Uric Acid: A Biomarker to Predict Clinical Progression of Parkinson Disease

Whitni Friberg
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Abstract
Background: Parkinson disease (PD) is a prevalent progressive neurodegenerative disorder, affecting millions. Research continues to evolve and the medical community continues to gain knowledge surrounding the complex mechanism and pathophysiology of depletion of dopamine neurons in the substantia nigra. Researchers continue to search for new links and possible disease-modifying therapies, as treatment options for PD are primarily symptomatic. Serum uric acid, a powerful antioxidant, has been associated with a decreased risk of Parkinson disease at elevated levels in several studies, indicating a possible neuroprotective effect. Two prospective observational cohort studies established an inverse association between clinical progression of PD and urate levels, with a slower progression noted with elevated UA levels. This systematic review will examine whether uric acid levels can predict the clinical progression of Parkinson disease.

Methods: An exhaustive search of literature databases was conducted using Medline-OVID, CINAHL, EBMR Multifile, and Web of Science, using the following keywords: Parkinson disease, uric acid, and disease progression. Relevant articles were included if they were primary research evaluating uric acid levels predicting progression of Parkinson disease. Each article was evaluated for quality using GRADE criteria.

Results: Five articles met inclusion criteria, with two studies excluded due to being secondary analyses and to utilize the most current research. The three studies included in this systematic review are case-controlled observational studies that compared serum uric acid levels with disease progression. All studies showed an association between serum uric acid levels and disease progression of PD, with elevated levels being more favorable with a slower rate of decline.

Conclusion: The results of this systematic review demonstrate the association between serum urate and the rate of PD progression, supporting future studies exploring potential disease-modifying therapy, and evaluating long-term risks of elevated serum urate levels.

Degree Type
Capstone Project

Degree Name
Master of Science in Physician Assistant Studies

First Advisor
Anjanette Sommers, PA-C, MS

Keywords
parkinson disease, uric acid, urate, disease progression

Subject Categories
Medicine and Health Sciences

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Uric Acid: A Biomarker to Predict Clinical Progression of Parkinson disease

Whitni Friberg

A Clinical Graduate Project Submitted to the Faculty of the
School of Physician Assistant Studies
Pacific University
Hillsboro, OR
For the Masters of Science Degree, August 8, 2015

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Biography

Whitni Friberg is a native of Washington state. She graduated in 2008 from Western Washington University, receiving a Bachelor of Science degree in Cellular Molecular Biology. While at WWU, she worked as a research assistant in a biology research lab. Prior to PA school she worked as a certified nursing assistant, phlebotomist and volunteered at a local hospital in Vancouver, WA.
Abstract

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Keywords: Parkinson disease, uric acid, urate, disease progression
Acknowledgements

[Redacted for privacy]
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**List of Abbreviations**

BMI........................................................................................................................Body mass index  
CSF..........................................................................................................................Cerebrospinal fluid  
DATATOP............................................................Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism  
H&Y.....................................................................................................................Hoehn and Yahr Staging  
HDL....................................................................................................................High density lipoprotein  
L-dopa....................................................................................................................Levodopa  
LDL.......................................................................................................................Low density lipoprotein  
NSAID..................................................................................................................Non-steroidal anti-inflammatory drug  
PD............................................................................................................................Parkinson disease  
PON-1....................................................................................................................Paroxonase-1  
PRECEPT..............................................................Parkinson Research Examination of CEP-1347 Trial  
RCT.......................................................................................................................Randomized control trial  
Rs.........................................................................................................................Spearmans rank  
SCr.........................................................................................................................Serum creatinine  
TC............................................................................................................................Total cholesterol  
TG..............................................................................................................................Triglyceride  
UA............................................................................................................................Uric Acid  
UKPD.....................................................................................................................United Kingdom Parkinson Disease  
UPDRS....................................................................................................................Unified Parkinson Disease Rating Scale
Uric acid: a Biomarker to Predict Clinical Progression of Parkinson disease

