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Low uric acid levels in patients with Parkinson's disease: evidence from meta-analysis

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ABSTRACT

Objective: The association between Parkinson's disease (PD) and uric acid levels has gained intensive interest in recent years. We applied meta-analysis to investigate serum uric acid levels in patients with PD in comparison with healthy controls.

Design: We searched three electronic databases and reference lists up to January 2013. Two collaborators reviewed all the articles and data disagreement was resolved through discussion. Six studies met the eligibility criteria and were included in the meta-analysis of uric acid levels in patients with PD in comparison with controls.

Participants: 1217 patients with PD and 1276 matched healthy controls.

Results: The meta-analysis results showed that patients with PD had lower levels of uric acid than healthy controls (summary standardised mean difference (SMD)=−0.52, 95% CI (−0.72 to −0.31)). Further gender subgroup analysis (summary SMD=−0.56, 95% CI (−0.72 to −0.41) for women; summary SMD=−0.62, 95% CI (−0.94 to −0.31) for men) indicated lower uric acid levels in patients with PD than healthy controls in women and men.

Conclusions: It was found that patients with PD had lower serum levels of uric acid than healthy controls and this association was more significant in men than in women. More efforts are encouraged to explore the prognostic and therapeutic implications for PD of the present findings.

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder and with the accelerated ageing of human society, the prevalence of this disorder is expected to rise steadily in future.[1] [2] The cause of PD remains unclear, but oxidative stress has been strongly implicated.[3] Uric acid, an important endogenous antioxidant with high concentrations in serum and in brain, can prevent oxidative stress owing to its ability to scavenge various reactive oxygen species (ROS) and reactive nitrogen species (RNS).[4] Uric acid has been hypothesised to reduce oxidative stress on

Strengths and limitations of this study

- Confirmed the lower serum uric acid levels in patients with Parkinson's disease than in healthy controls.
- Major limitation is the relatively limited studies included.

the central nervous system.[5] Therefore, in recent years the association between uric acid levels and PD, has gained intensive interest.[6–11] It has been widely demonstrated by many studies that high levels of uric acid predict a decreased risk of developing PD.[10] [11] In recent years, accumulating evidence indicated the difference in uric acid levels between patients with PD and healthy controls,[8] [9] [12] while there is no comprehensive evaluation on this issue. The purpose of the present study was to perform a meta-analysis to evaluate serum uric acid levels in patients with PD in comparison with healthy controls, which has important implications for the prevention and treatment of this disease.

MATERIALS AND METHODS

Literature search

We identified procurable published articles in English through a computerised PubMed, EMBASE and Cochrane Library databases search for English language literature up to January 2013. We used the following key words to search the aforementioned databases: uric acid or urate and PD. We also examined conference proceedings, and the references in all articles retrieved were cross-checked to obtain all pertinent publications on the uric acid levels in patients with PD.

Selection criteria

For inclusion in the meta-analysis of uric acid levels in patients with PD in comparison with controls, we considered only papers showing
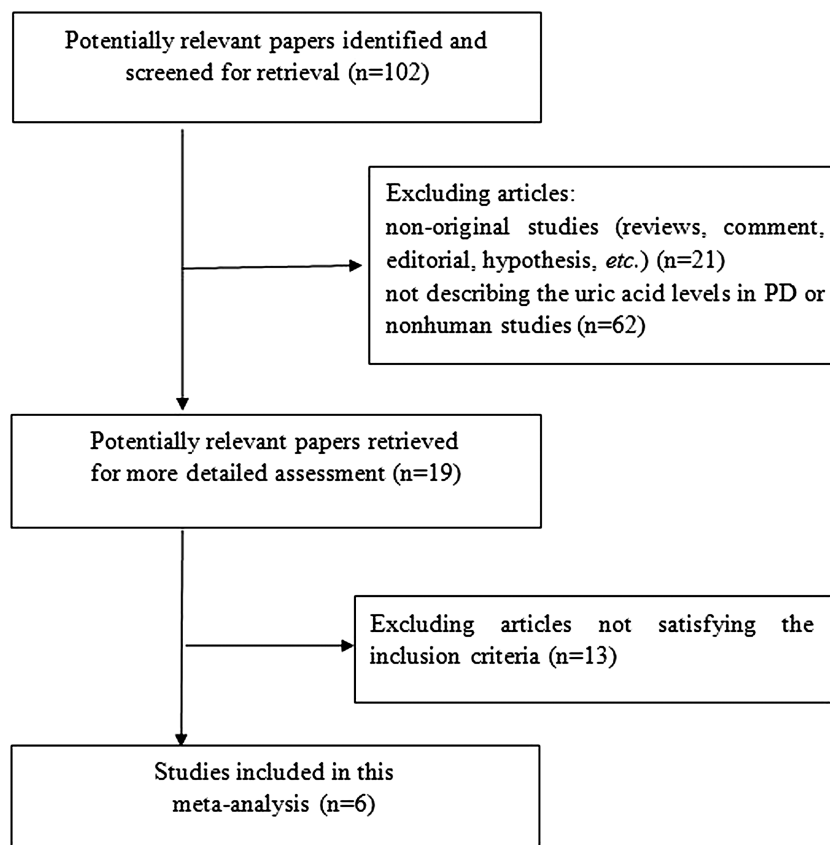
Figure 1 Selection of studies for inclusion in the present meta-analysis.

