Relationship between Uric Acid and Subtle Cognitive Dysfunction in Chronic Kidney Disease

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Key Words

Cognitive function • Chronic kidney disease • Uric acid

Abstract

Background: Elevated serum uric acid has been associated with cognitive dysfunction and vascular cognitive impairment in the elderly. Serum uric acid is also commonly elevated in chronic kidney disease (CKD), but its relationship with cognitive function in these patients has not been addressed. **Methods:** Subjects with CKD (defined as eGFR <60 ml/min/1.73 m²) were evaluated for cognitive dysfunction using the validated Standardized Mini-Mental State Examination (SMMSE). Individuals with dementia, depression or other psychiatric disorders were excluded, as were subjects on uric acid-lowering therapy or with serious illnesses such as severe anemia or active or ongoing cardiovascular or cerebrovascular disease. **Results:** 247 subjects were enrolled. SMMSE scores showed stepwise deterioration with increasing quartile of serum uric acid (26.4; 26.1; 25.5; 25.3, score range 20–30, $p = 0.019$). Post-hoc analysis demonstrated that there was no linear trend and only groups 1 and 4 were different with respect to SMMSE scores ($p = 0.025$). Stepwise multivariate linear regression revealed that age, educational status, pres-

ence of cerebrovascular disease, and serum uric acid were independently related to SMMSE scores. **Conclusion:** Serum uric acid levels are independently and inversely associated with mild cognitive dysfunction in subjects with CKD.

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Introduction

Chronic kidney disease (CKD) is an independent risk factor for cognitive dysfunction and dementia [1–4]. Cognitive decline in patients with kidney disease may be caused by various factors such as clinical and subclinical cerebrovascular disease and various comorbidities such as anemia, hypertension, diabetes, and malnutrition [5]. A better understanding of potential etiologies could lead to earlier interventions that might help reduce this important morbidity.

One of the most common causes of dementia is vascular cognitive impairment (VCI), which is strongly associated with chronic hypertension, cerebral microvascular disease, and the development of diffuse lesions of the white matter [6]. One of the key risk factors appears to be disease of the cerebral arterioles, which results in altered

cerebral autoregulation that makes the distal cortex vulnerable to changes in blood pressure (BP), thereby increasing the risk to reduced cerebral pressure in the presence of low BP or to elevated cerebral pressure with sudden increases in systemic BP [6].

Hypertension is also associated with microvascular disease of the kidney (arteriolosclerosis), and experimental studies have also shown that its presence also alters renal autoregulation and increases the risk for renal progression (the Herrera hypothesis) [7, 8]. Since hypertension is associated with both renal and cerebral arteriolar disease, one might expect the two conditions to be commonly present in the same individual, thus providing a link between CKD and VCI. Indeed, in subjects with type 2 diabetes, the presence of cerebral microvascular disease (as manifested by silent cerebral infarction) is associated with increased risk for progression of renal disease [9].

While these studies implicate hypertension as the cause of arteriolar disease that then predisposes subjects to CKD and VCI, recent studies have suggested that elevated serum uric acid could also act as an etiologic factor [10]. Hyperuricemic rats develop renal microvascular disease involving the afferent arteriole that alters the autoregulatory response and results in glomerular hypertension [11, 12]. In the remnant kidney model of CKD, the induction of hyperuricemia does not result in severe preglomerular arteriolar disease, and is associated with accelerated decline in renal function [13]. Importantly, the control of hypertension by thiazides in hyperuricemic rats does not block the development of renal arteriopathy [14]. Rather, uric acid may directly induce vascular smooth muscle cell proliferation through a mechanism involving the stimulation of platelet-derived growth factor [15, 16].

Studies in humans have also linked uric acid with small vessel disease both in the kidney [17] and in the heart [18]. Elevated serum uric acid has been associated with increased risk for VCI and cerebral microvascular disease in the elderly [19–21]. Thus, we hypothesized that elevated uric acid might also be a risk for cognitive dysfunction in the CKD population. To test this hypothesis, we examined the relationship of serum uric acid with cognitive performance as determined using the Standardized Mini-Mental State Examination (SMMSE), which is a validated assessment tool for determining cognitive dysfunction [22, 23].

