Urate as a Predictor of the Rate of Clinical Decline in Parkinson Disease

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Background: The risk of Parkinson disease (PD) and its rate of progression may decline with increasing concentration of blood urate, a major antioxidant.

Objective: To determine whether serum and cerebrospinal fluid concentrations of urate predict clinical progression in patients with PD.

Design, Setting, and Participants: Eight hundred subjects with early PD enrolled in the Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP) trial. The pretreatment urate concentration was measured in serum for 774 subjects and in cerebrospinal fluid for 713 subjects.

Main Outcome Measures: Treatment-, age-, and sex-adjusted hazard ratios (HRs) for clinical disability requiring levodopa therapy, the prespecified primary end point of the original DATATOP trial.

Results: The HR of progressing to the primary end point decreased with increasing serum urate concentrations (HR for highest vs lowest quintile=0.64; 95% confidence interval [CI], 0.44-0.94; HR for a 1-SD increase=0.82; 95% CI, 0.73-0.93). In analyses stratified by α-tocopherol treatment (2000 IU/d), a decrease in the HR for the primary end point was seen only among subjects not treated with α-tocopherol (HR for a 1-SD increase=0.75; 95% CI, 0.62-0.89; vs HR for those treated=0.90; 95% CI, 0.75-1.08). Results were similar for the rate of change in the Unified Parkinson's Disease Rating Scale score. Cerebrospinal fluid urate concentration was also inversely related to both the primary end point (HR for highest vs lowest quintile=0.65; 95% CI, 0.44-0.96; HR for a 1-SD increase=0.89; 95% CI, 0.79-1.02) and the rate of change in the Unified Parkinson's Disease Rating Scale score. As with serum urate concentration, these associations were present only among subjects not treated with α-tocopherol.

Conclusions: Higher serum and cerebrospinal fluid urate concentrations at baseline were associated with slower rates of clinical decline. The findings strengthen the link between urate concentration and PD and the rationale for considering central nervous system urate concentration elevation as a potential strategy to slow PD progression.

Arch Neurol. 2009;66(12):1460-1468

IN HUMANS, URATE IS A MAJOR ANTIOXIDANT as well as the end product of purine metabolism.1,2 Its high concentrations in cerebrospinal fluid (CSF) and blood have been attributed to a mutation in the urate oxidase gene occurring late in hominid evolution.3 Oxidative damage is suspected to contribute to the neurodegenerative process in Parkinson disease (PD).4-5 and antioxidants like urate may provide an endogenous defense against the development and progression of PD.

Prospective epidemiological studies have demonstrated that healthy individuals with higher blood urate concentrations are at reduced risk for developing PD.6-8 Similarly, a lower risk of PD has also been reported among individuals consuming diets that increase serum urate concentration9 and among those with a history of gout.10,11 Recently, we found that higher urate blood concentrations in patients in the early stages of PD predict a slower rate of disease progression, assessed by both clinical and neuroimaging measures.12 These studies suggest that urate concentration measured systemically may serve as a robust predictor of the brain neurodegeneration that leads to the initiation and progression of PD.

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The studies also raise the possibility that central nervous system urate directly protects against the neuronal degeneration underlying clinical deterioration in PD. Ce-
Participants were enrolled between September 1987 and November 1988 at 28 sites across the United States and Canada.

STUDY DESIGN

The DATATOP study was a 2-year, double-blind, randomized trial originally designed to test the hypothesis that long-term treatment of early PD with the monoamine oxidase type B inhibitor deprenyl (selegiline hydrochloride) and/or the antioxidant α-tocopherol would extend the time until the emergence of disability requiring therapy with levodopa. The 800 participants were enrolled between September 1987 and November 1988.

STUDY POPULATION

Subjects enrolled in the study had typical and early PD (Hoehn and Yahr stages 1 and 2) of less than 5 years’ duration and were excluded if they used symptomatic PD medication or had severe tremor, serious dementia (Mini-Mental State Examination score ≤22), or depression (Hamilton Scale for Depression score ≥16). Subjects were reviewed and examined by neurologists who were PD specialists. After baseline evaluation, study participants were randomized according to a 2:2:2 treatment assignment: deprenyl (10 mg/d) and α-tocopherol (2000 IU/d) and deprenyl placebo, active deprenyl and active α-tocopherol, or double placebo.

