Serum Urate as an Independent Predictor of Poor Outcome and Future Vascular Events After Acute Stroke

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Background and Purpose—Serum urate concentration is associated with cardiovascular disease, and hyperuricemia predicts first-ever stroke. We explored the association of admission urate level with mortality, placement, and risk of further vascular events after acute stroke.

Methods—In patients with ischemic stroke or primary intracranial hemorrhage, we determined the association of urate level with 90-day placement (alive at home, good outcome; dead or living in care, poor outcome) and with the subsequent occurrence of ischemic stroke, myocardial infarction, or vascular death. In multivariate analysis (logistic regression for 90-day placement, proportional-hazards regression for time to further vascular event), we adjusted for stroke severity (modified National Institutes of Health stroke scale) and other clinical, biochemical, and radiological variables known to influence stroke outcome.

Results—We studied 3731 patients and measured serum urate in 2498. Elevated urate level predicted a lower chance of good 90-day outcome (odds ratio, 0.78 per additional 0.1 mmol/L; 95% confidence interval [CI], 0.67 to 0.91) independently of stroke severity and other prognostic factors. Vascular event risk increased with urate level (relative hazard, 1.27 per additional 0.1 mmol/L; 95% CI, 1.18 to 1.36). Higher urate levels have a greater effect on vascular event rates in the presence of diabetes (additional relative hazard, 1.22 per additional 0.1 mmol/L; 95% CI, 1.06 to 1.41).

Conclusions—Independently of other prognostic factors, higher serum urate levels predicted poor outcome (dead or in care) and higher vascular event rates. The role of urate in stroke pathophysiology remains uncertain, but intervention to lower urate may be worth considering. (Stroke. 2003;34:1951-1957.)

Key Words: mortality ■ stroke, acute ■ survival ■ urate

There is a well-recognized epidemiological link between elevated serum uric acid and increased cardiovascular risk. Several large studies have identified an elevated serum uric acid concentration as a predictor of cardiovascular events such as myocardial infarction.1–3 Hyperuricemia also predicts the development of both hypertension4 and coronary artery disease5; it is increased in patients with hypertension, and when present in hypertension, an elevated uric acid level is associated with increased cardiovascular morbidity and mortality.6

It is a matter of controversy whether serum uric acid is an independent predictor of mortality and morbidity in patients with vascular disease or whether it represents an indirect marker of adverse outcome by reflecting the association between uric acid and other well-defined cardiovascular risk factors. Uncertainty about the mechanism by which uric acid could cause or exacerbate cardiovascular disease, coupled with the inconclusive clinical and epidemiological data, has left the issue unresolved.

Despite the clinical and epidemiological evidence, many authorities do not consider elevated uric acid to be a true cardiovascular risk factor but instead view it as a surrogate marker. Patients with hyperuricemia often have other well-established risk factors for cardiovascular disease such as hypertension, renal disease, obesity, dyslipidemia, and insulin resistance.

Elevated serum uric acid independently predicts stroke and excess mortality in patients with non–insulin-dependent diabetes mellitus,7 whereas in the general elderly population, it is independently associated with increased incidence of fatal stroke.8 In diabetic patients, elevated serum uric acid is thought to play a role, along with obesity, blood pressure, and insulin resistance, in the metabolic syndrome that may be responsible for endothelial dysfunction. However, no such association has been reported thus far in the nondiabetic stroke population.

Over the last few years, considerable progress has been made in identifying and treating modifiable risk factors for stroke. Serum uric acid has traditionally been thought of as an
inert byproduct of the catabolism of ingested and endogenous nucleoproteins and purines.\textsuperscript{9} However, if identified as an etiological agent in the pathogenesis of vascular disease, hyperuricemia could be targeted therapeutically in the same way that we now routinely treat other risk factors such as dyslipidemia and blood pressure after stroke.

We sought, in a population with a diagnosis of acute stroke or transient cerebral ischemia, to explore the association between urate level and any prognostic role in outcome or future vascular morbidity and mortality.

