Yin and Yang of Uric Acid in Patients With Stroke

To the Editor:

We have read with interest the article by Weir and colleagues,\(^1\) which concludes that independently of other prognostic factors, high serum urate levels predict poor outcome and higher vascular event rates in patients with stroke. In agreement with these findings, the authors advise interventions aimed at lowering urate to decrease the risk of stroke.\(^1\) In an accompanying editorial,\(^2\) it is concluded that elevated uric acid is injurious rather than protective in subjects with stroke. We are addressing the correspondence section of *Stroke* because we believe that these conclusions are controversial.

Uric acid is recognized by many but not all epidemiological studies as a marker of increased cardiovascular risk. General population studies\(^3–8\) and case series of patients with diabetes\(^9\) or hypertension\(^10\) have shown elevated serum uric acid in subjects at greater risk of cardiovascular events. Weir and colleagues’ work is an additional step demonstrating a greater cardiovascular burden in stroke patients with elevated uric acid, but it does not demonstrate the pernicious nature of this natural antioxidant. Weir and colleagues measured urate levels in 2498 stroke patients within 24 to 48 hours of admission and found poorer outcome in subjects with higher urate levels. We concur with the careful methodology used by the authors to control for the effects of confounders. Nevertheless, their main conclusion, clashing with our previously reported study,\(^7\) that found an independent neuroprotective effect of uric is intriguing and deserves further explanation.

The authors discuss plausible mechanisms whereby hyperuricemia could be deleterious, including increased lipid peroxidation and platelet adherence.\(^1\) The stimulation of the synthesis of monocyte chemotactic protein-1, interleukin-1β, interleukin-6, and tumor necrosis factor α could be added to this list without frustrating the benefits associated with uric acid that we\(^2\) and others\(^1\) have observed. Furthermore, the administration of uric acid to adult rats 24 hours before the experimental ischemia or 1 hour after reperfusion results in a significant reduction in ischemic damage and improves behavioral outcome.\(^9\) Uric acid also suppresses the accumulation of reactive oxygen species and lipid peroxidation after cerebral ischemia or exposure to glutamate.\(^1\) The free-radical scavenging properties of uric acid have been recently assessed in a randomized double-blind placebo controlled crossover study in healthy volunteers without safety concerns.\(^10\)

What is the explanation for the discrepancies between our study and that reported by Weir and colleagues? If Weir et al disregard as we do the genetic traits of Scottish and Catalan patients, a likely explanation is the methods used in both studies to measure clinical outcome. In our study, bad outcome referred to neurological impairment at hospital discharge below a threshold in areas of mentation, speech, cranial nerves, motor power, reflexes, sensation, and an overall disability scale.\(^11\) In contrast, Weir and colleagues’ study described bad outcome at 90 days in patients who after the index stroke were dead or alive in care, instead of alive at home. However, they did not report which neurological changes occurred during the acute phase of stroke, or whether late-onset complications influenced final outcome. The authors defend this method as a reliable marker for functional outcome, but we believe it is subject to unmeasured biases, including economical factors, social status, and medical comorbidities. Expectedly, medical comorbidities are more frequent and severe in patients with more advanced atherosclerosis, which are the individuals with higher urate levels. However, this association does not exclude that during the ischemic episode, higher urate levels prevented or diminished the extent of brain damage, as we described.\(^7\)

It would be crucial to know in Weir and colleagues’ study if the longitudinal changes in the modified NIHSS were inversely related to baseline urate levels. Meanwhile, the study suggests that elevated uric acid translates a more aggressive history of oxidative stress, proatherogenic factors, and greater odds of being dead or institutionalized 3 months after stroke. Whereas chronic lowering of urate levels might independently decrease the risk of stroke, as suggested by the authors, abundant preclinical research supports the beneficial effects of increasing uric acid during the early stages of ischemia. At last, both scenarios are not mutually exclusive.

In summary, we propound prospective intervention trials in stroke that would clarify whether the administration or uric acid is beneficial. A phase 2 placebo-controlled study aimed at establishing the safety and adequate dosing of uric acid is currently underway at our center.

Angel Chamorro, MD, PhD
Stroke Unit
Neurology Service
Hospital Clinic
Institut d’Investigations Biomediques August Pi i Sunyer
Barcelona, Spain

Anna M. Planas, PhD
Pharmacology and Toxicology Department
Institut d’Investigations Biomediques de Barcelona Consejo Superior de Investigaciones Cientificas
Institut d’Investigations Biomediques August Pi i Sunyer
Barcelona, Spain


Response

We are pleased with the interest generated by our report in 2498 patients. Drs Chamorro and Planas question whether our
study demonstrates a deleterious effect of elevated uric acid levels. It would have been inappropriate for us to infer causality in such an observational analysis, since that remains the reserve of the randomized controlled study. However, our findings did illustrate associations between elevated urate level and poor outcome on two clinically relevant endpoints. The associations remained after rigorous adjustment for known prognostic factors.

We accept that despite adjusting for medical comorbidity, the outcome measure of placement at 90 days (alive at home, versus alive in care or dead) may be susceptible to biases due to economic factors and social status. However, the other primary analysis, of vascular event-free survival times, would have been unaffected by such confounding factors.

A recent editorial offers an explanation as to why uric acid may have shown a beneficial effect in the study in rats cited by Chamorro and Planas. At lower concentrations, as might be found in rats due to the presence of uricase, the antioxidant and hence potentially neuroprotective properties of uric acid may be preserved. At high concentrations, and particularly in the presence of the low ascorbate (vitamin C) levels that occur following acute stroke, urate may adopt a pro-oxidant role with the accompanying adverse effects on outcome.

Was our study able to exclude the possibility that during the ischemic episode, higher urate levels may prevent or diminish the extent of brain damage as Chamorro and Planas have described? Although we cannot answer this categorically, we do show early separation, apparent within approximately 14 days, in the Kaplan-Meier curves for vascular event-free survival. This suggests that the adverse effects of elevated uric acid outweigh any advantage of reduced brain damage due to higher urate levels.

We did not routinely record modified NIHSS scores after the initial admission score. As a surrogate, duration of admission is associated with the extent of the ischemic injury. In our cohort, patients who survived the initial stroke event and had admission urate level above the upper quartile (0.38 mmol/L) had a longer duration of hospital stay than surviving patients with lower urate levels (median 11 days versus 8 days, Mann-Whitney test; \( P=0.003 \)). Death rates in the acute phase were similar between the 2 groups.

In summary, we agree with the call from Chamorro and Planas for further investigation of the relationship between urate level adjustment and stroke outcome in randomized controlled studies. At this stage, we believe that the rationale for intervention to lower urate is at least as strong as that for the administration of additional uric acid.

Christopher J. Weir, PhD
Department of Cerebrovascular Medicine
Division of Cardiovascular and Medical Sciences
and Robertson Centre for Biostatistics
Boyd Orr Building
University of Glasgow

Scott W. Muir, MBChB, MRCP
Matthew R. Walters, MD, MRCP
Kennedy R. Lees, MD, FRCP
Department of Cerebrovascular Medicine
Division of Cardiovascular and Medical Sciences
University of Glasgow
Gardiner Institute
Western Infirmary
Glasgow, United Kingdom

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