Serum Urate as a Predictor of Clinical and Radiographic Progression in Parkinson Disease

Michael A. Schwarzschild, MD, PhD; Steven R. Schwid, MD; Kenneth Marek, MD; Arthur Watts, MS; Anthony E. Lang, MD; David Oakes, PhD; Ira Shoulson, MD; Alberto Ascherio, MD; and the Parkinson Study Group PRECEPT Investigators

**Objective:** To determine whether concentration of serum urate, a purine metabolite and potent antioxidant that has been linked to a reduced risk of Parkinson disease (PD), predicts prognosis in PD.

**Design:** Prospective study.

**Setting:** The Parkinson Research Examination of CEP-1347 Trial (PRECEPT) study, which investigated the effects of a potential neuroprotectant on rates of PD progression, was conducted between April 2002 and August 2005 (average follow-up time 21.4 months).

**Participants:** Eight hundred four subjects with early PD enrolled in the PRECEPT study.

**Main Outcome Measures:** The primary study end point was progression to clinical disability sufficient to warrant dopaminergic therapy. Cox proportional hazards models were used to estimate the hazard ratio (HR) of reaching end point according to quintiles of baseline serum urate concentration, adjusting for sex, age, and other potential covariates. Change in striatal uptake of iodine 123–labeled 2-beta-carbomethoxy-3-beta-(4-iodophenyl)tropane ([123I]H9252-CIT), a marker for the presynaptic dopamine transporter, was assessed with linear regression for a subset of 399 subjects.

**Results:** The adjusted HR of reaching end point declined with increasing baseline concentrations of urate; subjects in the top quintile reached the end point at only half the rate of subjects in the bottom quintile (HR, 0.51; 95% confidence interval [CI], 0.37-0.72; P for trend <.001). This association was markedly stronger in men (HR, 0.39; 95% CI, 0.26-0.60; P for trend <.001) than in women (HR, 0.77; 95% CI, 0.39-1.50; P for trend =.33). The percentage of loss in striatal [123I]β-CIT uptake also improved with increasing serum urate concentrations (overall P for trend =.002; men, P = .001; women, P = .43).

**Conclusions:** These findings identify serum urate as the first molecular factor directly linked to the progression of typical PD and suggest that targeting urate or its determinants could be an effective disease-modifying therapy in PD.

**Trial Registration:** clinicaltrials.gov Identifier: NCT00040404.

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A consequence of mutations in the urate oxidase gene early in primate evolution, urate in humans circulates at high concentrations near the limits of its solubility and constitutes the main end product of purine metabolism. Urate has an antioxidant efficacy comparable with that of ascorbate, and thus, its high level may serve as one of our major defenses against oxidative damage caused by reactive nitrogen and oxygen species. Because oxidative stress may contribute to the loss of dopaminergic neurons in the substantia nigra of individuals with Parkinson disease (PD) and to the pathophysiology of other neurodegenerative diseases, blood urate concentration could be an important determinant of disease susceptibility and progression.

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Supporting this notion, the results of prospective epidemiological studies consistently indicate that among healthy people the risk of PD declines with increasing uricemia. Whether uricemia also predicts a better prognosis in established PD has not, to our knowledge, been in-
investigated. To address this question efficiently, we sought completed, rigorously conducted clinical studies of PD progression in which prospectively determined (baseline) levels of urate were available. We identified a large randomized clinical trial entitled Parkinson Research Examination of CEP-1347 Trial (PRECEPT), which was originally designed to investigate a candidate neuroprotectant in PD using clinical and imaging assessments of neurodegeneration, as an ideal opportunity to evaluate the potential association between serum urate concentration and subsequent rates of PD progression.

METHODS

STUDY DESIGN

We conducted a longitudinal cohort investigation among participants in the PRECEPT study, a 2-year, double-blind, randomized trial of oral CEP-1347, an antiapoptotic mixed lineage kinase inhibitor that has been found to be neuroprotective in animal models of PD. The PRECEPT study was designed to determine whether this drug could slow the progression of early PD. It was carried out by the Parkinson Study Group and sponsored by Cephalon, Inc and H. Lundbeck A/S. The participants (n = 806) were enrolled between April 2002 and April 2004 at 65 sites across the United States and Canada. All participating sites obtained approval of the protocol by their institutional review boards, and all subjects gave written consent for study participation.