Subjects and Methods

Study Population

The current study was conducted in the outpatient nephrology unit of Zonguldak Ataturk State Hospital between May 2007 and

May 2010. The study was in accordance with the declaration of Helsinki, and informed consent was obtained from all patients before enrolment. The study population comprised patients with CKD defined as 24-hour creatinine clearance <60 ml/min/1.73 m². Of 299 subjects that were screened for the study, 52 were excluded for the following prespecified reasons: unwillingness to participate in the study ($n = 16$), dementia and Alzheimer disease (diagnosed by a neurologist; $n = 3$), use of antidepressants or depression (diagnosed by a psychiatrist; $n = 14$), acute coronary syndrome (within the last 6 months; $n = 4$), acute cerebrovascular disease (within the last 6 months; $n = 2$), active peripheral arterial disease ($n = 1$), hyper- or hypothyroidism ($n = 4$), severe anemia (defined as hemoglobin <8 g/l; $n = 2$), and 6 subjects (of whom 4 had a history of gout) who were actively using hypouricemic drugs. None of the patients reported any alcohol abuse. 247 subjects thus constituted the study population.

Measurement of Cognitive Function

The SMMSE was used to assess cognitive function and results in a score 30 (unimpaired) to 0 (impaired) [22]. It provides a global score of cognitive ability that correlates with function in activities of daily living. The SMMSE measures various domains of cognitive function including orientation to time and place, registration, concentration, short-term recall, naming familiar items, repeating a common expression, and the ability to read and follow written instructions, write a sentence, construct a diagram, and follow a three-step verbal command. The SMMSE takes approximately 10–15 min to administer, provides a baseline score of cognitive function and pinpoints specific deficits that can aid in forming a diagnosis. The SMMSE is a reliable instrument that allows practitioners to accurately measure cognitive deficits and deterioration over time [23]. The Turkish version of the SMMSE has been validated and shown to be reliable in the Turkish population [24]. Assistance was provided for patients who were illiterate. Informed consent was obtained from all participating patients. Permission for the study was obtained by the local ethics committee (Institutional Review Board).

Additional Assessments

Subjects with CKD also underwent the following assessments: medical history and physical examination, office BP measurements and 24-hour urinary creatinine clearance and albumin excretion. Sociodemographic and clinical assessment included age, gender, presence of diabetes and hypertension, alcohol use, smoking status, presence of coronary artery, cerebrovascular and peripheral artery diseases and current medications. Body mass index was calculated as the ratio of weight (in kilograms) to height squared (in square meters). Fasting blood samples were measured for serum hemoglobin, glucose, albumin, blood urea nitrogen, creatinine, uric acid, calcium, phosphorus, thyroid-stimulating hormone, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, and high sensitive C-reactive protein.

Office BP Measurements

Office BP measurements were performed using a mercury sphygmomanometer. Adequately sized cuffs (standard cuff of 23×12 cm or a large cuff of 34×15 cm) according to arm circumference were placed on the nondominant arm. The first and fifth phases of Korotkoff sounds were taken as the systolic and dia-

stolic BP, respectively. The measurements were taken after the patients had rested for 10 min in the sitting position with the arm comfortably placed at the heart level. Two measurements were taken at 5-min intervals. Each set of two measurements was averaged to give the office systolic and diastolic BPs. Clinical hypertension was defined as a BP $\geq 140/90$ mm Hg.

Statistical Analyses

Statistical analysis was performed using SPSS 15.0 for Windows (SPSS Inc., Chicago, Ill., USA). For the correlation of SMMSE score with various parameters Spearman and Pearson correlation coefficients were used as appropriate. Stepwise multivariate linear regression analyses were performed to assess the independent association of several variables with SMMSE score. The effects were measured by odds ratios and 95% confidence intervals based on logistic regression models. Analysis of SMMSE scores according to uric acid quartiles was carried out by analysis of variance. For the post-hoc analysis of groups according to serum uric acid quartiles, Tukey's b test was used.

Results

The demographic characteristics, laboratory parameters, BP and SMMSE scores of the 247 enrolled subjects are shown in tables 1 and 2, respectively. Ninety-two subjects were hypertensive, and their treatment consisted of alpha-blockers ($n = 29$), beta-blockers ($n = 75$), calcium channel blockers ($n = 72$), ACE inhibitors ($n = 49$), angiotensin receptor blockers ($n = 31$), loop diuretics ($n = 81$) and thiazide diuretics combined with ACE inhibitors or angiotensin receptor blockers ($n = 46$).