SERUM AND CSF URATE CONCENTRATIONS AND COVARIATES

Urate concentration was measured in serum samples collected at the baseline visit prior to treatment assignment. Serum was shipped without freezing to a central commercial clinical laboratory (SciCor, Indianapolis, Indiana) for immediate enzymatic assay of urate concentrations, which were available for 774 of the 800 enrolled subjects. Values maintained in a digitized database were not analyzed with respect to disease progression outcome measures until their retrieval in May 2006 specifically for this purpose.

Cerebrospinal fluid was collected at baseline after overnight bed rest from 730 subjects (ie, 91.2% of enrollees), with technical difficulties in performing lumbar punctures precluding the collection from the others and at the end of the study in 486 subjects. Specimens were rapidly frozen for storage at −70°C after first splitting all CSF collection tubes into aliquots with or without metabisulfite preservative added. Baseline and final CSF urate concentrations were measured in 1991 by high-performance liquid chromatography with electrochemical detection from collection tubes containing the 18th to 20th milliliter of lumbar CSF flow in 2 selected subsets totaling 290 subjects who had provided both baseline and final CSF collections. The values of CSF urate concentrations at baseline correlated well with those at the end of treatment or follow-up in both subsets (Spearman coefficient = 0.69; P < .001), a result that supports the reproducibility of the assay as well as relatively stable within-person CSF urate concentrations. For the present analyses, in 2008 we obtained CSF aliquots from the same collection tubes (containing no metabisulfite preservative) and repeated the measurement of urate concentrations by high-performance liquid chromatography with electrochemical detection. For these assays, 30 µM α-methyldopa served as an internal standard. Baseline CSF urate concentrations could be determined in 713 participants (ie, 97.7% of those from whom a baseline CSF sample was obtained and stored). Although mean CSF urate concentrations were lower than those measured in 1991, a good correlation was found between original urate concentrations and those measured in 2008 among the 277 individuals in both sets (Spearman coefficient = 0.72; P < .001). Furthermore, baseline serum urate concentrations correlated more strongly with baseline CSF urate concentrations measured in 2008 (r = 0.73) than in 1991 (r = 0.58). These results provide evidence of the stability of urate in these samples and of the accuracy of CSF urate concentration measurements.

CLINICAL EVALUATION AND OUTCOMES

Following the baseline visit and initiation of study drugs, subjects were scheduled for visits every 3 months until 24 months had elapsed. At each visit the site investigator evaluated the subject for disability sufficient to require dopaminergic therapy, the primary end point for the study, and for the secondary response variables, including the Unified Parkinson’s Disease Rating Scale (UPDRS) score (sum of the motor, cognitive, and activities of daily living subscale scores). Because the UPDRS score is modified by the dopaminergic treatment instituted at the primary end point, the annualized rate of change in the UPDRS score was determined based on change from baseline to the primary end point (or the final visit if the primary end point was not reached) for each subject and was calculated as follows: [total UPDRS score at the last assessment before initiation of dopaminergic treatment – total UPDRS score at baseline] / number of days between the 2 assessments × 365 d/y. The vital status and date of death of participants in the DATATOP trial were collected in 2001 to 2002 as previously described. The shortest time elapsed between enrollment and vital status update was 13 years. Information was available for 768 subjects with baseline serum urate concentration measurement.

STATISTICAL ANALYSIS

In the original trial, the hazard ratios (HRs) for the primary end point were 0.50 (95% confidence interval [CI], 0.41-0.62) among patients assigned to deprenyl and 0.91 (95% CI, 0.74-1.12) among patients assigned to α-tocopherol. Accordingly, all of the analyses were adjusted for assignment to deprenyl vs placebo.

Cox proportional hazards models were used to estimate the HRs of reaching the primary end point according to quintiles of baseline serum urate concentration, adjusting for sex, age (in 5-year groups), and treatment assignment (deprenyl vs placebo). Initial analyses were conducted using quintiles based on the combined urate concentration distribution in men and women. However, because this categorization resulted in a markedly skewed distribution within sex as expected, we also conducted analyses based on sex-specific quintiles. Tests for trend were conducted by including serum urate concentration as a continuous variable in the proportional hazards models. Potential confounding was assessed by adjusting the regression analyses for body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) and use of antihypertensive drugs or nonsteroidal anti-inflammatory drugs (use vs no use). With the exception of BMI, these adjustments did not affect the results. Therefore, only the treatment-, age-, and sex-adjusted results or the treatment-, age-, sex-, and BMI-adjusted results are presented.
RESULTS

SERUM URATE CONCENTRATION

Serum urate concentration at baseline was available for 774 of the 800 subjects (96.8%; 510 men and 264 women) enrolled in the trial. Selected characteristics of these subjects are shown in Table 1. As expected, serum urate concentrations correlated positively with being male, BMI, use of thiazide diuretics, and hypertension. Use of calcium channel blockers was reported by only 17 patients and showed no relationship to serum urate concentration.

