

Urate and Parkinson's Disease: A Novel Biomarker with Potential Prognostic and Therapeutic Values

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Urate is a potent antioxidant that effectively scavenges reactive nitrogen and oxygen radicals,¹ and therefore, has been thought to have a favorable role in pathogenesis of Parkinson's disease (PD). Experimental studies showed that urate reduced oxidative stress primarily through its actions as an effective scavenger of peroxynitrite (ONOO⁻) and hydroxyl radicals.^{1,2} Urate completely prevented the death of the dopaminergic cells in culture induced by homocysteine plus rotenone or by homocysteine plus iron.³ To test the hypothesis that urate is neuroprotective for PD, several epidemiologic studies have been conducted.

Prospective Studies of Serum Urate and Parkinson's Disease Risk And Progression

The first prospective study of serum urate and Parkinson's disease was published in 1996.⁴ Among ~8,000 men of Japanese ancestry in the Honolulu Heart Program, 92 incident Parkinson's disease cases were identified after 30 years follow-up. The age- and smoking-adjusted relative risk (RR) of Parkinson's disease was 0.6 (95% confidence interval (CI): 0.4, 1.0) for serum urate above vs. below the median value. A similar inverse association between urate and Parkinson's disease risk was observed in the Rotterdam Study (adjusted RR=0.71 for each standard deviation increase in urate concentration; 95% CI: 0.51, 0.98) which included 4,695 men and women and 68 incident cases of Parkinson's disease during 9.4 years of follow-up.⁵ In a recent nested case-control study (86 incident PD cases) among participants in the Health Professionals Follow-up Study (HPFS), a large ongoing cohort of US men,⁶ Weisskopf et al. found a clear dose-dependent relationship between serum urate concentration and PD risk; adjusted RR of PD comparing two extreme quartile of urate concentration was 0.43 (95% CI: 0.18, 1.02; $p_{\text{trend}} = 0.017$), after adjustment for age, smoking, and caffeine. This association was stronger in analyses excluding PD cases diagnosed within 4 years

(median) from blood collection (RR= 0.17, 95% CI: 0.04, 0.69; $p_{\text{trend}} = 0.01$). In a meta-analysis including these three prospective studies, the pooled RR of PD was 0.80 ($P < 0.001$) for a SD increase in urate (1.32 mg/dl).⁶

Serum urate concentration has also been shown to be associated with a slower PD progression, as suggested by a prospective study conducted among 804 subjects with early PD enrolled in the Parkinson Research Examination of CEP-1347 Trial (PRECEPT) study, in which progression to clinical disability sufficient to warrant dopaminergic therapy was used as primary endpoint.⁷ Likelihood of reaching end point declined with increasing baseline concentrations of urate; adjusted RR was 0.51 (95% CI: 0.37, 0.72, $P_{\text{trend}} < 0.001$) for subjects in the top quintile of urate relative to those with the lowest urate. This association was markedly stronger in men (RR, 0.39; P for trend < 0.001) than in women (RR, 0.77; P for trend = 0.33).

Gout and Parkinson's Disease

If a higher urate concentration is neuroprotective for PD, individuals with gout should be expected to have a lower risk of PD. Two prospective studies have been done to test this hypothesis. In a case-control study nested into the General Practice Research Database,⁸ a computerized database that gathers information on >3 million Britons followed by their general practitioners, Alonso et al. found that individuals with gout had a lower risk of developing PD (OR=0.69, 95% CI: 0.48, 0.99) and in a subgroup analysis, the association was observed in men (OR=0.60, 95% CI: 0.40, 0.91) but not in women (OR=1.26, 95% CI: 0.57, 2.81). We observed a similar inverse association between presence of gout and risk of developing PD (OR=0.70, 95% CI: 0.59, 0.83) in a prospective case-control study including 11,258 gout patients and 56,199 controls.⁹

Dietary Urate Index and PD Risk

A possible explanation for the association between a higher plasma urate and a lower PD risk or progression is that still unknown genetic factors could affect both. It is therefore important to establish whether variations in plasma urate that is due to exogenous factors are also related to risk of PD. To address this, we prospectively examined the relation between the uricemic potential of diet – assessed by a newly established, empirically derived dietary urate index – and risk of PD in the HPFS (n=47,407).¹⁰ The dietary urate index includes alcohol, dairy protein, fructose, and vitamin C.¹⁰⁻¹²

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After 14 years follow-up, we documented 248 incident PD cases. We found the index is significantly associated with a lower PD incidence (P for trend = 0.0008). Men in the highest urate index quintile were associated with 53% less likelihood to develop PD relative to those in the lowest quintile.¹⁰ These results support a possible neuroprotective effect of urate or its precursors in PD pathogenesis and suggest that dietary modulation of plasma urate may have a role in the prevention and treatment of PD.

In conclusion, neuroprotective effect of urate on PD has been supported by several prospective studies. Further studies are needed to clarify the causality. As most studies included only men, investigation the urate-PD relation in women should also be a priority.

References

1. Ames BN, Cathcart R, Schwiers E, Hochstein P. Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: a hypothesis. *Proc Natl Acad Sci U S A*. 1981;78:6858-6862.
2. Hooper DC, Scott GS, Zborek A, et al. Uric acid, a peroxynitrite scavenger, inhibits CNS inflammation, blood-CNS barrier permeability changes, and tissue damage in a mouse model of multiple sclerosis. *FASEB J*. 2000;14:691-698.
3. Duan W, Ladenheim B, Cutler RG, et al. Dietary folate deficiency and elevated homocysteine levels endanger dopaminergic neurons in models of Parkinson's disease. *J Neurochem*. 2002;80:101-110.
4. Davis JS, Grandinetti A, Waslien CI, et al. Observations on serum uric acid and the risk of idiopathic Parkinson's disease. *Am J Epidemiol*. 1996;144:480-484.
5. de Lau LM, Koudstaal PJ, Hofman A, Breteler MM. Serum uric acid levels and the risk of Parkinson disease. *Ann Neurol*. 2005;58:797-800.
6. Weisskopf MG, O'Reilly E, Chen H, et al. Plasma urate and risk of Parkinson's disease. *Am J Epidemiol*. 2007;166:561-567.
7. Schwarzschild MA, Schwid SR, Marek K, et al. Serum urate as a predictor of clinical and radiographic progression in Parkinson disease. *Arch Neurol*. 2008;65:716-723.
8. Alonso A, Rodriguez LA, Logroscino G, Hernan MA. Gout and risk of Parkinson disease: a prospective study. *Neurology*. 2007;69:1696-1700.
9. De Vera M, Rahman MM, Rankin J, et al. Gout and the risk of Parkinson's disease: a cohort study. *Arthritis Rheum*. 2008;59:1549-1554.
10. Gao X, Chen H, Choi HK, et al. Diet, urate, and Parkinson's disease risk in men. *Am J Epidemiol*. 2008;167:831-838.
11. Gao X, Curhan G, Forman JP, et al. Vitamin C intake and serum uric acid concentration in men. *J Rheumatol*. 2008;35:1853-1858.
12. Gao X, Qi L, Qiao N, et al. Intake of added sugar and sugar-sweetened drink and serum uric acid concentration in US men and women. *Hypertension*. 2007;50:306-312.