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# Uric Acid's Relationship with Stroke and Parkinson's Disease: A Review

*Could uric acid levels be modulated to help prevent or manage neurologic diseases? Here's what recent data show.*

In recent years, much attention has been paid to the role of uric acid in disease modification. It has been hypothesized that uric acid reduces oxidative stress on neurons. This may have a significant bearing on therapeutic management of disease, as many neurological disorders are believed to result from oxidative stress. As a potentially modifiable risk factor, the prospect for uric acid and its derivatives to play a role in disease modification or prevention has great potential.

Uric acid is primarily produced as an end product of purine metabolism. Dietary purine intake accounts for a smaller percentage of the body's total uric acid production; however, it is more commonly formed from de novo synthesis or degradation of nucleic acids. Its chemical composition consists of carbon, nitrogen, oxygen, and hydrogen with the formula  $C_5H_4N_4O_3$ . Uric acid is excreted in the urine.<sup>1</sup>

Stroke and Parkinson's Disease (PD) are two disorders that carry a correlation with uric acid. This review is designed to help clarify the relationship, if any, that exists between uric acid and these two extremely widespread disorders.

## Uric Acid and Stroke

Hyperuricemia has long been associated with cardiovascular disease, hypertension, metabolic syndrome, and renal disease.<sup>2</sup> The link between uric acid and stroke is less clear. Some authors have suggested that elevated uric acid levels are closely associated with stroke risk factors and therefore hyperuricemia is a marker in patients at high risk for stroke. Others contend that uric acid is an independent risk factor for stroke and is directly involved with the pathophysiology of cerebrovascular disease. Still others believe that the antioxidant properties of uric acid may provide some protection against ischemic damage in the brain. Currently, the role uric acid plays in cerebrovascular disease is a matter of ongoing debate.

UA can act as an antioxidant and therefore is part of the body's protective mechanism against oxygen radical induced toxicity.<sup>3</sup> Oxidants cause lipid peroxidation, which results in

the generation of reactive species, which in turn can damage cellular components including DNA, cellular membranes, and other organelles.<sup>3</sup> UA may suppress lipid peroxidation, thereby reducing oxidative damage.<sup>2,3</sup>

Theoretically, owing to its antioxidant properties, UA could be protective against oxidative and ischemic damage in the brain. Following this logic, investigators have examined the possibility of a protective relationship between hyperuricemia and stroke. Low plasma antioxidant levels have been associated with poor outcome from ischemic stroke.<sup>4</sup> Yet only one small study has confirmed the hypothetical protective effect of hyperuricemia in stroke patients. Chamorro et al. report a 12 percent increase in the odds of a good recovery from ischemic stroke for each milligram per deciliter increase of uric acid.<sup>5</sup> Based on these results the same group has suggested giving uric acid as a therapeutic agent in patients with acute stroke.<sup>6,7</sup> In contrast to these studies, several researchers have implicated uric acid as a marker for vascular disease or even a direct agent of vascular damage.

Several studies have reported increased risk of stroke in patients with elevated UA levels.<sup>8,9,10,11</sup> Hyperuricemia has also been found to predict poor outcome in patients with previous stroke.<sup>10,11,12,13</sup> These patients may be at increased risk of recurrent stroke and cardiac causes of mortality. Elevations in UA have been linked to stroke risk factors such as insulin resistance,<sup>9</sup> hypertension,<sup>2,9</sup> obesity, lipid abnormalities as well as coronary artery disease.<sup>8</sup> Even when other cardiovascular risk factors are controlled for, a significant association between stroke and hyperuricemia remains, indicating that UA levels may be an independent predictor of stroke risk and not just a marker for disease state.<sup>8,9</sup>

The mechanism by which hyperuricemia is related to atherosclerotic disease is unclear. One hypothesis is that hyperuricemia increases stroke risk through its association with stroke risk factors. Hyperuricemia may perpetuate hypertension by causing renal injury which disrupts the rennin-angiotensin sys-

tem.<sup>10</sup> It is also linked to insulin resistance/metabolic syndrome,<sup>14</sup> and low HDL cholesterol levels.<sup>10</sup>

Direct effects of UA on vascular physiology have also been explored. Elevated UA levels are associated with increased arterial stiffness, endothelial dysfunction and blunted vasodilatory response.<sup>15</sup> UA may contribute to endothelial dysfunction by promoting LDL-C oxidation, stimulating granulocyte adherence and promoting macrophage infiltration of the vascular wall.<sup>10,16</sup> Although UA is typically an anti-oxidant some authors have suggested that it can take on pro-oxidant properties under certain conditions.<sup>17</sup> Oxidative damage is known to take part in cerebral ischemia and increase infarct size.

### Uric Acid and Parkinson's Disease

PD is the second most common age related neurodegenerative condition in the US, affecting approximately one percent of the population over the age of 65 in North America and Europe.<sup>18</sup> The symptoms of PD are characterized by loss of dopaminergic neurons in the substantia nigra. While the cause of this loss is thought to be multifactorial, there is evidence to support oxidative stress as a factor in neurodegeneration.<sup>19</sup> As discussed above, hyperuricemia is associated with antioxidant effects.<sup>3</sup> Many researchers have proposed that elevated levels of uric acid yield a protective effect against the development and progression of PD on the basis of these principles.<sup>23-25, 27</sup> In addition, it has been suggested that a diet rich in purines may play a role in prevention of PD.<sup>20</sup> At this point in time we can only note that there is an association between PD and uric acid. Whether this is a cause or an effect of the disease remains to be proven.