SSME scores ranged between 20 and 30 in all subjects, and showed a normal distribution. When SSME scores were categorized according to quartiles of serum uric acid, a progressive worsening of SSME scores were observed with increasing quartile of serum uric acid suggestive of worsening cognitive dysfunction (fig. 1; $p = 0.019$). However, post-hoc analysis demonstrated that there was no linear trend, and only groups 1 and 4 were different with respect to SMMSE scores ($p = 0.025$).

By univariate analysis, SSMSE scores correlated with age ($\rho: -0.337$, $p < 0.0001$), serum creatinine ($\rho: -0.132$, $p = 0.039$), blood urea nitrogen ($\rho: -0.159$, $p = 0.012$), diastolic BP ($\rho: +0.125$, $p = 0.01$) and serum uric acid ($\rho: -0.261$, $p \leq 0.0001$). A weak but statistically significant relationship between uric acid (logarithmic values) and SMMSE score was observed (fig. 2; $r = 0.297$, $p < 0.001$).

Stepwise multivariate linear regression analysis was performed to assess the independent effects of age, gender, smoking status, body mass index, systolic and diastolic BPs, educational status, presences of diabetes mellitus, coronary artery disease, cerebrovascular disease,

Table 1. Demographic characteristics and SMMSE scores of 247 chronic renal failure patients ($n = 247$; mean $\pm$ SD)

Age, years	60.5 $\pm$ 11.0
Males/females	118/129
Illiterate and primary school graduate vs. other	127/120
Body mass index	29.0 $\pm$ 4.6
Present/absent diabetes mellitus	108/139
Smokers/nonsmokers	66/181
Present/absent coronary artery disease	81/166
Present/absent cerebrovascular disease	65/182
Present/absent peripheral artery disease	38/209
Present/absent hypertension	155/92
Systolic BP, mm Hg	143.5 $\pm$ 17.0
Diastolic BP, mm Hg	80.2 $\pm$ 15.2
SMMSE score	25.9 $\pm$ 2.3

Table 2. Laboratory parameters of 247 CKD patients

Hemoglobin, g/l	115.7 $\pm$ 18.3
Blood glucose, mmol/l	8.8 $\pm$ 4.0
Albumin, g/l	37.8 $\pm$ 7.1
Blood urea nitrogen, mmol/l	14.3 $\pm$ 7.2
Creatinine, μ mol/l	239.0 $\pm$ 134.1
Sodium, mmol/l	138.4 $\pm$ 4.2
Potassium, mmol/l	4.8 $\pm$ 0.7
Calcium, mmol/l	2.25 $\pm$ 0.16
Phosphorus, mmol/l	1.30 $\pm$ 0.24
Uric acid, μ mol/l	455.6 $\pm$ 115.8
High sensitive C-reactive protein, mg/dl	1.23 $\pm$ 1.7
Total cholesterol, mmol/l	4.97 $\pm$ 3.6
LDL-C, mmol/l	2.86 $\pm$ 1.02
HDL-C, mmol/l	1.04 $\pm$ 0.32
Triglyceride, mmol/l	1.88 $\pm$ 0.99
Thyroid-stimulating hormone, mU/l	1.87 $\pm$ 1.36
Creatinine clearance, ml/min	32.3 $\pm$ 14.3

Values are expressed as means $\pm$ SD. LDL-C = Low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol.

hemoglobin, thyroid-stimulating hormone level, 24-hour creatinine clearance and albumin excretion, serum uric acid, high sensitive C-reactive protein and use of alpha-blockers, beta-blockers, calcium channel blockers, ACE inhibitors, angiotensin receptor blockers, loop diuretics and thiazide diuretics combined with ACE inhibitors or angiotensin receptor blockers with SMMSE score. Age, educational status, presence of cerebrovascular disease, and serum uric acid were found to be independently related to SMMSE scores (table 3).

Fig. 1. Mean SMMSE scores according to uric acid quartiles. Subjects were divided into 4 groups based on uric acid quartiles: <25th quartile (58 patients): uric acid levels <380.7 $\mu\text{mol/l}$; 25th–50th quartile (63 patients): uric acid levels 380.7–434.8 $\mu\text{mol/l}$; 50th–75th quartile (64 patients): uric acid level 434.8–517.5 $\mu\text{mol/l}$, and >75th quartile (62 patients): uric acid level >517.5 $\mu\text{mol/l}$ ($p = 0.019$).

