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Research article

Low serum uric acid levels in chronic insomnia patients: A case-control study

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HIGHLIGHTS

- Serum UA levels were lower in chronic insomnia patients than in normal control subjects.
- Low serum UA levels were associated with higher PSQI scores in chronic insomnia patients.
- Low UA levels were associated with the presence and severity of chronic insomnia.

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ABSTRACT

Recent studies have demonstrated the presence of oxidative stress in insomnia patients. Uric acid (UA) is regarded as one of the most important antioxidants that may attenuate oxidative stress. The aim of our study was to investigate whether there is an alteration of serum UA levels in chronic insomnia patients. The association between sleep quality and serum UA in chronic insomnia patients was also investigated. We recruited 300 chronic insomnia patients and 300 age- and gender-matched normal controls. The uricase-PAP method was used to measure the concentration of UA both in patient and normal control subjects. The Pittsburgh Sleep Quality Index (PSQI) was used to assess the sleep quality of chronic insomniac participants. As a result, significantly lower serum UA levels were observed in patients with chronic insomnia when compared with normal control subjects (279.56 ± 65.80 vs. 299.10 ± 61.17 μmol/L, $t = -3.991$, $p < 0.001$). Low serum UA levels were correlated with high PSQI scores in multiple linear regression models ($\beta = -0.322$, $p < 0.001$). Our results suggested that low serum UA levels were associated with the presence and severity of chronic insomnia.

1. Introduction

Chronic insomnia is one of the most common healthy complaints characterized by difficulties in falling or staying asleep, early wake-up, and poor daytime function. These symptoms last for at least 3 months [1,2]. Epidemiological studies have shown that about 30% of the general population complained of insomnia, and approximately 6% had chronic insomnia [3,4]. In its chronic form, insomnia has been found to be associated with multiple physical and psychiatric disorders [5].

Oxidative stress describes a state of imbalance between the oxidants and antioxidant defenses that results from overproduction of reactive oxygen species(ROS) or a reduction in defense, which can consequently cause neural cell damage [6]. Oxidative stress has been suggested to play an important role in the course of many degenerative disorders [7], as well as psychiatric disorders [8,9]. Recently, several researchers have reported higher levels of malondialdehyde (MDA) and thiobarbituric acid reactive substances (TBARS), along with the decreased levels of some antioxidant enzyme in insomnia patients when compared with normal controls [10–12].

Uric acid (UA) is the ultimate oxidative catabolite of purine metabolism. On the one hand, it performs as a pro-oxidant in the cells [13]. Elevated serum UA is a risk factor for development of cardiovascular disease, hypertension, and chronic kidney disease

Abbreviations: UA, uric acid; BMI, body mass index; LDL-C, low density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; PSQI, Pittsburgh sleep quality index; TC, total cholesterol; TG, triglycerides; IQR, interquartile range; SD, standard deviation; CI, confidence interval; ANOVA, analysis of variance; NA, not applicable.

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[14,15]. On the other hand, UA is considered as a major antioxidant and accounts for approximately 60% of the antioxidant capacity in humans [16]. Several studies have indicated that elevated oxidative stress can cause decreased UA level [17,18]. Furthermore, UA levels is reduced in subjects who have had oxygen stress related to diseases, such as Depression [19], Amyotrophic lateral sclerosis (ALS) [20], and Alzheimer's disease (AD) [21].

To the best of our knowledge, the relationship between UA and chronic insomnia has not been studied. Therefore, our aim in this study was to explore the difference of serum UA levels between chronic insomnia patients and normal controls subjects. Additionally, the association between serum UA levels and sleep quality of chronic insomnia patients were also investigated.

