender, smoking, cholesterol, hypertension</td>
<td>1.74</td>
<td>1.16–2.61$^\ddagger$</td>
</tr>
<tr>
<td>Age, gender, smoking, cholesterol, hypertension, and other risk factors*</td>
<td>1.91</td>
<td>1.24–2.94$^\ddagger$</td>
</tr>
</tbody>
</table>

*$^\ddagger$Body mass index, total triglycerides, HDL cholesterol, plasma glucose, previous history of stroke, use of diuretics, and duration of diabetes.

$^\dagger P=.008$, $^\ddagger P=.003$, and $^\ddagger P<.001$. 

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**TABLE 1.** Characteristics of the Study Population According to the Median Value of Serum Uric Acid ($\leq 295$ μmol/L=low uric acid, $>295$ μmol/L=high uric acid)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low uric acid (n=257)</th>
<th>High uric acid (n=294)</th>
<th>Low uric acid (n=251)</th>
<th>High uric acid (n=215)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>57.2±0.3</td>
<td>57.3±0.3</td>
<td>58.4±0.3</td>
<td>59.7±0.3$^\ddagger$</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.9±0.3</td>
<td>29.5±0.2$\ddagger$</td>
<td>29.3±0.3</td>
<td>31.7±0.4$^\ddagger$</td>
</tr>
<tr>
<td>Previous stroke, %</td>
<td>5.8</td>
<td>6.8</td>
<td>3.6</td>
<td>7.0</td>
</tr>
<tr>
<td>Previous MI, %</td>
<td>13.6</td>
<td>24.1$^\dagger$</td>
<td>8.4</td>
<td>14.4*</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>41.2</td>
<td>67.3$^\ddagger$</td>
<td>61.4</td>
<td>79.5$^\ddagger$</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>24.9</td>
<td>25.5</td>
<td>8.0</td>
<td>4.7</td>
</tr>
<tr>
<td>Diuretics, %</td>
<td>12.8</td>
<td>32.3$^\ddagger$</td>
<td>26.7</td>
<td>56.3$^\ddagger$</td>
</tr>
<tr>
<td>Serum creatinine, μmol/L</td>
<td>81.2±0.7</td>
<td>86.7±0.8$^\ddagger$</td>
<td>68.6±0.7</td>
<td>76.8±0.9$^\ddagger$</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>6.41±0.08</td>
<td>6.52±0.09</td>
<td>7.09±0.12</td>
<td>7.04±0.12</td>
</tr>
<tr>
<td>Calculated LDL cholesterol, mmol/L</td>
<td>4.35±0.07</td>
<td>4.27±0.07</td>
<td>4.75±0.08</td>
<td>4.46±0.05$^*$</td>
</tr>
<tr>
<td>Total triglycerides, mmol/L</td>
<td>1.95±0.90</td>
<td>2.76±0.14$^\ddagger$</td>
<td>2.45±0.20</td>
<td>3.31±0.25$^\ddagger$</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.25±0.02</td>
<td>1.10±0.02$^\ddagger$</td>
<td>1.32±0.02</td>
<td>1.20±0.03$^\ddagger$</td>
</tr>
<tr>
<td>Plasma glucose, mmol/L</td>
<td>11.6±0.2</td>
<td>10.7±0.2$^\ddagger$</td>
<td>12.9±0.2</td>
<td>11.6±0.3$^\ddagger$</td>
</tr>
<tr>
<td>Glycated hemoglobin A1c, %</td>
<td>10.1±0.1</td>
<td>9.3±0.1$^\ddagger$</td>
<td>10.4±0.1</td>
<td>9.9±0.1$^\ddagger$</td>
</tr>
<tr>
<td>Duration of diabetes, y</td>
<td>8.5±0.3</td>
<td>7.5±0.2$^*\ddagger$</td>
<td>8.1±0.2</td>
<td>7.8±0.3</td>
</tr>
</tbody>
</table>

*Body mass index, total triglycerides, HDL cholesterol, plasma glucose, previous history of stroke, use of diuretics, and duration of diabetes.

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Seven-year incidence (%) of stroke events (fatal or nonfatal stroke) with respect to the quartiles of serum uric acid concentration (expressed as micromoles per liter) (quartile limits: $<243$, 243 to 295, 296 to 357, and $>357$). ***$P<.001$. 

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hyperuricemia has been associated with elevated circulating perinsulinemia and reduced insulin sensitivity, components of the metabolic syndrome. We also observed this association and the presence of multiple risk factors is likely to explain a substantial part of increased risk of stroke. However, even after extensive adjustment for cardiovascular risk factors, serum uric acid remained an independent risk factor for stroke.

Elevated levels of serum uric acid are due to either an increase in uric acid production or a decrease in its excretion. Differences in dietary purine intake are unlikely to explain the association of hyperuricemia with stroke, although this was not directly assessed in our study. However, there are other physiological and pathological factors that influence serum uric acid levels. Ferris and Gorden demonstrated in normal subjects that sympathetic nervous system stimulation induced by norepinephrine or angiotensin II infusion caused a simultaneous increase in serum uric acid levels and blood pressure. These changes were reversible after the discontinuation of the pressor agent. Serum uric acid levels have been reported to be inversely related to renal blood flow and directly to renal vascular resistance in both normotensive and hypertensive humans. Cappuccio et al demonstrated that high uric acid levels were independently associated with increased proximal tubular sodium reabsorption in men. This association is strikingly similar to the ability of insulin to promote renal sodium reabsorption that has been suggested to be one of the reasons for the high frequency of hypertension in metabolic syndrome and NIDDM. In insulin-resistant states the vasodilatory effect of insulin mediated by nitric oxide is blunted, leading to disturbances in arterial blood flow. On the other hand, hyperuricemia has been associated with elevated circulating endothelin levels, and one of the major sites of the production of uric acid in the cardiovascular system is the vessel wall and particularly the endothelium. Recently, we have demonstrated that cardiac autonomic neuropathy is an independent predictor of stroke in patients with NIDDM. Taken together, these findings suggest that high uric acid could also be a marker of sodium retention coupled with impaired hemodynamic reserves and/or disturbed blood flow.

Uric acid is one of the major endogenous water-soluble antioxidants of the body. There is accumulating evidence that increased oxidative stress is closely related to diabetes and its vascular complications. Thus, high circulating uric acid levels may be an indicator that the body is trying to protect itself from the deleterious effects of free radicals by increasing the products of endogenous antioxidants, eg, uric acid. Interestingly, uric acid prevents oxidative modification of endothelial enzymes and preserves the ability of endothelium to mediate vascular dilatation in the face of oxidative stress. There is also some evidence that uric acid may have a direct role in the atherosclerotic process, because human atherosclerotic plaque contains more uric acid than do control arteries. Inflammation is one of the features of atherosclerosis, and uric acid crystals may induce inflammatory responses that are reduced by lipoproteins which have an ability to bind uric acid crystals. Hyperuricemia via purine metabolism may also promote thrombus formation. Serum uric acid was measured only once, and we therefore have no information on the stability of uric acid levels over time. However, a single measurement of a parameter usually weakens the associations observed.

In conclusion, our results suggest that hyperuricemia is a strong predictor of stroke events in middle-aged patients with NIDDM, and this association is independent of other cardiovascular risk factors. The mechanisms through which hyperuricemia increases the risk of stroke should be the focus of further research.

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References


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