BACKGROUND

Parkinson disease (PD) is the second most common neurodegenerative disorder, with the prevalence estimated to be 1% of the population over 60 years of age.\textsuperscript{1,2} PD leads to a progressive depletion of dopaminergic neurons in the basal ganglia, particularly in the substantia nigra, affecting motor control. The prevalence of people with PD over age 50 in 10 of the most populous countries was between 4.1 and 4.6 million in 2005, with an estimated projected increase between 8.7 and 9.3 million by 2030.\textsuperscript{3} Many studies also suggest the disease to be more common in men than women. The male predominance has been hypothesized to be due to head trauma, more common in males, neuroprotection from estrogen in females, pesticide exposure in agriculture jobs often held by males, or genetic influences of X linked genes expressed in the substantia nigra.\textsuperscript{2,4}

The key clinical features of a decrease in dopamine include: bradykinesia, resting tremor, rigidity, and impaired gait. Parkinson disease can also cause depression, anxiety, stress intolerance, and impaired cognition. No cure exists for Parkinson disease, but medications can provide symptom relief for patients. Levodopa (L-dopa), dopamine agonists, MAO-B inhibitors, and anticholinergic medications are most commonly used to treat the symptoms caused by PD. Clinical trials of new medications are focusing on neuroprotective or disease modifying therapies.\textsuperscript{5}

Diagnosis and progression of Parkinson disease is based on clinical impression of symptoms, neurologic physical examination, and patient response to dopaminergic medication. Currently there is no laboratory or imaging method to confirm diagnosis. Staging and
The etiology of PD still remains largely unknown, with the general consensus involving both genetic and environmental factors. Various hypotheses have explored the pathophysiology mechanism of neurodegeneration, including: genetic factors, mitochondrial dysfunction, protein processing abnormalities, oxidative stress, inflammation, and environmental factors.\textsuperscript{2,15} Exposure to pesticides, tobacco, coffee, alcohol, variation in diet, hormones, uric acid, and susceptible genes have all been associated with PD.\textsuperscript{2} Oxidative stress from excess free radicals and peroxides damage cells, a mechanism involved in aging and many disease processes. In autopsies of patients with PD, oxidative damage to lipids, proteins, and DNA in the substantia nigra was discovered and supports the evidence of oxidative stress contributing to the mechanism of PD.\textsuperscript{16} Clinical trials\textsuperscript{5} using antioxidants, which are substances that inhibit oxidation and help scavenge free radicals, have shown mixed results. Two antioxidants were examined in the DATATOP trial\textsuperscript{17} in 1989, with $\alpha$-tocopherol (vitamin E) showing no benefit,
however a MAO-B inhibitor, deprenyl (selegiline) showed a delay in requiring L-dopa to help control motor symptoms.

One antioxidant, urate or uric acid, has shown promise in decreasing the risk of PD in several studies.\textsuperscript{18-20} Uric acid (UA) is an end product of purine metabolism and has been shown to be a potent antioxidant by scavenging hydroxyl radicals and singlet oxygen, thereby decreasing oxidative stress.\textsuperscript{21} One study\textsuperscript{22} showed a decrease in both urate levels by 54\% and dopamine levels by 85\% in post-mortem substantia nigra tissue from patients with PD. This evidence supports the hypothesis that oxidative stress makes dopamine neurons more susceptible to degeneration, particularly in a low urate environment.\textsuperscript{23} Much still remains unknown about the link between PD and uric acid, and whether low uric acid is causative of PD or a consequence of the disease.