Methods

Study Design

This retrospective analysis was performed on data collected from 3731 patients consecutively admitted to our acute stroke unit between May 1990 and September 1998. All patients within the catchment area of our acute stroke unit were admitted within 48 hours of experiencing a new focal or global neurological event. Brain imaging (either CT or MRI) was performed routinely within 24 to 48 hours of admission. Subjects with subarachnoid or subdural hemorrhage were excluded. Data were collected with regards to patient demography, medical history, and risk factors for stroke or vascular disease.

Strokes were classified according to the Oxfordshire Community Stroke Project (OCSP) system.\textsuperscript{10} Indexes of stroke severity included the modified National Institutes of Health Stroke Scale (NIHSS)\textsuperscript{11} and the Glasgow Coma Scale (GCS).\textsuperscript{12} Serum urate was measured as part of a fasting biochemical profile taken on the morning after admission. The above information was then recorded prospectively into a computerized database. Serum urate was measured with standard analytical methods in the hospital biochemistry department.

Follow-up was by record linkage\textsuperscript{13} to death records from the Registrar General of Scotland and to hospital discharge records to obtain information on medical events after stroke. This technique has been previously validated.\textsuperscript{14} Record linkage is reliable; however, admissions to private hospitals or institutions outside Scotland are not recorded. Study patients were monitored until the end of June 2000, allowing at least 21 months of potential follow-up for each patient. Outcome was categorized as alive at home, alive in care, or dead at 90 days after the index stroke. A good outcome after the index stroke was defined as alive at home after 90 days and bad outcome as alive in care or dead at 90 days. This outcome was a marker for functional outcome, which is frequently used as an end point in trials of therapeutic agents in stroke.

We were granted local Research Ethics Committee approval for the analysis of the anonymous clinical data. The Privacy Advisory Committee of the Chief Medical Officer for Scotland approved the linkage of the clinical data to death and hospital discharge records.

Statistical Analysis

We assessed the effect of serum urate concentration on the 2 outcome possibilities described above. Fisher’s exact test (binary variables), the \(\chi^2\) test (categorical variables), the Mann-Whitney test (continuous variables), and \(\chi^2\) test for linear trend (ordered categorical variables) were used to explore univariate differences in clinical features between outcome groups. Using multiple logistic regression, we assessed the effect of serum urate concentration after controlling for factors known to influence acute stroke outcome. The modeling had 2 stages. First, the effect of urate level was quantified after correcting for baseline stroke severity (modified NIHSS). Diabetes was included in the model, and an interaction term between urate and presence of diabetes was permitted. This explored the hypothesis that any effect of urate might be augmented in diabetics. Second, clinical variables that differed significantly between outcome groups in the univariate analysis or that are already established as predictors of stroke outcome were added to the model. Quadratic and log transformations of variables were included when exploratory analyses showed these to be merited.

Results

In total, 3731 patients with a diagnosis of acute stroke were studied. Demography and risk factor profiles are shown in Table 1. Median age was 72 years (interquartile range [IQR], 63 to 80 years), and median GCS score was 15 (IQR, 14 to 15). The median modified NIHSS score was 3 (IQR, 2 to 8); the total NIHSS score had median of 6 (IQR, 3 to 11). Median urate level was 0.31 mmol/L (IQR, 0.25 to 0.38 mmol/L). Urate level was missing in 1233 (33%) of the subjects with
data on 90-day placement outcome. We found that 355 patients (10%) had primary intracerebral hemorrhage and 3376 (90%) had ischemic stroke.

### Outcome at 90 Days

At 90 days, 2361 (64%) were alive at home (good outcome), whereas 498 (13%) were alive in care and 835 (23%) were dead (bad outcomes). We lost 37 patients (1%) to follow-up.

Variables associated with bad outcome on univariate analysis included older age, female sex, elevated glucose concentration, primary intracerebral hemorrhage, increased modified NIHSS, and higher urate values ($P < 0.0001$ for all).

Stepwise multiple logistic regression confirmed the relationship between higher urate levels and bad outcome at 90 days (Table 2). This association remained after correcting for all other known or potential prognostic indicators and allowing for an effect of diabetes (any type versus none) on outcome. There was no interaction between urate effect and the presence of diabetes. Diabetes itself was not significantly associated with bad outcome at 90 days independently of glucose concentration.