comparative analysis of patients with PD against healthy controls. We also required that studies explicitly present uric acid mean and SD values for patients and control groups. Two collaborators reviewed all articles and data disagreement was resolved through discussion. In total, six studies were identified and included in the meta-analysis on uric acid levels in patients with PD.[8] [9] [12–15] In each study, the patients with PD were diagnosed according to the clinical criteria of the UK Parkinson's Disease Society Brain Bank. The inclusion criteria for the control must be age-matched and have no PD history. In the patients with PD and control groups, the individuals with current use of uric acid lowering agents were excluded. In four of the six studies, severity of the diseases was evaluated according to Hoehn-Yahr (H-Y) stage diagnosis criteria and the patients were divided into several subgroups.[9] [13–15]

Data extraction and meta-analysis
We extracted information from the six included papers including first author, year of publication, the number of PD cases and healthy controls, the mean of uric acid levels and the SD of uric acid levels. We used the data to obtain 95% CI and the SMD. Sex subgroup analysis was also conducted to investigate the effect of gender on the uric acid levels in patients with PD. Statistical computation was performed using the STATA V.12.0 statistical software (StataCorp LP, College Station, Texas, USA).

RESULTS
Search results and characteristics of the included studies
The details of study selection processes were shown in figure 1. Through the computerised databases search, 102 potentially relevant papers were identified and screened for retrieval. After reviewing the title and abstract, 83 studies, which included non-original or non-human studies, or those not investigating the uric acid levels in patients with PD, were excluded. Of the remaining 19 studies, 13 were then excluded for not satisfying the inclusion criteria based on full-text review. Finally, there were six studies in total that met the eligibility criteria and were included in the meta-analysis.[8] [9] [12–15] Among the six studies, two were conducted in Finland,[8] [12] two in China,[13] [15] one in Greece[9] and one in Spain.[14] The participants included in each of the six studies included both male and female patients.

Uric acid levels in patients with PD
A total of 1217 patients with PD and 1276 healthy controls were enrolled in the six studies.[8] [9] [12–15] The extracted information from each paper including first author, year of publication, the number of cases and controls, the mean levels of uric acid and the SD of uric acid levels, is shown in table 1. According to the meta-analysis results as shown in figure 2, it was found that patients with PD had lower serum levels of uric acid than healthy controls (summary SMD=−0.52, 95% CI (−0.72 to −0.31)) and the six sets of results showed statistically significant heterogeneity (p=0.001, I^2=75.6%).

Table 1 Summary of studies included in the meta-analysis of uric acid levels in patients with PD

References	Year	Country	N		Uric acid levels (μM/L)		Weight (%)	SMD	95% CI
			PD	Control	PD	Control			
Annanmaki et al[9]	2007	Finland	40	29	278.5±77.4	319.7±76.0	10.64	−0.54	(−1.02 to −0.05)
Andreadou et al[9]	2009	Greece	43	47	325.4±83.3	378.3±255.8	12.74	−0.27	(−0.69 to 0.14)
Annanmaki et al[12]	2011	Finland	28	12	285.0±63.8	309.1±87.5	6.72	−0.34	(−1.02 to 0.34)
Zhang et al[13]	2012	China	534	614	278.10±87.31	348.17±86.25	24.88	−0.81	(−0.93 to −0.69)
Sun et al[15]	2012	China	411	396	243.38±78.91	282.97±90.80	24.15	−0.47	(−0.61 to −0.33)
Jesús et al[14]	2013	Spain	161	178	278.4±98.7	319.4±95.2	20.87	−0.42	(−0.64 to −0.21)

PD, Parkinson's disease; SMD, standardised mean difference.