Several studies\textsuperscript{18-20,24,25} have shown a decreased risk of developing Parkinson disease with elevated levels of uric acid, although this relationship may be weak or even non-existant for women as data differed in two studies\textsuperscript{18,25}. Similarly a history of gout or hyperuricemia has been associated with a decline in risk of PD, with results still inconclusive for women.\textsuperscript{26,27} After this association between risk of PD and urate levels was established, two groups conducted prospective observational cohort studies\textsuperscript{10,14} using participants enrolled in larger randomized control trials (RCTs). Both studies\textsuperscript{10,14} showed similar results with the overall trend showing a decrease in the progression of Parkinson disease with patients that have higher levels of uric acid. In the Schwarzschild et al study\textsuperscript{14}, subjects in the highest serum urate quintile reached the primary clinical endpoint at half of the rate of the lowest serum urate quintile (HR=0.51; 95\% CI: 0.37 to 0.72; p=0.0002). Ascherio et al\textsuperscript{10} demonstrated a 36\% reduction in reaching the primary endpoint of requiring levodopa therapy (HR=0.64; 95\% CI 0.44 to 0.94; p=0.002),
compared to the lowest serum urate quintile. While there are several limitations with secondary analyses, both were able to test an unforeseen hypothesis to help lay the groundwork in suggesting an inverse correlation between serum UA levels and disease of progression of PD.

The focus of this systematic review is to examine recent studies involving serum urate levels and clinical progression, a link made possible by the results shown in two prospective observational cohort studies\textsuperscript{10,14} first pointing to a trend of slowed PD progression with elevated UA levels. With the majority of research pointing to an association between uric acid levels and Parkinson disease, the next clinical question is: can uric acid levels predict the progression of Parkinson disease?

**METHODS**

An exhaustive search of available literature databases was conducted using Medline-OVID, CINAHL, EBMR Multifile, and Web of Science. Keywords used included: Parkinson disease, uric acid, and disease progression. Eligibility criteria included studies which were primary research articles evaluating uric acid levels predicting clinical progression of Parkinson disease, conducted on humans, and in the English language. References of studies and other related articles were searched for further sources. The included articles were evaluated for quality using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE).\textsuperscript{32}

**RESULTS**

The initial results of the search yielded 60 articles for review. Three articles met eligibility criteria. Two prospective observational cohort studies\textsuperscript{10,14} were excluded from this
systematic review, due to being secondary analyses. This allows for focus on the most current data. These two excluded articles, \(^{10,14}\) as previously discussed, did however show significant results to help establish this association. Three case controlled observational studies\(^{11-13}\) were evaluated for quality and included in this systematic review. See table 1 for GRADE analysis. Summary of findings are presented in Tables II-IV.

**Andreadou et al**

In 2009, Andreadou et al\(^{11}\) conducted a case-controlled observational study examining the relationship between serum UA levels of 43 PD patients and 47 age and gender matched controls. The outcomes assessed in the study included: H&Y stage, disease duration in months, UPDRS part III score, and daily dose of levodopa. Enrollment criteria for patients with PD was diagnosis based on the UKPD Society Brain Bank, \(^{33}\) with exclusion criteria being the use of uric acid lowering agents or diuretic use. Controls were selected if they were healthy, excluded if they had a family history of PD or an abnormal neurologic exam.\(^{11}\)

Participants in the PD group were separated into subgroups of those treated with anti-PD medication (n=22) and those untreated (n=21); all were assess using H&Y stage scale and UPDRS part III to determine disease progression. All participants enrolled in the study underwent a controlled diet for 5 days prior to collection of blood samples. No follow up was conducted, as observations were made from group data, not individual progression of PD.\(^{11}\)

Lower serum UA levels were found in the PD group, both treated and untreated, compared to the control group (p=0.009). This finding was slightly less significant when analysis was separated into each sex, however it still remained significant for both men and women. Possible confounders were analyzed showing only significance in gender contributing to serum UA levels, but no significance in age or BMI.\(^{11}\)
The Andreadou et al study demonstrated Hoehn & Yahr stages inversely associated with serum urate levels, with higher serum UA in stage 2, compared to stage 2.5 (p=0.01), and stage 3 (p=0.003). Interestingly, they did not find a significant effect of UPDRS scores and serum UA concentrations for either men or women (All PD patients p=0.15; men Rs= 0.078, p=0.73; women Rs= 0.109, p=0.637). Serum UA concentrations were noted to be inversely correlated for both disease duration and daily levodopa dose in both men and women (Table IV shows All PD patients Rs= -0.397, p=0.009; men Rs= -0.441, p=0.04; women Rs= -0.221, p=0.337) and daily levodopa dose (All PD patients: Rp= -0.498, p=0.026; Men Rs= -0.717, p=0.03; women Rs= -0.17, p=0.966).11