Overall, 369 (47.7%) of these participants progressed to disability sufficient to require levodopa therapy during follow-up. The HR of reaching this primary end point declined with increasing concentrations of serum urate (P for trend=.002) and was 36% lower among subjects in the top quintile of serum urate concentration (HR=0.64; 95% CI, 0.44-0.94) (Table 2). This association was stronger in men than in women, although a test for interaction of urate concentration with sex was not significant (P=.54). Further, in both sexes, the HR for reaching the primary end point decreased with increasing BMI (P for trend=.05 in men, P for trend=.02 in women). After adjustment for BMI, the association between serum urate concentration and the primary clinical end point was partially attenuated; the HRs for a 1-SD increase in serum urate concentration were 0.89 in all subjects (P=.07), 0.85 in men (P=.04), and 1.01 in women (P=.94).

When subjects were classified simultaneously according to serum urate concentration and α-tocopherol treatment, a decreasing HR for reaching the primary end point with increasing serum urate concentration was observed among untreated subjects (HR=0.75; 95% CI, 0.62-0.89; P=.001) but not among those treated (HR=0.90; 95% CI, 0.75-1.08; P=.24), consistent with comparisons of baseline urate concentration quintiles (Figure 1A) and unadjusted Kaplan-Meier analyses (eFigure; http://www.archneurol.com) in subgroups without or with α-tocopherol treatment. Conversely, randomization to α-tocopherol treatment appeared to lower the HR of reaching the primary end point among subjects in the lowest quintile of serum urate concentration (HR=0.59; 95% CI, 0.36-0.97) but not among those with a higher serum urate concentration (Figure 1A). Further analyses were conducted within sex. In men, the HRs for a 1-SD increase in serum urate concentration were 0.74 (95% CI, 0.59-0.92; P=.008) among subjects not receiving α-tocopherol and...
Table 2. Hazard Ratios for Reaching the Primary End Point According to Common Quintiles of Baseline Serum Urate Concentration or Corresponding to a 1-SD Increase in Serum Urate Concentrationa

<table>
<thead>
<tr>
<th>Serum Urate Concentration Quintile</th>
<th>All Subjects (N=774)</th>
<th>Men (n=510)</th>
<th>Women (n=264)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Value</td>
<td>Value</td>
<td>Value</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>No.</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>1</td>
<td>0.82 (0.73-0.93)</td>
<td>162</td>
<td>1 [Reference]</td>
</tr>
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<td>0.81 (0.70-0.94)</td>
<td>140</td>
<td>0.88 (0.52-1.49)</td>
</tr>
<tr>
<td>3</td>
<td>0.80 (0.44-0.94)</td>
<td>158</td>
<td>0.65 (0.41-1.11)</td>
</tr>
<tr>
<td>4</td>
<td>0.78 (0.48-1.29)</td>
<td>165</td>
<td>0.67 (0.41-1.11)</td>
</tr>
<tr>
<td>5</td>
<td>0.58 (0.23-1.50)</td>
<td>158</td>
<td>0.58 (0.23-1.50)</td>
</tr>
</tbody>
</table>

1-SD increase in serum urate concentration

Abbreviations: CI, confidence interval; HR, hazard ratio.

a A 1-SD increase indicates an increase of 1.4 mg/dL. The HRs are adjusted for age, sex, and treatment group (deprenyl or placebo).

0.88 (95% CI, 0.71-1.08; P=.21) among subjects receiving α-tocopherol. In women, the corresponding HRs were 0.73 (95% CI, 0.52-1.02; P=.06) for subjects not receiving α-tocopherol and 1.04 (95% CI, 0.69-1.59; P=.84) for subjects receiving α-tocopherol. The interaction between α-tocopherol and serum urate concentration was nonsignificant for men and for women (P for interaction=.55 in men, and P for interaction=.06 in women). No significant interaction was found between serum urate concentration and deprenyl treatment; a decreasing HR with increasing serum urate concentration was found in the placebo-placebo and deprenyl-placebo groups but not in the placebo–α-tocopherol and deprenyl–α-tocopherol groups (eTable 1).