STUDY POPULATION

Subjects to be enrolled in the study had to have early PD (modified Hoehn and Yahr stage of ≤ 2.5 with 2 of the cardinal signs: resting tremor, bradykinesia, or rigidity), not require the use of dopaminergic therapy within 6 months prior to randomization, or an expected lifetime of study enrollment. Subjects were randomly assigned to receive placebo or 10, 25, or 50 mg of CEP-1347 twice daily. The primary end point was time to disability requiring dopaminergic therapy, determined by individual investigators masked to treatment assignment. Secondary end points included changes in the Unified Parkinson's Disease Rating Scale (UPDRS) (sum of the motor, mentation, and activity of daily living subscales, termed total in this study) score and 2-beta-carbomethoxy-3-beta-(4-iodophenyl)tropane (β-CIT) single-photon emission computed tomography (SPECT) imaging of ligand binding to striatal dopamine transporter, a marker for nigrostriatal dopaminergic nerve terminals. Because the UPDRS score was modified by the dopaminergic treatment instituted at end point, the annualized rate of change in UPDRS score was determined based on change from baseline to end point for each subject and was calculated as [(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 days/yr].

NEUROIMAGING SUBSTUDY

Single-photon emission computed tomography of iodine I 123–labeled ([123I] β-CIT uptake was used at baseline to measure striatal dopamine transporter density. Each subject in the trial imaging was carried out at the Institute for Neurodegenerative Disorders in New Haven, Connecticut, with methods as described previously. All subjects were invited to repeat the SPECT at the end of the follow-up. The 399 subjects with repeated SPECT imaging completed as of May 2005 and with baseline serum urate concentration were included in a subanalysis on the relation between baseline serum urate level and percentage of change in the ratio of the specific striatal [123I]β-CIT uptake to the nondisplaceable striatal [123I]β-CIT uptake between the 2 images. Mean interval between the 2 SPECT scans was 22 months.

STATISTICAL ANALYSIS

Cox proportional hazards models were used to estimate the hazard ratios (HRs) of reaching the end point according to quintiles of baseline serum urate concentration, adjusting for sex and age (5-year groups). Initial analyses were conducted using quintiles based on the combined urate distribution in men and women (“common quintiles”). An important advantage of using common quintiles is that the HRs in men and women estimate the effects of similar levels of serum urate. However, because of the expected higher level of urate in men, this categorization resulted in a markedly skewed distribution within sex, with most men in the top quintiles and most women in the bottom quintiles of serum urate level, and thus in a loss of power of analyses within sex. These analyses were therefore complemented by estimating HRs for sex-specific quintiles. In these analyses, the advantage of a more balanced distribution of subjects across quintiles was in part offset by the lack of comparability of the HRs; for example, in men the cutoffs for lowest and highest quintiles were less than 4.9 and more than 7.0 mg/dL vs less than 3.7 and more than 5.6 mg/dL in women. Tests for
The relation between serum urate level and rate of change in UPDRS score or percentage of change in striatal $[123$I]$\textit{I}$-catechol-o-methyltransferase (COMT) uptake was assessed by linear regression. For each of these outcomes, we fitted regression models including age, sex (for analyses including men and women combined), and either common quintiles of serum urate level or sex-specific quintiles, as outlined earlier. Because of the skewed distribution of UPDRS rates, analyses for this outcome were also conducted using Spearman correlation. All the $P$ values presented are for 2-tailed tests with levels $\leq 0.05$ defined as significant.

**RESULTS**

Serum urate concentration at baseline was available for 804 (517 men and 287 women) of the 806 subjects enrolled in the trial. Selected characteristics of these subjects are shown in **Table 1**. As expected, serum urate concentrations were positively correlated with male sex, body mass index, use of thiazide diuretics, and history of gout and hypertension (Table 1).
A significant inverse association between baseline serum urate level and rate of UPDRS score change (Spearman correlation coefficient = −0.10; P = .02). A significantly lower rate of change in UPDRS score was observed among patients in the highest as compared with those in the lowest sex-specific quintile of serum urate level (adjusted difference = 7.0; P = .02). In contrast, no significant association was found in women (Spearman r = −0.03; P = .52).

The percentage of change in striatal \([^{123}\text{I}]\beta\text{-CIT}\) uptake also declined with increasing serum urate concentrations (P for trend = .002), although the trend was largely driven by a lower percentage of change among subjects in the top quintile of serum urate level, with little or no differences between quintiles 1 through 4 (Figure 2).