The authors concluded that the relationship between urate and PD should be further explored with altering serum UA levels in future clinical trials, in hopes that increasing urate levels will have a neuroprotective effect. They also discuss future research to clarify conflicting data differences between men and women, theorizing PD pathophysiology, diet preferences, age onset, and hormonal influence on serum UA levels may be contributing to variations between men and women. Small sample size was the limitation mentioned by the investigators, possibly negatively influencing precision of data.11

Ikeda et al

Ikeda et al12 conducted an observational cohort study in 2011 comparing urate, paroxonase-1 (PON1), iron, ferritin, and lipid serum levels in Japanese PD patients and controls. The study12 enrolled a total of 119 patients with PD (n=56 men, n=63 women), diagnosed using the UKPD Society Brain Bank criteria.33 Disease progression was evaluated by Hoehn and Yahr stage and disease duration. Controls were matched to the PD group based on sex, age, and BMI. Exclusion criteria included: support with ambulation, use of diuretics, urate- or cholesterol-
lowering medications, iron supplementation, or the presence of gastrectomy or gastrostomy, requiring tube feedings. Samples analyzed were drawn from fasting study participants, measuring total cholesterol (TC), triglyceride (TG), HDL cholesterol (HDL-C), serum iron, serum ferritin, and paraoxon. LDL cholesterol (LDL-C) was calculated by using the Friedewald formula (LDL-C (mg/dl)=TC (mg/dl) – HDL-C (mg/dl) – 0.2 X TG (mg/dl)). No follow up was discussed in this study. The PON1 levels were measured indirectly by using a paraoxon serum measurement, calculating the paraoxonase activity. Paraoxonase-1 is a type of high-density lipoprotein (HDL) bound enzymes that has shown to have antioxidant effects.12

Serum levels of TC, LDL-C, urate, and PON1 activity were substantially decreased in both female and male PD patients (p<0.01), compared to their matched controls. An increase in serum ferritin levels were noted in both male and female patients, compared to controls (p<0.05). No significance difference resulted in comparison of HDL-C and TG levels of PD patients and controls.12

Results for serum urate demonstrated a decrease in disease progression measured by Yahr stage (Men: Rs=-0.38, p<0.01; Women Rs= -0.36, p<0.01) and disease duration in years (Men: Rs= -0.39, p<0.01; Women: Rs= -0.30, p<0.05) for both men and women, respectively. The authors also discovered a similar inverse relationship between serum PON1 activity and both Yahr stage and PD duration in both genders. The authors did not discover any relationships between the patient daily dose of L-dopa and the serological data.12

The investigators found limitations in this study, with lack of prospective study design and lack of diet control methodology of participants. They discussed the link they found between the serological data collected, and disease progression of PD, suggesting the use of these biomarkers to monitor disease progression.12
Sun et al

In this observational cohort study performed in 2012, Sun et al researched serum UA levels in Chinese patients with PD, compared to age and gender matched controls. The investigators assessed PD progression by two outcomes of disease duration and H&Y staging. They also measured the concentration of serum creatinine to exclude the possibility that renal excretion of SCr affects serum UA levels.

A total of 411 patients diagnosed with PD at the First Affiliated Hospital of Sun Yat-sen University in China, were enrolled in this study. Diagnosis was in concordance with the clinical criteria of the UKPD Society Brain Bank and assessed clinically based on the Hoehn and Yahr staging scale. Age and gender matched controls were excluded if they had a history of chronic disease, used medications possibly affecting serum uric acid levels, history of smoking or alcohol consumption, family history of PD, or if they had an abnormal neurologic exam. The authors divided the PD group into H&Y stage subgroups, early stage (H&Y 1.0-1.5), middle stage (H&Y 2.0-2.5), and late stage (H&Y ≥3.0). No medications used were discussed in any PD group. Diet was controlled and managed for two weeks prior to samples being drawn. Two fasting blood sample were drawn two weeks apart, with diet managed for two weeks prior to the study. Since the authors did not find much difference between the values of the two draws, the average value was used in statistical analysis. No follow up was discussed in this study, thus progression was not observed to change over time.