The change in UPDRS score between baseline and either the time of reaching the primary end point or the end of follow-up was available for 760 of the 774 subjects with baseline serum urate concentrations. Overall, the rate of UPDRS score change declined with increasing serum urate concentration (P for trend=.03). As observed previously for the primary end point, results were more robust in men, although there was no statistically significant interaction with sex. Among men, the adjusted rate of UPDRS score change declined from 14.8 points per year for subjects in the lowest quintile of serum urate concentration to 8.9 points per year for those in the highest quintile (P for trend=.03); comparable results among women were 11.0 and 8.2 points per year, respectively (P for trend=.35). The relationship between serum urate concentration and the rate of UPDRS score change was modified by α-tocopherol treatment (P for interaction=.009) (Figure 2A). In separate models, among subjects not assigned to receive α-tocopherol, the rate of UPDRS score change was 9.8 points per year lower in the highest quintile of serum urate concentration than in the lowest quintile (P=.003), whereas no difference was observed for subjects assigned to receive α-tocopherol (0.5 points per year higher in the highest quintile as compared with the lowest quintile; P=.89). In analyses based on repeated measures, the overall association between higher urate levels at baseline and a slower rate of UPDRS score increase was even stronger (P=.001). There was also a significant interaction between urate concentration and α-tocopherol treatment (P=.003), and consistent with results observed in the primary analyses, higher levels of serum urate were strongly associated with a slower rate of UPDRS score increase among patients not treated with α-tocopherol (P=.001) but not in those treated with α-tocopherol (P=.37). No significant interaction was found between serum urate concentration and deprenyl treatment (eTable 2).

Two hundred eleven men (41.4%) and 81 women (30.7%) were identified as having died after 13 years of
follow-up. In men and women combined, after adjustment for deprenyl treatment, age, sex, and pack-years of smoking (Table 3) and after adjustment for deprenyl treatment, age, sex, pack-years of smoking, and cardiac comorbidity at baseline (Table 4), serum urate concentration was not significantly associated with mortality. In men, however, the relationship between serum urate concentration and mortality was a U-shaped curve, with the lowest mortality in the fourth quintile of urate concentration. In women, a suggestion of increased mortality at any urate concentration higher than that in the lowest quintile was not substantiated statistically. No significant interactions between serum urate concentration and \( \alpha \)-tocopherol were found in analyses on mortality.

**CSF URATE CONCENTRATION**

Mean urate concentrations in CSF collected at baseline were higher in men (0.42 mg/dL) than in women (0.28 mg/dL) and, as expected, were substantially lower than in serum.21 Despite the lower concentrations of CSF urate, a strong correlation was found between CSF and serum urate concentrations \( (r = 0.73; P < .001) \).

The primary clinical end point of disability was reached by 342 of the 713 subjects (48%) for whom CSF urate concentrations were available. Overall, the HR of reaching the primary end point of disability was significantly lower among individuals with higher concentrations of CSF urate. The HR comparing subjects in the highest quintile of CSF urate concentration with those in the lowest quintile was 0.65 (95% CI, 0.44-0.96; \( P = .03 \)); the HR associated with a 1-SD increase in CSF urate concentration was 0.89 (95% CI, 0.79-1.02; \( P = .09 \)) (Table 5). Results were not significantly different by sex, although a strong interaction was found between \( \alpha \)-tocopherol assignment and CSF urate concentration \( (P \text{ for interaction} = .009) \) (Figure 1B). As for serum urate concentration, a significant decrease in the HRs for the primary end point with increasing CSF urate concentration was observed only among subjects not receiving \( \alpha \)-tocopherol. The HR corresponding to a 1-SD increase in CSF urate concentration was 0.77 (95% CI, 0.62-0.96; \( P = .02 \)) among men not treated with \( \alpha \)-tocopherol and 1.10 (95% CI, 0.90-1.34; \( P = .34 \)) among those receiving \( \alpha \)-tocopherol. In women, the corresponding HRs were 0.64 (95% CI, 0.40-1.03; \( P = .07 \)) for subjects not assigned to \( \alpha \)-tocopherol and 0.77 (95% CI, 0.43-1.37; \( P = .37 \)) for subjects treated with \( \alpha \)-tocopherol. No significant interaction was found between CSF urate concentration and deprenyl treatment (eTable 3).