### Relationship to Risk of Major Vascular Events

In total, 1855 patients (51%) suffered a recurrent ischemic stroke, nonfatal myocardial infarction, or death caused by any vascular cause. The mean duration of follow-up was 2.7 years. The high event rate results partly from our use of the vascular event definition from the Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events trial, in which deaths resulting from the index stroke event counted as vascular death events.

In univariate analysis, diabetes, previous stroke, previous myocardial infarction, history of claudication, atrial fibrillation, increased age, higher urate level, prestroke diuretic use, and low-dose aspirin usage all had hazard ratios $>1$, indicating an increased risk of a major vascular event. In the Figure,
Kaplan-Meier curves show the event rates according to urate level subdivided by quartile.

Multivariate analysis confirmed that higher urate levels independently increased event risk (hazard ratio, 1.27 per additional 0.1 mmol/L; 95% confidence interval [CI], 1.18 to 1.36; \( P<0.0001 \)). Moreover, the effect of urate on the vascular event rate was greater when diabetes was present (a further hazard ratio of 1.22 per additional 0.1 mmol/L when diabetes present; 95% CI, 1.06 to 1.41; \( P=0.0011 \)) (Table 3). These effects of urate persisted after all other variables associated with vascular event risk were added to the multivariate model.

**Discussion**

Serum urate measured within the first 24 hours after hospital admission for acute stroke is an independent marker of poor outcome and can predict future vascular events. Urate levels independently predict a bad outcome as defined by death or survival in care (indicating a poorer functional outcome) at 90 days after the index stroke. Cerebrovascular patients with higher serum urate levels are also more likely to experience a major vascular event. This relationship holds true even after correction for the presence of established cardiovascular and cerebrovascular risk factors such as hypertension, diabetes mellitus, and hyperlipidemia. Although other studies have found the effect of urate to be related to use of thiazide diuretics,\(^7\) we found it to be independent of thiazide diuretic use in multivariate analysis.

It is difficult in an observational study to demonstrate a causal relationship between a factor and disease incidence or outcome, particularly if the factor is strongly correlated with other medical conditions known to affect outcome. Criteria have thus been established\(^8\) that determine whether an observed association may be considered causal. A commentary on the causality of urate in cardiovascular disease\(^9\) concluded that because of the statistical complexity created by the strong correlation between urate level and known vascular risk factors, the only way to demonstrate an independent effect of urate is to study its effect in patients who were homogeneous with respect to all other vascular risk factors. We further analyzed the effect of urate in 2 such subgroups. Group 1 contained nonsmokers who did not have diabetes mellitus, hypertension, previous myocardial infarction, atrial fibrillation, hyperlipidemia, or intermittent claudication. Group 2 consisted of hypertensive smokers who had none of the other risk factors. Analysis in each subgroup gave results consistent with our main findings.

Previous studies have shown a relation between urate levels and poor outcome in diabetic cerebrovascular patients.\(^7\) We have shown that this relationship extends to the cerebrovascular population as a whole. Allowing for the effect of diabetes (any type versus none) on outcome and permitting the effect of urate to vary according to whether diabetes was present, we found no interaction between urate effect and the presence of diabetes. However, the lower limit of the CI for the interaction indicates that a more potent adverse effect of increased urate in diabetics may exist. Diabetes itself was not significantly associated with a bad 90-day outcome. In the vascular event data, we found that the effect of urate on the event rate was greater when diabetes was present. The lower limit of the CI for the interaction (hazard ratio, 1.06) indicates that this augmentation may be small. The upper limit shows that the interaction may add as much as 150% to the basic urate effect (1.41 versus the basic urate effect of 1.27). Diabetes itself was also significantly associated with increased vascular event risk.