Sex subgroup analysis of uric acid levels in patients with PD

To explore the effect of gender on the uric acid levels in patients with PD, we then performed a sex subgroup analysis. Among the six studies, four present the information of women and men subgroups as shown in table 2.[9] [13–15] In the women subgroup, there were 489 patients with PD and 516 healthy controls in total. In total, 660 patients with PD and 719 healthy controls were included in men subgroup analysis. The meta-analysis results (summary SMD=−0.56, 95% CI (−0.72 to −0.41), figure 3) indicated lower uric acid levels in patients with PD than healthy controls for women. Similar results were also obtained for men (summary SMD=−0.62, 95% CI (−0.94 to −0.31), figure 3) indicative of lower uric acid levels in patients with PD. In addition, according to the present results this association was relatively significant in men more than in women.

DISCUSSION

This meta-analysis suggests that patients with PD had lower serum levels of uric acid than healthy controls. To our knowledge, this is the first meta-analysis of uric acid levels in patients with PD. The antioxidant potential of uric acid should be the predominant mechanism

underlying the association between uric acid levels and PD. Despite the cause of PD is complicated, oxidative stress, which is caused by increased content of ROS and/or RNS damage, has widely been accepted to be implicated.[3] [16] [17] Uric acid is an important endogenous antioxidant that can scavenge ROS and RNS and also chelate iron ion.[4] [18] [19] It has been reported that in humans over half of the antioxidant capacity of blood plasma arises from uric acid.[20] For instance, uric acid can scavenge peroxynitrite,[21] [22] which is proven to play an important role in the pathogenesis of PD.[23] [24] Therefore, the protective antioxidant effects of high levels of uric acid may lower the risk of PD, while the lower level of uric acid in patients with PD may arise from the increased consumption of uric acid as a scavenger in alleviating the oxidative stress. In addition, it has been found that SLC2A9 splice variants act as the most effective of all uric acid transporters.[25] A recent study investigated the association between SLC2A9 polymorphisms and age at the onset of PD and provides evidence of an association between age at the onset in PD and variants within the SLC2A9 gene,[26] which may account for the observed lower uric acid levels in patients with PD than in the controls.

Certainly, there may exist other mechanisms to interpret the association between uric acid levels and PD as

Figure 2 Overall pooled estimate of standardised mean difference (SMD) and 95% CI of uric acid levels in Parkinson's disease and healthy controls.
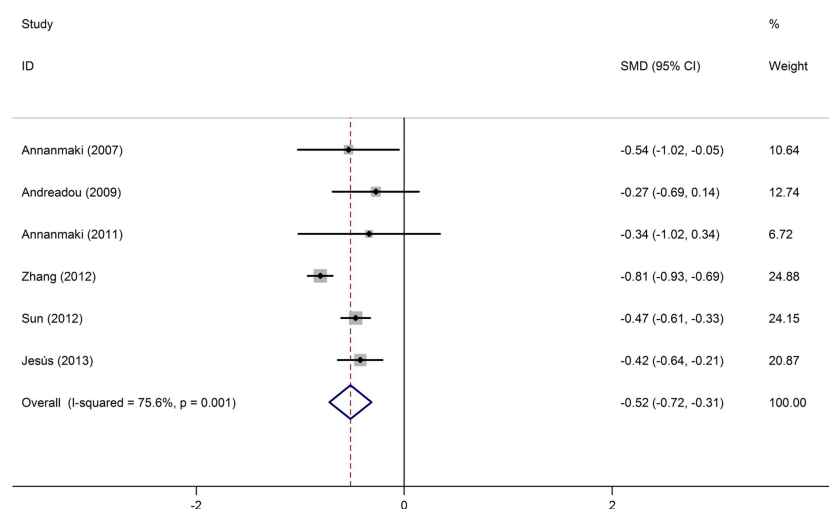
Table 2 Summary of studies included in the sex subgroup meta-analysis of uric acid levels in patients with PD

| Subgroup	References	N		Uric acid levels (µM/L)		Weight (%)	SMD	95% CI
		PD	Control	PD	Control			
Women	Andreadou et al[9]	21	22	275.4±69.0	323.0±94.0	5.82	−0.58	(−1.19 to 0.04)
	Zhang et al[13]	193	230	248.95±75.71	301.71±71.05	15.60	−0.72	(−0.92 to −0.52)
	Sun et al[15]	204	194	234.00±67.73	270.30±95.80	15.56	−0.44	(−0.64 to −0.24)
	Jesús et al[14]	71	70	237.3±89.2	278.4±77.9	11.39	−0.49	(−0.83 to −0.16)
Men	Andreadou et al[9]	22	25	366.4±67.2	427.7±124.9	6.16	−0.60	(−1.19 to −0.01)
	Zhang et al[13]	341	384	294.60±89.21	376.00±82.55	16.91	−0.95	(−1.10 to −0.80)
	Sun et al[15]	207	202	252.62±87.75	295.14±84.18	15.62	−0.49	(−0.69 to −0.30)
	Jesús et al[14]	90	108	311.1±82.1	346.2±95.8	12.94	−0.39	(−0.67 to −0.11)