The change in UPDRS score between baseline and either the time of reaching the primary end point or the end of follow-up was available for 702 of the 713 subjects with baseline CSF urate concentrations. Overall, the rate of UPDRS score change was not related significantly to CSF urate concentration. As observed for serum urate concentration, however, the relationship between CSF urate concentration and the rate of UPDRS score change was modified by \( \alpha \)-tocopherol treatment \( (P \text{ for interaction} = .04) \) (Figure 2B). Among subjects not treated with \( \alpha \)-tocopherol, the rate of UPDRS score change declined with increasing CSF urate concentrations \( (P \text{ for trend} = .05) \). Conversely, randomization to \( \alpha \)-tocopherol treatment appeared to lower the rate of UPDRS score change among subjects in the lowest quintile of urate concentration measured either in CSF (Figure 2B) or in serum (Figure 2A) but not among those with higher urate concentrations. No significant interaction was found between CSF urate concentration and deprenyl treatment (eTable 4).

**COMMENT**

Among subjects with early PD participating in a large randomized trial, we found that both serum and CSF urate concentrations measured at baseline were inversely related to clinical progression of PD. The internal consistency of the results across the primary and secondary end points supports their validity. These findings, like data from a similar early PD trial (the Parkinson Research Examination of CEP-1347 Trial [PRECEPT] study),13 demonstrate a robust link between blood urate concentrations and the rate of clinical progression in PD. In addition, the association of CSF urate concentration with disease progression...
strengthens the possibility that brain urate concentration (or its determinants) might protect against the neurodegeneration of PD. Taken together, these data establish urate as the first molecular predictor of clinical progression in PD and provide a rationale for investigating the possibility that a therapeutic increase of urate in patients with PD might act favorably to slow the disease course. Interestingly, the inverse relationship between urate concentration and clinical progression was not observed among patients randomized to vitamin E at a dosage of 2000 IU/d, suggesting that there may be an interaction between these antioxidants.

There is strong evidence that oxidative stress and nitrosative stress are major pathogenetic mechanisms in PD.13,22,23 Urate is an effective antioxidant,1 peroxynitrite scavenger,24-27 iron chelator,28 and ascorbate stabilizer.29 In cellular models of PD neurodegeneration, urate can reduce oxidative stress, mitochondrial dysfunction, and cell death occurring spontaneously in culture or induced by the pesticide rotenone, 1-methyl-4-phenylpyridinium, glutamate, and iron ions.30-32 Although urate appears to have the potential for neuroprotection, it is possible that the predictive association between urate concentration and PD progression reflects instead the effect of a urate precursor, such as adenosine or inosine, or another determinant of systemic and CSF urate concentrations.

As compared with serum urate concentration, the weaker association of CSF urate concentration to clinical progression of PD may seem at odds with the hypothesis that urate (or its metabolic precursors) exerts a beneficial effect through presence in the central nervous system. The CSF urate concentrations, how-

Table 3. Hazard Ratios for Death From Any Cause According to Common Quintiles of Baseline Serum Urate Concentration, Adjusted for Age, Sex, Treatment Group (Deprenyl or Placebo), and Pack-years of Smoking

<table>
<thead>
<tr>
<th>Serum Urate Concentration Quintile</th>
<th>All Subjects (n=768)</th>
<th>Men (n=504)</th>
<th>Women (n=264)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Reference)</td>
<td>1 (Reference)</td>
<td>1 (Reference)</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>2</td>
<td>1.17 (0.77-1.78)</td>
<td>0.66 (0.38-1.15)</td>
<td>1.68 (0.90-3.11)</td>
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<td>3</td>
<td>1.20 (0.78-1.83)</td>
<td>0.66 (0.38-1.12)</td>
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<td>4</td>
<td>1.11 (0.72-1.72)</td>
<td>0.60 (0.36-1.02)</td>
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<td>5</td>
<td>1.48 (0.96-2.27)</td>
<td>0.89 (0.53-1.50)</td>
<td>1.96 (0.89-4.33)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio.