Urate levels were missing in 1233 patients (33%) with 90-day outcome data because of the withdrawal by the biochemistry service of urate as a routine admission profile test. Although urate requests remained stroke unit policy for the next 2 years, this was not applied uniformly by junior medical staff. Consistency was restored when requests were again automated. We replaced missing data by the mean level from subjects in whom urate was measured. This is conservative in that it should dilute the true urate effect, assuming that the data were missing at random. Of the patients in whom urate was measured, 67% experienced a favorable outcome compared with 58% of those without urate data (\( P<0.0001 \), Fisher’s exact test). This may be due partly to patients who died soon after admission being unavailable for routine biochemistry testing. We repeated our analyses in the subset of patients in whom urate was measured. The results were similar, confirming that the association between urate level and outcome is large in magnitude and stable under several modeling strategies. Although more sophisticated imputation of the missing data or a prospective study with complete data is desirable to confirm our results, we have confidence that the association we observed is not artificial.

Although serum uric acid was found in previous studies to be an independent predictor of stroke or excess mortality in patients with non–insulin-dependent diabetes mellitus, no study has previously shown that serum urate independently predicts poor outcome in stroke patients regardless of diabetes. Several studies, however, have shown a relationship between serum urate and hypertension\(^4,20\) and serum urate and coronary heart disease\(^5\) in

**TABLE 3. Multivariate Analysis for Time to Major Vascular Event**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urate level (per additional 0.1 mmol/L)</td>
<td>1.27</td>
<td>1.18–1.36</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Modified NIHSS score (per additional unit)</td>
<td>1.11</td>
<td>1.10–1.12</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.29</td>
<td>1.11–1.50</td>
<td>0.0065</td>
</tr>
<tr>
<td>Diabetes and urate interaction (extra effect per additional 0.1 mmol/L urate if diabetes present)</td>
<td>1.22</td>
<td>1.06–1.41</td>
<td>0.0011</td>
</tr>
</tbody>
</table>

\( P\)-values were calculated using the log-rank test.
certain populations. Many studies have postulated no role for urate in vascular disease.\(^{21}\) A recent small study even suggested that high serum urate levels may be neuroprotective in acute stroke, resulting in better functional outcome at discharge.\(^{22}\)

Apart from the interactions between uric acid and other risk factors, there are several plausible mechanisms whereby uric acid may directly affect atherogenesis or the clinical course of cerebrovascular disease. Increased uric acid levels promote oxygenation of low-density lipoprotein cholesterol and facilitate lipid peroxidation.\(^{23}\) In addition, increased uric acid levels are associated with increased production of oxygen free radicals. Each of these factors is known to play a pivotal role in the progression of atherosclerosis. Moreover, increased uric acid levels may be associated with increased platelet adhesiveness, and this effect could potentiate thrombus formation.\(^{24}\) The Atherosclerosis Risk in Communities study\(^ {25}\) observed that the level of uric acid was directly associated with B-mode ultrasound carotid intima-media thickness. Studies of the composition of human atherosclerotic plaque have shown that urate crystals are more abundant in diseased atherosclerotic plaque than in control artery walls.\(^ {26}\) Although the precise role of uric acid in each of these mechanisms has yet to be delineated, it is clear that these effects provide a potential basis for uric acid as a primary cardiovascular risk factor.

Experimental findings indicate the potential role of uric acid in the development of hypertension through stimulation of the renin-angiotensin system\(^ {27}\) and induction of sodium sensitivity.\(^ {28}\) In rats, uric acid has been shown to mediate renal disease development by causing glomerular hypertension\(^ {29}\) and hence renal hypertrophy, glomerulosclerosis, and interstitial fibrosis.\(^ {30}\) Uric acid also induces renal arteriolar thickening independently of its effect on blood pressure.\(^ {31}\)

Cerebrovascular disease is the most common cause of disability and the third-most-common cause of death in the developed world. Traditional risk factors such as hypertension and hypercholesterolemia are now being treated more aggressively after ischemic stroke following the results of the Perindopril Protection Against Recurrent Stroke Study\(^ {32}\) and Heart Protection Study,\(^ {33}\) respectively. However, there is a pressing need to identify additional treatable risk factors that are easily measured and highly prevalent in the general population. Hyperuricemia is one such potential risk factor, but more research is needed at both the scientific and clinical levels before routine treatment of serum urate can be recommended.