2. Materials and methods

2.1. Participants

We recruited 300 chronic insomnia patients from outpatient clinic in the neurology department of the First Affiliated Hospital of Wenzhou Medical University from February 2014 to June 2015. The inclusion criteria were:(1) clinical diagnosis of insomnia disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders- Fifth Edition [1]; (2) complaints of difficultly falling or staying asleep, or waking up too early for at least 3 nights per week for at least 3 month; (3) significantly distress or daytime impairment caused by sleep disturbance; (4) being 18 year or older. Chronic insomnia patients were evaluated by an experienced neurologist. Trained researchers collected all patients' demographic and clinical information in face-to-face interviews via standardized questionnaires, which included age, gender, height, weight, medical history, duration of insomnia, medication/substance history. The exclusion criteria were (1) current diagnosis of any psychiatric disorder, including alcohol or substance abuse; (2) presence of untreated other sleep disorder; (3) shift work or abnormal sleep schedules; (4) subjects with a history of diabetes, hypertension, gout, renal impairment or neurological degenerative disease, such as Parkinson's disease; (5) treatment with the drugs that could increase or influence serum UA levels (allopurinol, thiazide diuretics, vitamin E or C, etc.).

Meanwhile, 300 normal controls with normal sleep were recruited from healthy individuals who visited the First Affiliated Hospital of Wenzhou Medical University for routine health examination. Healthy individuals had no self-reported personal psychiatric and physical disorders history. The normal controls were matched for age, gender with the chronic insomnia patients, and they reported normal sleep and satisfied with their sleep for at least 1 year. The normal control groups' sociodemographic information was collected from the physical examination center at The First Affiliated Hospital of Wenzhou Medical University.

The hospital's Medical Ethics Committee approved the study. All participants provided Written informed consents.

2.2. Clinical evaluation

The Pittsburgh Sleep Quality Index (PSQI) was used to assess the sleep quality of chronic insomniac participants [22]. The total score of PSQI is 21 points. Higher scores indicate worse sleep quality [23]. In the present study, the mean PSQI score of chronic insomnia patients was 14.66 ± 2.77 with a range of 7–21. Chronic insomnia patients who had used any sleeping pill during the past month were categorized as having received sleeping pills. Measurements were implemented by trained researchers who were blinded to all the variables of participants.

Table 1
Clinical and Demographic variables of the two groups under study.

Variables	Chronic insomnia patients (N = 300)	Healthy control (N = 300)	*P*
Age (years)	46.39 ± 10.53	45.74 ± 10.76	0.457
Gender, Female%	213(71.0)	208(69.3)	0.655
BMI, kg/m2	21.70 ± 2.49	23.00 ± 2.70	<0.001
Duration of insomnia (years)	7.8 ± 6.81	NA	
Receiving sleeping pills	140(46.7%)	NA	
TC, mmol/L	5.12 ± 0.97	5.00 ± 0.81	0.125
TG, mmol/L	1.11(0.8–1.52)	1.14 (0.8–1.59)	0.619
LDL, mmol/L	2.98 ± 0.88	2.94 ± 0.71	0.390
HDL, mmol/L	1.35(1.15–1.60)	1.31 (1.11–1.56)	0.162
SUA, μmol/L	279.56 ± 65.80	299.10 ± 61.17	<0.001

BMI = body mass index; HDL-C = high-density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; NA = not applicable; TC = total cholesterol; TG = triglycerides; SUA = serum uric acid.

2.3. Laboratory tests

Blood was obtained from the antecubital vein of all subjects during 24hr of baseline. The uricase-PAP method was used to measure the concentration of UA. The level of serum UA was measured by Beckman Coulter AU5800 (Beckman Coulter Inc., Brea CA, USA) in our hospital biochemistry department. In our hospital, the serum level ranging from 208 to 428 μmol/L in male patients and ranging from 155 to 357 μmol/L in female patients was categorized as normal.

2.4. Statistical analysis

The results were demonstrated as mean (standard deviation, SD) or median (interquartile range, IQR) for the continuous variables and percentages for categorical variables. Categorical variables were compared using the Chi square test, while the Pairs *t*-test or the Wilcoxon Signed-Rank Test were used to compare continuous variables between insomnia patients and controls as appropriate. Mixed-effects regression was used to evaluate the difference of serum UA levels between two groups with adjustment for BMI, and other clinical variables (age and gender as random variables). Difference in serum UA levels between male and female patients were examined using the Student's *t*-test. The Student's *t*-test was also used to evaluate the difference between patients with or without receiving sleeping pills. Correlation among PSQI scores and serum UA level was examined by Pearson's correlation coefficients. Furthermore, we used multiple linear regression analysis to evaluate the forecast value of different variables on PSQI scores. Statistical analyses were performed in SPSS software for windows version 21.0 (SPSS Inc., Chicago, IL, USA). Findings with $P < 0.05$(two-tailed) were regard as statistical difference.