Table 4. Hazard Ratios for Death From Any Cause According to Common Quintiles of Baseline Serum Urate Concentration, Adjusted for Age, Sex, Treatment Group (Deprenyl or Placebo), Pack-years of Smoking, and Cardiac Comorbidity at Baseline

<table>
<thead>
<tr>
<th>Serum Urate Concentration Quintile</th>
<th>All Subjects (n=768)</th>
<th>Men (n=504)</th>
<th>Women (n=264)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Reference)</td>
<td>1 (Reference)</td>
<td>1 (Reference)</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>2</td>
<td>1.12 (0.73-1.71)</td>
<td>0.63 (0.36-1.10)</td>
<td>1.66 (0.90-3.08)</td>
</tr>
<tr>
<td>3</td>
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<td>0.63 (0.37-1.08)</td>
<td>1.29 (0.63-2.64)</td>
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<tr>
<td>4</td>
<td>1.05 (0.68-1.62)</td>
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</tr>
<tr>
<td>5</td>
<td>1.38 (0.89-2.12)</td>
<td>0.83 (0.49-1.39)</td>
<td>1.89 (0.83-4.30)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio.

Table 5. Hazard Ratios for Reaching the Primary End Point According to Common Quintiles of Baseline Cerebrospinal Fluid Urate Concentration or Corresponding to a 1-SD Increase in Cerebrospinal Fluid Urate Concentration

<table>
<thead>
<tr>
<th>CSF Urate Concentration Quintile</th>
<th>CSF Urate Concentration, mg/dL</th>
<th>All Subjects (n=713)</th>
<th>Men (n=473)</th>
<th>Women (n=240)</th>
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<tr>
<td>1</td>
<td>&lt;=0.23</td>
<td>143</td>
<td>38</td>
<td>105</td>
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<tr>
<td>2</td>
<td>0.24-0.32</td>
<td>143</td>
<td>81</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td>0.32-0.39</td>
<td>144</td>
<td>109</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>0.39-0.50</td>
<td>142</td>
<td>117</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>&gt;=0.51</td>
<td>141</td>
<td>128</td>
<td>13</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CSF, cerebrospinal fluid; HR, hazard ratio.

A 1-SD increase indicates an increase of 0.16 mg/dL. The HRs are adjusted for age, sex, and treatment group (deprenyl or placebo).
ever, display a strong caudorostral gradient from the lumbar space, with lumbar region values approximately 50% higher than those arising at the cisterna magna (brainstem) level.\textsuperscript{33,34} Although we consistently used CSF aliquots obtained from the 18th to 20th millilitre of CSF flow, variations in CSF circulation patterns between patients\textsuperscript{35}—along with freezer storage for 20 years—may have contributed to a reduction of the accuracy of this measure compared with assays of freshly collected serum samples. In addition to technical variability, substantial biological differences between the urate in CSF sampled from the subarachnoid space and that in the degenerating neurons themselves may lessen the strength of a CSF urate concentration–clinical progression correlation in PD.

The finding that the inverse relationship between urate concentration and clinical progression of PD was modified by \(\alpha\)-tocopherol treatment was unforeseen because, as originally reported, no favorable effect of \(\alpha\)-tocopherol on PD progression was found among study participants in the DATATOP trial.\textsuperscript{16} The mechanisms for a possible interaction between urate and \(\alpha\)-tocopherol remain uncertain. Although hydrophilic (eg, urate) and hydrophobic (eg, \(\alpha\)-tocopherol) antioxidants target different subcellular compartments, their functional interactions have been described.\textsuperscript{36,37} Further, \(\alpha\)-tocopherol at doses commonly used in vitamin supplements may reduce concentrations of other endogenous antioxidants,\textsuperscript{38,39} and \(\alpha\)-tocopherol at high doses may have pro-oxidant rather than antioxidant effects.\textsuperscript{40,41} Alternatively, a simple competitive interaction or “ceiling effect” may have contributed to the observed lack of \(\alpha\)-tocopherol benefits among patients with PD with higher urate concentrations as well as to the loss of the inverse association between urate concentration and PD progression among those receiving supplemental \(\alpha\)-tocopherol. Regardless of the mechanism for a possible interaction between \(\alpha\)-tocopherol and urate, our results raise the possibility that such an interaction may have obscured a protective effect of \(\alpha\)-tocopherol among those subjects with low baseline concentrations of urate in the DATATOP trial. Further investigations are therefore needed to consider the possibility that \(\alpha\)-tocopherol supplementation may be beneficial in individuals with low urate concentrations.