Hoehn & Yahr stages were inversely associated with serum uric acid levels, with p values significant for both male and female respectively (male Rs= -0.360, p<0.01; female Rs= -0.516, p<0.01). Likewise results of disease duration demonstrated an inverse correlation between serum UA levels for both sexes (male Rs= -0.290, p<0.01; female Rs= -0.272, p<0.01). Comparison of
serum creatinine (SCr) concentrations between the control group and PD group exhibited no significant difference, however both serum UA and SCr were lower in women than men in both groups. Subgroups analyzed resulted in late stage PD with significantly lower UA levels compared to both middle and early stage groups (p<0.01).13

Sun et al13 investigators verified results of lower serum UA levels in PD patients among a Chinese population. They discussed the inverse association of serum urate levels with both disease duration and H&Y staging scale, which suggest a neuroprotective role of serum UA. Limitations considered by the authors included: not using UPDRS scores and not exploring possible interactions between dopaminergic therapy and serum UA, both of which would strengthen the observations of this study. They suggest the results point to a potential therapy application of increasing serum UA, since it is suggested that low serum UA levels may both increase risk of PD and possibly acceleration of disease progression.13

**DISCUSSION**

Measuring serum urate levels in patients with Parkinson disease may be used in the future to determine the progression of the disease. The majority of research may point to an association between elevated serum urate levels and a slower rate of PD progression, as seen in the three studies included in this systematic review.11-13 The result summaries presented in Tables II-IV justify the continuation of research in this field to understand the significance between uric acid and PD. Currently there is not enough quality data to suggest using serum UA levels in the clinical setting. Higher quality studies are needed to further demonstrate this association and to determine how urate can be used as a biomarker for the progression of PD. The results from these three studies, 11-13 and the two larger prospective cohort studies10,14 do warrant a future clinical trial using urate as a potential neuroprotective or disease-modifying medication. Much
still remains unknown regarding the mechanism of dopamine neuron degeneration in PD; therefore when a correlation is discovered, it is the duty of the research community to further investigate.

Overall all three studies\textsuperscript{11-13} demonstrated an inverse relationship between uric acid levels and disease duration; the longer a patient has had PD, the lower the levels of serum urate. Two studies found this association to be significant in both men (p<0.01 and p<0.01) and women (p<0.05 and p<0.01) respectively.\textsuperscript{12,13} Andreadou et al did not find a significant correlation with women (p=0.0337), but did with men (p=0.04); however this data is limited due to the low number of study participants.\textsuperscript{11} The Hoehn and Yahr stage correlated to serum UA levels in both Ikeda et al and Sun et al studies, for both men and women.\textsuperscript{12} The third study demonstrated that H&Y stage 2 had a higher mean serum UA level compared to stage 2.5 (p=0.001), and compared to stage 3 (p=0.003).\textsuperscript{11} This study did not present their data with spearman coefficients and did not gender stratify H&Y outcome results to distinguish any differences between men and women.\textsuperscript{11} The outcome of change in UPDRS score was only used in one of the included studies, and was not significantly affected by serum UA levels (R_s=0.078, p=0.73 for male and R_s=0.109, p=0.637 for female).\textsuperscript{11} The studies Sun et al and Ikeda et al would both have a higher quality of data if they would have also used the comprehensive UPDRS scale of motor and non-motor findings, as a measure of disease progression.\textsuperscript{12,13}