3. Results

3.1. Demographics and clinical data

The demographic and clinical variables of chronic insomnia patients and normal controls are summarized in Table 1. BMI in normal controls were higher than that of chronic insomnia patients ($P < 0.001$). There was no significant difference in age, gender, triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) between groups (all $P > 0.05$).

3.2. Serum UA levels in insomnia patients and normal controls

Chronic insomnia patients showed significantly lower serum UA levels than that of normal controls (279.56 ± 65.80 vs.

Table 2
Linear regression between PSQI and variables of chronic insomnia patients (N = 300).

Model	Standardized coefficients		95% CI for B	
	β	*P*	Lower bound	Upper bound
Age	0.102	0.131	−0.088	0.688
Gender	−0.110	0.192	−0.761	0.153
BMI	0.019	0.799	−0.461	0.355
Duration of insomnia	−0.121	0.057	−0.725	0.010
Receiving sleeping pills	0.300	<0.001	0.486	1.187
TG	−0.005	0.947	−0.392	0.423
TC	0.057	0.666	−0.581	0.907
LDL	−0.061	0.628	−0.910	0.557
HDL	−0.110	0.134	−0.684	0.092
SUA	−0.322	<0.001	−1.590	−0.498

95% CI = 95% confidence interval; BMI = body mass index; LDL-C = low density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; PSQI = Pittsburgh Sleep Quality Index; TC = total cholesterol; TG = triglycerides; SUA = serum uric acid

299.10 ± 61.17 μmol/L, t = −3.991, $P < 0.001$). After adjustment for the BMI, TC, TG, LDL and HDL, a significant difference between two groups' serum UA levels was still observed (t = −4.351, Estimate = −18.256, 95% CI: −26.50 to −10.11, $P < 0.001$).

We found that female (n = 213) patients have lower serum UA levels when compared to male (n = 87) patients (253.88 ± 48.82 vs. 342.44 ± 59.52 μmol/L, t = −12.291, $P < 0.001$). No significant difference in serum UA levels was observed between chronic insomnia patients with or without receiving sleeping pills. Also, no correlation was found between ages, duration of insomnia with serum UA levels in chronic insomnia patients.

3.3. Correlation between UA and sleep quality

There was a negative correlation between PSQI scores and serum UA levels ($r = -0.214$, $P < 0.001$). In Table 2, based on the multiple linear regression analysis, the PSQI scores and baseline data in chronic insomnia patents were evaluated. We found that receiving sleeping pills (β = 0.300, $P < 0.001$), and UA (β = −0.322, $P < 0.001$) were independent contributors to PSQI scores, while the other related clinical and demographic variables showed no effects ($P > 0.05$).

4. Discussion

In this study, we explored the differences in serum UA levels between chronic insomnia patients and normal control subjects. Our data showed that chronic insomnia patients had lower levels of serum UA when compared with normal controls. In addition, we also found that there was an independent negative correlation between PSQI scores and serum UA levels.

Recently, oxidative stress has received substantial attention, one explanation is that it's a potential mechanism associated with insomnia. The relationship between sleep disturbance and oxidative stress has been investigated in some animal experiments. Ramanathan et al. [24] demonstrated that prolonged (5–11 days) sleep deprivation induced decreased Superoxide dismutase (SOD) level in the rat hippocampus. Suer et al. [25] reported that long-term sleep deprivation elevated MDA levels, and decreased SOD and glutathione peroxidase (GSH-Px) activities both in the whole brain and hippocampus in animal model. Furthermore, clinical study also observed increased MDA and decreased GSH-Px activities in the whole blood of patient with primary insomnia [11]. These studies have provided strong support for Reimund's hypothesis that sleep loss causes free radicals accumulate and sleep may have an important role in attenuating oxidative stress [26].