Because there were only 4 women in the top quintile of serum urate level when the cutoffs for quintiles were generated from men and women combined, stratified analyses were only conducted using sex-specific quintiles. As in the end point analyses, a significant association was only seen in men (Figure 2).

**COMMENT**

In this large prospective investigation among subjects in the early stages of PD enrolled in a randomized clinical trial, we found that the rate of progression to the primary clinical end point declined with increasing levels of baseline serum urate. There was a clear dose-response relationship, with a 35% reduction in rate of progression among patients in the fourth quintile of serum urate level and a 49% reduction among those in the highest quintile, as compared with those in the lowest quintile. These associations were highly significant and corroborated by the finding that patients with a higher urate concentration also had a lower percentage of loss of striatal \([^{123}\text{I}]\beta\text{-CIT}\) uptake during the follow-up.

Strengths of this study include the longitudinal design, the measurement of serum urate level at baseline and before starting any antiparkinsonian treatment, the large number of participants, and the rigorous clinical assessment of all patients. We specifically examined the relation between serum urate level and PD progression because of the strong a priori evidence that individuals with high levels of serum urate have a
markedly reduced risk of developing PD. The convergence between the results of previous epidemiological studies and those of the present investigation is striking. Combined, these results support the continuity of the neurodegenerative process before and after the onset of the first motor symptoms that lead to the diagnosis of PD and imply that either a higher serum urate level itself is neuroprotective or it serves as an indirect marker of protection of the dopaminergic neurons that are lost in PD.

The inverse association between uricemia and PD progression could be explained if both were affected by a common factor or, in epidemiological lexicon, a confounder. In subjects without PD, the strongest correlates of serum urate level are male sex, obesity, and arterial hypertension. Further, use of thiazide diuretics is known to increase urate levels. These correlations were also found among participants in our study, suggesting that the main determinants of serum urate level are the same in individuals with or without PD. However, the relation between serum urate level and PD progression in our study was independent from these factors. Also, adjustment for cigarette smoking and use of nonsteroidal anti-inflammatory drugs, which have been related to PD risk, did not appreciably change the results. Genetic factors could also affect both serum urate level and PD progression and thus act as confounders. Heritability of serum urate level is estimated to range from 25% to 70%, and several genetic mutations that affect uricemia have been identified. Known mutations with marked effects on uricemia, however, are rare and seem unlikely to fully explain the strong inverse associations between uricemia and both PD risk and PD progression. Finally, dietary factors should also be considered. High dairy consumption has been associated with an increased risk of PD and with decreased serum urate concentration, but the latter association is weak and unlikely to account for much variation in urate levels. On the other hand, high alcohol consumption increases serum urate concentration, but in longitudinal studies, alcohol consumption was not consistently related to PD risk. Purine and fructose intakes also increase serum urate level, but these effects are modest and there is no evidence that these nutrients would affect PD risk or progression independently from their effects on uricemia. Overall, it seems therefore unlikely that the inverse relation between uricemia and PD progression is due to confounding by known factors. As in all observational studies, however, a role for unknown factors cannot be excluded.

Although several clinical features of PD (eg, prominent asymmetry, rest tremor predominance, absence of early cognitive or gait dysfunction) have been identified previously as predictors of a slower rate of clinical progression, these are complex behavioral characteristics of the disease and are thus likely to result from, rather than influence, pathogenic mechanisms. By contrast, as an antioxidant with peroxynitrite scavenging and metal chelating properties, urate is well positioned to serve as a neuroprotectant against the underlying neurodegeneration of PD. Considerable evidence from genetic as well as idiopathic forms of PD has implicated oxidative and nitrative stress as central pathogenic mechanisms. Urate at physiological concentrations is as effective an antioxidant as ascorbate. It also stabilizes ascorbate, possibly by forming complexes with iron ions, and scavenges nitrogen radicals. Further, administration of urate reduced the exacerbation of the oxidative stress and mitochondrial dysfunction in human dopaminergic cells exposed to the pesticide rotenone or to iron ions.

Alternatively, the predictive association between urate concentration and PD progression could reflect a neuroprotective effect of a urate precursor, rather than urate itself. For example, adenosine and its deaminated metabolite inosine (which is in turn deribosylated and oxidized to urate) both modulate neuronal death on their own. Adenosine may have either neuroprotective or neurotoxic effects on dopaminergic neurons via adenosine A1 and A2A receptors, respectively. Inosine has also shown potential as a neuroprotectant in models of stroke and multiple sclerosis. Whether urate, its metabolic precursors, or other determinants modulate neurodegeneration in PD, their potential is supported by lower levels of urate in cerebrospinal fluid and postmortem substantia nigra of patients with PD.