the physiological functions of uric acid should go beyond antioxidation in humans. For instance, based on human epidemiological evidences it has been proposed that uric acid may act as a neurotransmitter and high levels of uric acid will decrease the risk of PD.[27] This opinion gains evolutionary support that the levels of uric acid increased in humans due to the mutations in the uricase gene,[28 29] which can be considered as an adaptive neurochemical compensation to the progressive nervous system.[30] The comprehensive mechanisms underlying the association between uric acid and PD will be better understood with the better elucidation of the physiological functions of uric acid in future.

As it remains unclear whether the association between uric acid levels and PD is causal, more efforts are needed to comprehensively elucidate the biological basis underlying the gender differences as indicated by the meta-analysis. For instance, the sexual differences in uric acid levels, that is, men usually have higher uric acid levels (about 1 mg/dL) than women with the same age due to the promotion of excretion of uric acid by oestrogen, may be one factor. In addition, it has been reported that the risk of PD occurrence differs significantly

between men and women and higher incidence rate of PD in men was about 1.5 times greater than in women.[31] Other factors, such as gender differences in levels of oestrogen, which was found to be neuroprotective, should also be taken into consideration.[32]

In four of the six studies the patients were divided into several subgroups according to H-Y stage diagnosis criteria.[9 13–15] We cannot perform a meta-analysis on the correlation of serum uric acid levels with duration and progression of PD because the number of divided groups was different among these studies and also not enough data can be obtained to perform further analysis. However, these studies consistently showed an inverse correlation of uric acid levels with H-Y scales, and as the disease progressed, the serum uric acid levels gradually reduced.[9 13–15]

The major limitation of our study is the relatively limited available studies included in the meta-analysis. Another limitation is only the studies in English language were considered. In addition, the quality of the individual studies included in our study has not been assessed. Finally, patients with PD and their treatment with agents and lifestyle factors such as dietary habits

Figure 3 Pooled estimate of standardised mean difference (SMD) and 95% CI of uric acid levels in Parkinson's disease and healthy controls in women and men.
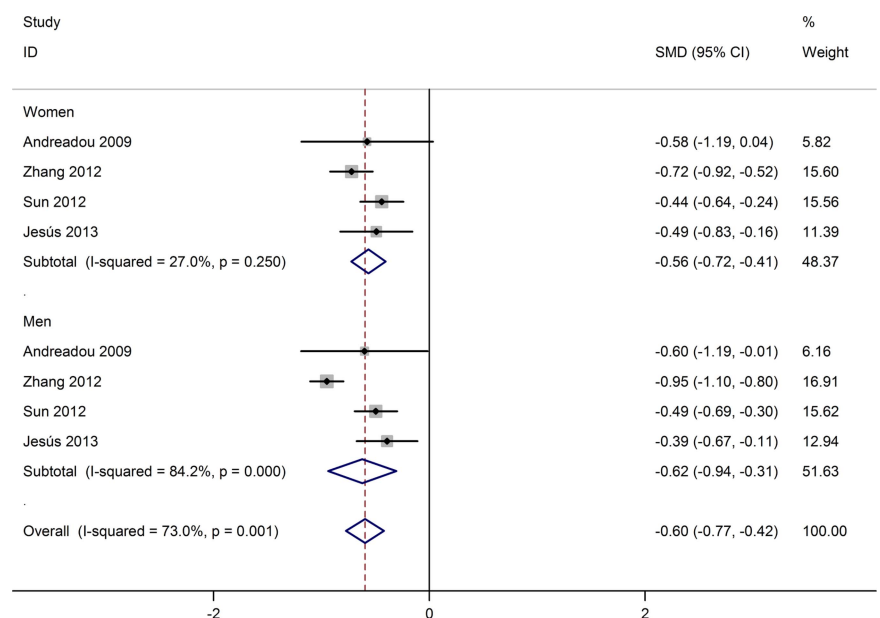
and physical exercise, might influence the metabolism of uric acid,[33] [34] while these factors cannot be considered in this meta-analysis.

CONCLUSIONS

In conclusion, this meta-analysis suggested that patients with PD had lower levels of uric acid than healthy controls and this association was more significant in men than in women. The evidence from the meta-analysis has implication that uric acid levels may potentially act as a biomarker for PD and its progression, which needs further verification especially after considering the gender differences. In addition, whether optimising uric acid levels, such as supplying adequate purine rich foods in diet of patients with PD to contribute to uric acid levels, is favourable for PD therapy also deserves further investigations.

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