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References

Hyperuricemia was first associated with hypertension and cardiovascular disease in 1879. Since that time, many have attributed this association to a simple clustering of hyperuricemia with well-established cardiovascular risk factors, and an elevated serum uric acid level by itself has generally been regarded as insignificant or incidental. A recent reanalysis of the Framingham study concluded that hyperuricemia was not an independent risk factor for cardiovascular events after controlling for these other associated factors. Nevertheless, other studies have found an elevated serum uric acid level to be an independent risk factor for cardiovascular and renal disease (reviewed elsewhere). In particular, several studies have reported that hyperuricemia is an independent predictor of stroke in diabetic subjects, individuals with isolated systolic hypertension, and the general population. A new study reported in this issue of Stroke examining 2498 subjects admitted with acute stroke found that the admission serum uric acid also independently predicted worse outcome and a higher rate of repeated stroke or other cardiovascular event. Others have also reported that a higher uric acid level in patients with acute stroke is associated with poorer outcome. These studies suggest that uric acid may be a true risk factor for stroke and for a poor outcome after stroke.

Experimental evidence could provide a mechanism to explain why an elevated serum uric acid at the time of stroke may be injurious. Recent evidence suggests that acute ischemic stroke results in generation of local oxidants that augment local injury and increase infarct size. Acute stroke is associated with a rapid decrease in serum antioxidants that recover slowly over the subsequent week. Individuals with lower plasma antioxidants at the time of acute stroke have a poorer outcome. Uric acid is often considered an antioxidant and has been shown to have a key role in stimulating macrophage infiltration in atherosclerotic vessels. It is of interest that uric acid is strongly associated with carotid and coronary atherosclerosis, especially in women.

There is also a potential pathogenetic mechanism to explain why an elevated serum uric acid during an acute stroke could predispose the serum uric acid to take on a crystalline-independent mechanism and can accelerate established renal disease; the mechanism is mediated by an elevation in glomerular pressure and renal vasoconstriction. Finally, uric acid stimulates synthesis of monocyte chemoattractant protein-1 by rat vascular smooth muscle cells, which is known to have a key role in stimulating macrophage infiltration in atherosclerotic vessels. It is of interest that uric acid is strongly associated with carotid and coronary atherosclerosis, especially in women.

One might therefore expect that having elevated uric acid during an acute stroke would be beneficial. However, only 1 small study has reported that elevated uric acid is associated with good outcome after an ischemic stroke, whereas 2 other studies, including the large series reported in the current issue, found the opposite. One explanation is that uric acid, being an aqueous antioxidant, can become a pro-oxidant under certain circumstances, particularly if other antioxidants such as ascorbate are low. Thus, the fall in ascorbate (vitamin C) levels with conditions, particularly if other antioxidants such as ascorbate are low. Thus, the fall in ascorbate (vitamin C) levels with
Further studies are needed to prove whether uric acid has a pathogenetic role in hypertension, vascular disease, atherosclerosis, and stroke. It will also be important to determine whether lowering uric acid levels reduces the frequency of stroke. One wonders if the increased benefit of losartan over atenolol in the Losartan Intervention For Endpoint Reduction in Hypertension Study may relate in part to the uricosuric effect of losartan and the consequent lower uric acid levels.31 It is also important to assess whether elevated uric acid levels, especially when coupled with low ascorbate levels, may function more as a pro-oxidant than as an antioxidant. It is of interest that there is often a J-shaped curve when one compares uric acid levels with cardiovascular events,3 because this might suggest that low uric acid levels may increase mortality as a result of inadequate antioxidant levels and high levels of uric acid may function more as an antioxidant because uric acid levels are lower in rats as a result of the presence of the enzyme uricase. In the meantime, studies such as the one in the current issue provide strong evidence that an elevated uric acid is injurious rather than protective in subjects with acute stroke.

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Editorial Comment—Elevated Uric Acid and Ischemic Stroke: Accumulating Evidence That It Is Injurious and Not Neuroprotective

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