One of the inherent challenges of studying PD progression and designing a study, lie in the fact that diagnosis and staging are largely a subjective determination by clinicians. No standard exists clinically or in research to measure disease progression or staging. This inconsistency was demonstrated in the studies included in this systematic review, as each differed in methodology of determining PD progression and clinical outcomes. All three of the
studies\textsuperscript{11-13} included showed methodological weakness through subjective measurement of disease duration, resulting in a quality downgrade to “very low”, as shown in Table I. This supports the potential for detection bias, with variations in clinical judgment of diagnosis of Parkinson disease to measure how long a participant has had the disease. A tremor may initially be misdiagnosed as essential tremor, making it possible that patients are not diagnosed with PD the same time of symptom onset. Using H\&Y scale and change in UPDRS scale are more objective measures of PD progression. Sun et al discussed using the UPDRS scale would have increased the quality of data, by using a more comprehensive measure of both motor and non-motor findings in PD.\textsuperscript{13} A higher level of credibility would be given if investigators described in the methodology how clinicians made the determination of clinical endpoints. A standard for diagnosis and following progression should be established for clinical trials and in the clinical setting, particularly for more subjective outcomes.

Another major limitation resulting in downgrading of two studies was small sample size, leading to possible imprecision of results and overestimate of the significance of findings.\textsuperscript{11,12} Serum urate levels were compared to a point in time of a patient’s clinical stage for all three studies,\textsuperscript{11-13} compiling data with no follow up completed. In future studies it would be beneficial to follow disease progression over time to determine if an individual’s rate of progression corresponds to serum urate levels.

Other limitations that do not necessarily warrant quality downgrading, but must be taken into consideration are possible confounding factors. Diet, age, gender, levodopa dose, BMI, serum creatinine levels, and other medications have the potential to influence serum urate levels. Two studies\textsuperscript{11,13} included in the systematic review controlled diet prior to sample collection; however, one study\textsuperscript{12} did not control diet or obtain self-reported information about diet for PD
patients or controls. Sun et al did not evaluate dose of dopaminergic medication and its effect on serum UA.\textsuperscript{13} One research study\textsuperscript{34} showed a significant association between the daily dose of levodopa and urine uric acid levels; another study\textsuperscript{11} found this correlation only to be found in men.

Lower mean levels of serum urate have been associated in women, compared to men. Research has continued to show conflicting associations between urate and PD progression of men and women, which several study results demonstrate significant for men only.\textsuperscript{10,11,14} There are many suggested theories for this gender difference, small study population of women in studies,\textsuperscript{10,14} lower percentage of women represented in higher serum urate quintiles,\textsuperscript{10} biological effect of gender on disease, and estrogen influencing renal excretion of urate.\textsuperscript{35} Much remains unknown regarding the mechanism of dopamine neuron degeneration in PD, the complexity increasing with possible differences in gender. Future studies are needed to clarify the difference in gender and its potential application to variations in treatment therapy between male and female patients with PD.

The next step to assess the relationship between uric acid and PD is to conduct a larger scale, long-term, randomized control trial using urate as a therapy to increase serum urate levels and to assess the impact on progression of Parkinson disease. With observational studies it is challenging to perform blinding, especially with studying disease progression, thus using an RCT would provide higher quality of evidence. Future studies should use subgroups of PD patients treated with levodopa and untreated, stratifying results by gender, and evaluating progression with UPDRS scale, H\&Y scale, daily dose of levodopa, and in untreated patients measuring time until the participant reaches disability sufficient enough to begin levodopa therapy. A study\textsuperscript{36} has already been performed to evaluate the safety of increasing serum urate levels, which is the first
step required before a large scale RCT was conducted. Some research shows evidence for increased cardiovascular events and other adverse effects of elevated urate levels.\textsuperscript{30-32} A long-term study is necessary to determine if benefits from the medication would outweigh any increased cardiovascular risks that may result.\textsuperscript{28-30}