There have been several studies supporting the hypothesis that elevated levels of uric acid are associated with a decreased incidence of idiopathic PD.<sup>21,22</sup> In 1996, Davis et al. reported data from the Honolulu Heart Program suggesting that men with uric acid levels above the median level had a 40 percent reduction in the incidence of idiopathic PD. The Honolulu Heart Program was a prospective study that followed men of 8006 Japanese or Okinawan men for 30 years. The reduction in IPD was only marginally statistically significant (RR=0.6, CI: 0.4-1.0); however, this was one of the first large studies showing a clear relationship between uric acid levels and IPD.<sup>21</sup>

In a prospective study of 18,000 men in the Health Professionals Follow-up Study, Weisskopf et al. examined the relationship between uric acid levels and PD. In this study, a statistically significant association was seen between uric acid levels drawn four years prior to the diagnosis of PD and incidence of IPD. The men in the top quartile of plasma urate concentration had a 55 percent lower rate of PD than did men in the bottom quartile, and the decrease in rate of IPD was greater once the data was modified to include only men with blood collected at least four years prior to the diagnosis. This modification of the data

suggested that the decreased levels of uric acid seen in PD patients occurs prior to neurological symptoms and is unlikely a side effect of behavior changes or medication.<sup>22</sup>

Following the results of these studies, several authors looked at the relationship between gout, a clear hyperuricemic state, and PD. In 2007, Alonso et al. utilized the General Practice Research Database, where they identified 1,052 cases of PD and 6,634 matched controls. They found that patients with a prior diagnosis of gout had a 30 percent reduction in the incidence of PD. This association was significant in men, but not in women.<sup>23</sup> Approximately one year later, de Vera et al. reported similar results using the British Columbia Linked Health Database and PharmaCare data. In this study the authors identified 11,258 gout patients and 56,199 controls and estimated the relative risk of PD among patients with gout. They found a 30 percent reduction in the risk of PD among individuals with gout. Subgroup analysis did show that the lower rate of PD existed in both men and women.<sup>24</sup>

Taking the relationship of elevated serum urate levels and PD one step further, in 2007, Gao et al. examined the relationship between diets high in urate and the incidence of PD. They used 47,406 men from the Health Professionals Study, and calculated a dietary urate index for all participants. The authors used 14 years of follow up data and documented 248 incident cases of PD. They found that a higher dietary urate index was associated with a lower risk of PD. A greater than twofold reduction in risk of PD was seen between the highest and lowest quintiles of dietary urate. Ingredients such as fructose and ethanol were found to be associated with an increased rate of gout, and led to a higher dietary urate index. Vitamin C was also found to be associated with both a lower incidence of PD and gout, which was the only hypouricemic food to be associated with a lower incidence of PD. Other antiuricemic foods such as dairy proteins were not found to be significant.<sup>20</sup>

Most recently, Schwarzschild et al. used data from the Parkinson's Research Examination of CEP-1347 (PRECEPT) study to assess the relationship between levels of serum urate and the progression of PD, both clinically and radiographically by single photon emission computed tomography (SPECT). In this study, the authors followed 804 subjects with a diagnosis of early PD, prior to dopaminergic therapy. Baseline uric acid levels were used, and the endpoint signifying rate of progression was initiation of dopaminergic therapy. There was a 49 percent reduction in rate of progression among those in the highest quintile of uric acid as compared with those in the lowest quintile, and a 35 percent reduction in the rate among those in the fourth quintile as compared with the lowest quintile. Compared to the lowest quintile, there were 35 percent and 49 percent reductions in rate of progression in the 4th and 5th quintiles respectively. In addition, patients with a higher initial

urate concentration had a lower percentage loss of striatal uptake of iodine I 123-labeled B-CIT by (SPECT) imaging. When subgroup analysis was completed, the rate of change in Unified Parkinson's Disease Rating Scale (UPDRS) was inversely associated with urate concentrations in men while this relationship was not significant in women.

Overall, recent research supports an inverse relationship between serum urate levels and the incidence of PD in men. There is also evidence to support the association between high dietary urate and a decreased incidence of PD. It should be noted that there are numerous risks associated with hyperuricemic diets, such as gout, stroke and hypertension. At this point, the data we have suggests an association, but not a causal relationship between low serum urate and the incidence of PD. This association is intriguing as there is the potential that in the future physicians could modify a patient's risk for PD by suggesting dietary changes or using pharmacological supplement. More research must be done before we can translate this information into treatment plans. It is still debatable whether the association is causal in nature or a side effect of behavioral changes or an effect of the disease itself. However, the current data has certainly given many clues as to the many factors that play a role in the development and progression of Parkinson's disease.

UA was once thought to be an inert substance with minimal physiological impact. It has become increasingly clear that UA is part of a complex network of factors that may influence risk for diseases such as cardiovascular disease, stroke, inflammatory states and even neurodegenerative conditions. Future work will likely concentrate on the utility of manipulating UA levels in attempts to modify disease. PN

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