The exact role of UA in the pathophysiology of insomnia is still unknown. Nevertheless, UA has diverse antioxidant effects that including scavenging of free radicals, suppression of the Fenton reaction, chelation of transition metals, and prevention of lipid peroxidation [27,28]. Therefore, one of the possible mechanisms between UA and insomnia is the antioxidant effect of UA by providing a defense against oxidative stress. In this study, our data showed that chronic insomnia patients had lower serum UA levels compared with normal controls. This result may be due to the metabolism of UA by the direct reaction between UA and excessively accumulated free radicals in the central nervous system as well as other tissues [29].

According to the analysis of data, there was a dramatically independent negative relationship between PSQI scores and the levels of serum UA. This inverse correlation between sleep quality of chronic insomnia patients and serum UA level suggested that low serum UA levels were associated with the severity of chronic insomnia. Recently, a significant negative association was found between UA and the non-motor symptoms (NMS) of burden of sleep/fatigue in Parkinson's disease(PD) patients [30], which was in accordance with our finding. As mentioned earlier, a growing body of evidence showed that low serum UA levels are linked to a variety of neurodegenerative and cognitive disorders, such as ALS [20], PD [30], and AD [21]. The exact effect of UA on neurodegenerative and cognitive disorders is still uncertainty. It is possible that individuals with decreased serum UA levels may not have the ability to prevent against the toxicity of free radical, resulting in the development of inflammation [31]. Nevertheless, it is also possible that the inflammation occurring in neurodegenerative disorders directly accelerates the production of free radicals, leading to a vast consumption of UA [32]. Comorbid insomnia is common in patients with neurodegenerative and cognitive disorders, including PD and dementia such as AD [33]. A community-based study found that about 60% of the PD patients reported sleep problems, significantly more than in normal control subjects, and the most common sleep problems reported by PD patients were sleep maintenance and early morning awakening insomnia [34]. Moreover, Suresh et al. [35] reported that the insomnia in patients with PD were more frequently associated with increased severity of PD. Likewise, Guarnieri et al. [36] found that insomnia affect 49% of patients with AD, and commonly reveal various symptoms, including sleep fragmentation and decreased slow-wave sleep (SWS). Therefore, UA may play a crucial role in the presence and progression of sleep disturbance in neurodegenerative and cognitive disorders, such as PD.

Both gender and age can influence the serum UA level. In the present study, it was found that man had higher mean serum UA levels than that of woman, which was concordant with previous studies [37,38]. However, there was no significant correlation between age and serum UA levels of chronic insomnia patients; this may be relevant to sampling error. The result of chronic insomnia patients having lower BMI in our present study is broadly agreed with a recently published study evaluating BMI in patients with primary insomnia [39]. The reduced weight in insomnia patients may be explained by their dietary habits [40]. In addition, the hyperarousal state, which was suggested to be a major etiological factor for perpetuate insomnia, is associated with a chronic stress response [41], which may consequently prevent weight gain.

In our study, there were some limitations should be noted. First, as the design of present study was a case-control study, the relationship between chronic insomnia and serum UA may be bidirectional. Future longitudinal studies are needed to evaluate whether low serum UA levels in chronic insomnia patients is the reason or the consequence of insomnia. Second, we lack of polysomnography to provide information about objective sleep impairment in support of our diagnoses. Although it is not sug-

gested for routinely screen or diagnose of insomnia complaints in clinical practice [42,43]. Third, the study subjects came from only 1 clinic. Therefore, whether our results are appropriate for other Chinese patients is uncertain, further research is needed.

In conclusion, we have shown that patients with chronic insomnia had lower serum UA levels when compared with normal controls. Among chronic insomnia patients, decreased serum UA levels were associated with poor sleep quality. The present findings supported the hypothesis that insomnia represents an oxidative challenge; serum UA level could possibly serve as a serum marker for diagnosis of chronic insomnia. For further studies, larger numbers of patients and more study sites are needed to explore the specific pathogenesis of UA and chronic insomnia, which may lead to new directions for future sleep research.

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