In 2014 the Parkinson Study Group SURE-PD published data from the randomized control trial\textsuperscript{36} of 75 participants, investigating the safety, tolerability, and efficacy of inosine, a urate precursor, to elevate serum and CSF urate concentrations. Results showed that serious side effects, such as cardiovascular events are lower or similar in the inosine group compared to placebo. Three patients experienced urolithiasis, one confirmed uric acid stone and no participant experienced gout while using the medication. No adverse event resulted in participant withdrawal and at 6 months of therapy, 95\% of participants tolerated inosine. Inosine was efficacious at elevating serum urate levels, 2.3 and 3.0mg/dL respectively in both inosine groups (p<0.01) vs the placebo group. CSF was also higher in the both inosine groups (p=.006 and p<0.001) than placebo, indicating inosine crosses the blood brain barrier. This study performed a primary analysis with findings supporting use of inosine as a possible disease-modifying agent, hopeful in slowing the progression of PD.\textsuperscript{36}

\textbf{CONCLUSION}

There still is not enough high quality data available to support clinicians measuring serum UA levels routinely among patients with Parkinson disease to determine progression or diagnosis. All three studies showed an inverse association between serum urate and rate of clinical progression of Parkinson disease, differing primarily in outcomes measuring disease progression and significance of findings with gender. Although the prospective cohort studies
that helped establish this correlation between PD progression and urate were of higher quality due to their larger size, the three studies echoed their results and support future research. The evidence found in studies measuring serum UA levels and PD progression in this systematic review, along with the recent Parkinson Study Group SURE PD trial, warrant a future clinical trial using inosine as a possible disease-modifying treatment. Long-term use of elevated serum urate levels must determine if a potential benefit is worth any adverse events.

While future research is required, the trend continues toward urate being a promising treatment option, possibly slowing the rate of decline in PD, and may be considered a biomarker for the progression and management of the disease. With so many unknown factors contributing to Parkinson disease, the hope and goal of the medical community is to one day discover treatment options to delay the progression of the disease.
References


Table I. GRADE assessment

<table>
<thead>
<tr>
<th>Quality Assessment</th>
<th>Downgrade Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Outcome</td>
</tr>
<tr>
<td>Andreadou et al</td>
<td>Observational</td>
</tr>
<tr>
<td></td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>Ikeda et al</td>
<td>Observational</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Sun et al</td>
<td>Observational</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a: subjective determination of disease duration (possible detection bias)
b: small sample size

Table II. Summary of findings Andreadou et al\textsuperscript{11}

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Correlation to serum UA levels</th>
<th>Men (n=22)</th>
<th>Women (n=21)</th>
<th>Total PD (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease Duration (months)</td>
<td>Spearman coefficient (Rs)</td>
<td>-0.441</td>
<td>-0.221</td>
<td>-0.397</td>
</tr>
<tr>
<td></td>
<td>P value</td>
<td>0.04</td>
<td>0.337</td>
<td>0.009</td>
</tr>
<tr>
<td>Daily levodopa dose (mg)</td>
<td>Spearman coefficient (Rs)</td>
<td>-0.717</td>
<td>-0.17</td>
<td>R_p = -0.498</td>
</tr>
<tr>
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<td>P value</td>
<td>0.03</td>
<td>0.966</td>
<td>0.026</td>
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</table>

Table III. Summary of finding Ikeda et al\textsuperscript{12}

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Correlation to serum UA levels</th>
<th>Men (n=56)</th>
<th>Women (n=63)</th>
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</thead>
<tbody>
<tr>
<td>H&amp;Y Stage</td>
<td>Spearman coefficient (Rs)</td>
<td>-0.38</td>
<td>-0.36</td>
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<td></td>
<td>P value</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
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<tr>
<td>Disease Duration (years)</td>
<td>Spearman coefficient (Rs)</td>
<td>-0.39</td>
<td>-0.30</td>
</tr>
<tr>
<td></td>
<td>P value</td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
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</table>

Table IV. Summary of findings Sun et al\textsuperscript{13}

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Correlation to serum UA levels</th>
<th>Men (n=207)</th>
<th>Women (n=204)</th>
<th>Total (n=411)</th>
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</thead>
<tbody>
<tr>
<td>H&amp;Y Stage</td>
<td>Spearman coefficient (Rs)</td>
<td>-0.360</td>
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<tr>
<td>Disease Duration (years)</td>
<td>Spearman coefficient (Rs)</td>
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<td>P value</td>
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<td>&lt;0.01</td>
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