Whereas the concentration-dependent inverse relationship was robust and highly significant statistically in men, it appeared as a weak nonsignificant trend among women. This difference between men and women (also noted for the association between urate level and [18F]FET uptake neuroimaging) could result in part from a biological effect of sex on urate mechanisms in PD. Alternatively, it may reflect the substantially lower average urate concentrations in women, who account for only 16% of the subjects in the 2 uppermost quintiles in which the substantially slower rates of disease progression were observed.

That urate and its metabolic pathway are particularly amenable to existing pharmacological and dietary manipulations enhances the potential therapeutic significance of the present findings. A purine-rich diet can elevate serum urate concentration, and the purine supplement inosine, used as a potential therapy for multiple sclerosis in a phase 2 randomized clinical trial, markedly raised urate concentrations in the long-term without inducing gout or other adverse effects. It is also well known that thiazide diuretics even at low doses elevate urate concentration by reducing its renal clearance. Individuals with a higher serum urate level, however, have an increased risk of hypertension, coronary heart disease, and stroke. Although these associations may in part be confounded by obesity and other risk factors, a long-term neuroprotective effect of urate or its precursors would have to be weighed against potential adverse cardiovascular effects.

Measurement of urate on its own in patients with newly diagnosed PD as an indicator of an individual patient’s future rate of progression is likely to be of modest clinical utility. On the other hand, urate testing may aid the rational design of neuroprotective trials in PD, particularly those targeting mechanisms (antioxidant chelating or purinergic) that are potentially shared with urate. For example, coenzyme Q10, creatine, and rasagiline—potential neuroprotections targeting oxidative stress pathways in planned neuroprotec-
tion trials—might be most effective in patients with PD whose endogenous antioxidant pool (including urate) is lowest at baseline; thus, controlling for an interaction with or stratifying by urate levels at baseline may improve the power of such trials. The present discovery of a urate concentration link to PD progression was achieved through additional analyses of a rigorously conducted clinical trial whose database was made available to test unforeseen hypotheses on conclusion of the primary investigation.8 The findings thus reflect a broader opportunity to retrospectively explore a growing repository of high-quality data from neuroprotection trials for PD, Alzheimer disease, and other progressive degenerative disorders.

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Author Affiliations: MassGeneral Institute for Neurodegenerative Disease, Massachusetts General Hospital (Dr Schwarzschild), and Departments of Nutrition and Epidemiology, Harvard School of Public Health, and Channing Laboratory, Brigham and Women's Hospital and Harvard Medical School, Boston (Dr Ascherio); Departments of Neurology and Biostatistics, University of Rochester, Rochester, New York (Drs Schwid, Oakes, and Shoulson and Mr Watts); Institute for Neurodegenerative Disorders, New Haven, Connecticut (Dr Marek); and Toronto Western Hospital, Toronto, Ontario, Canada (Dr Lang). The Parkinson Study Group PRECEPT (Parkinson Research Examination of CEP-1347 Trial) Investigators and Steering Committee and their author affiliations are listed on page 721.

Correspondence: Alberto Ascherio, MD, Harvard School of Public Health, 665 Huntington Ave, Bldg 2, Boston, MA 02115 (aascherio@hsph.harvard.edu).

Author Contributions: Dr Ascherio had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Schwarzschild, Marek, Oakes, Shoulson, and Ascherio. Acquisition of data: Schwarzschild, Schwid, Marek, and Shoulson. Analysis and interpretation of data: Schwarzschild, Schwid, Marek, Watts, Lang, Oakes, Shoulson, and Ascherio. Drafting of the manuscript: Schwarzschild, Oakes, and Ascherio. Critical revision of the manuscript for important intellectual content: Schwarzschild, Schwid, Marek, Watts, Lang, Oakes, Shoulson, and Ascherio. Statistical analysis: Watts, Oakes, and Ascherio. Obtained funding: Schwarzschild, Marek, and Shoulson. Administrative, technical, and material support: Schwarzschild, Schwid, Marek, Watts, and Shoulson. Study supervision: Schwarzschild and Schwid.

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REFERENCES