Serum urate may also affect the progression of cognitive impairment in that higher concentrations seem to be associated with slower rates of cognitive decline and lower risk of dementia.\textsuperscript{42-44} As in the present study, among participants in a randomized trial, this association was observed in patients treated with placebo but not in those treated with \(\alpha\)-tocopherol.\textsuperscript{45} Higher serum urate concentration has also been linked to a lower rate of worsening in Huntington disease.\textsuperscript{46} Although each of these neurodegenerative disorders manifests differently from PD, the relationships between urate concentration and these disorders may be indicative of a more general influence of urate (or its precursors) on neuronal cell death.

The main results of this study are strikingly consistent with those recently reported from the PRECEPT study.\textsuperscript{13} Although the overall inverse relationship between serum urate concentration and the clinical progression of PD was greater in the PRECEPT study than in the DATATOP study, results among subjects in the DATATOP study not assigned to \(\alpha\)-tocopherol were virtually identical to those observed in the PRECEPT study (which did not include an \(\alpha\)-tocopherol treatment arm). In both trials, HRs for risk of disability progression showed a decline in patients whose values were higher than the median concentration but still within the normal range of serum urate concentrations. Moreover, in both trials, the concentration-dependent inverse relationship was robust in men but weak and nonsignificant among women. This consistent difference between men and women could result in part from a biological effect of sex on urate mechanisms in PD\textsuperscript{46} or could simply reflect the small number of women with urate concentrations high enough to slow disease progression if urate were protective.

A potentially therapeutic effect of elevating serum urate concentration warrants consideration. Urate levels can be elevated by dietary means, including increased intake of fructose\textsuperscript{47,48} or purines,\textsuperscript{50} or by pharmacological means. The latter may include administration of the purine metabolite and urate precursor inosine, which is being investigated as a therapy for multiple sclerosis.\textsuperscript{49,50} The potential benefit of elevating urate concentration in individuals with PD, however, has to be weighed against possible adverse effects, which may include an increased risk of hypertension, coronary heart disease, and stroke\textsuperscript{4,51,52} in addition to the known risks of gout and urolithiasis. Available data are therefore insufficient to support a therapeutic recommendation.

The discovery of a urate link to PD progression was achieved through additional analyses of 2 rigorously conducted clinical trials whose databases were made available to test an unforeseen hypothesis months\textsuperscript{53} or decades\textsuperscript{54,55} after conclusion of the primary investigations. These latent insights highlight a broader opportunity to achieve further advances through explorations of the growing repository of high-quality data collected from neuroprotection trials of PD and other neurodegenerative disorders.

**Accepted for Publication:** May 27, 2009.

**Published Online:** October 12, 2009 (doi:10.1001/archneurol.2009.247).

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Financial Disclosure: Dr LeWitt reports receiving lecture fees from Allergan, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Schwarz Pharma (now UCB), Solstice Neurosciences, and Vernalis (now Ipsen), consulting fees from Asubio Pharmaceuticals, Boehringer Ingelheim, Britania Pharmaceuticals, Eisai, Neurologix, Novartis, Orion, Prestwick Pharmaceuticals (now Biovail), Santhera Pharmaceuticals, Schering-Plough, Schwarz Pharma, Solvay, Spheres, Supernus Pharmaceuticals, Valeant Pharmaceuticals International, Vernalis, and XenoPort, and grant support from Boehringer Ingelheim, Chelsea Therapeutics, Novartis, Santhera Pharmaceuticals, Schering-Plough, and Schwarz Pharma.

Funding/Support: This work was supported by grants NS24778, NS27892, NS048517, NS054978, and NS060091 from the National Institutes of Health, by grant W81XWH-04-1-0881 from the US Department of Defense, and by the RJG Foundation, the Beeson Scholars/Hartford Collaborative Research program of the American Federation for Aging Research, and a data-mining research award from the Parkinson Disease Foundation and the Parkinson Study Group.

Role of the Sponsors: The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Additional Information: The eFigure and eTables are available at http://www.archneur.org.

Additional Contributions: Ellis O’Reilly, ScD, conducted an expert secondary review of statistical programs and reported results, Andrew McAleavy, AB, provided excellent technical assistance in preparing neurochemical analyses, and Leslie Unger, BA, provided technical assistance in preparing the manuscript.

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