Fig. 2. Regression graphic for logarithmically converted uric acid levels and SMMSE score ($r = -0.297$, $p < 0.0001$).

Table 3. Linear regression analysis of factors related to SMMSE scores

Parameter	B	95% CI	p
Educational status (illiterate and elementary school vs. higher educational level)	–1.427	–2.004 to –0.851	<0.0001
Age	–0.030	–0.059 to –0.002	0.039
Presence of cerebrovascular disease	–1.341	–1.940 to –0.742	<0.0001
Serum uric acid	–0.005	–0.007 to –0.002	<0.0001

Discussion

In this study, we performed a simple cognitive function test (SMMSE) in subjects with CKD, and used this to identify risk factors for cognitive dysfunction. Univariate analysis identified diastolic BP, renal function (creatinine clearance and 24-hour urinary albumin excretion), and serum uric acid as risk factors. By multi-

variate analysis, age, educational level, presence of cerebrovascular disease, and serum uric acid levels remained significant predictors.

The major new finding is that elevated serum uric acid was independently associated with worse cognitive function in subjects with CKD. Our data are consistent with previous reports – mainly from healthy elderly – suggesting that serum uric acid predicts cognitive decline and

white matter lesions are consistent with cerebral ischemia [19, 21]. Elevated serum uric acid has also been shown to predict both hypertension and stroke by meta-analyses [25, 26]. The observation that elevated uric acid can also induce vascular smooth muscle cell proliferation in vitro [14, 15] and induce renal microvascular disease in vivo [12, 27] suggests that it may also be able to induce cerebral microvascular disease, which underlies the development of VCI [28].

Of note, there are some contradictory data. Serum uric acid levels tend to be low in subjects with established Alzheimer's dementia or VCI [29–31]. Some studies also suggest that elevated uric acid might reduce the risk for progression of dementia in subjects with underlying impaired cognitive function [32]. One study reported that the risk for developing dementia in subjects with a high uric acid is due to the frequent coexistence of hypertension and cardiovascular disease, and in the absence of such associated risk factors, elevated uric acid may actually reduce the risk for dementia [33].

Several potential mechanisms might account for such an apparent paradox. For example, since serum uric acid reflects to some extent the nutritional status, a lower uric acid could reflect a reduction in intake as may be observed in subjects with progressive dementia. In dialysis patients, for example, lower uric acid levels are associated with low serum albumin, a bedridden state, or a history of cerebrovascular accident [34]. A lower serum uric acid may also reflect a reduction in serum antioxidants, which has been postulated to increase the risk for Alzheimer's dementia [29–31]. This possibility is based on studies that show that uric acid is a major antioxidant in human plasma and can scavenge numerous oxidants in vitro, including superoxide, hydroxyl radical and peroxynitrite [35, 36]. However, when uric acid reacts with peroxynitrite, it will also generate free radicals in the process, including triuretcarbonyl and aminocarbonyl radicals [37]. Furthermore, while uric acid is an antioxidant in the extracellular environment, inside the cell it induces endothelial dysfunction [38], oxidative stress [39–41], inflammation [42, 43] and stimulation of vasoactive mediators such as thromboxane and angiotensin II [13, 39, 40]. Thus, it remains possible that uric acid might have both deleterious and beneficial effects on neural function. Nevertheless, our studies suggest that in CKD the presence of elevated uric acid is associated with worse cognitive function. Furthermore, pilot studies suggest that lowering uric acid in subjects with CKD may have beneficial effects on renal function, BP, and inflammation, and in one study it was associated with a marked (70%) reduction in cardiovascular events [44–46].

Our study has limitations. First, our study is cross-sectional, and hence cause and effect can not be ascertained. Second, the overall impact of elevated uric acid on cognitive function was relatively weak, even though it was statistically significant. Third, we did not perform computed tomography or MRI in our patients to determine a relationship of uric acid with white matter lesions such as observed in subjects with VCI. Thus, we can not rule out the possibility of subtle/silent cerebral lesions. Fourth, the SMMSE is not the gold standard for the detection of cognitive dysfunction; however, it is easy to administer and provides a global score of cognitive ability that correlates with function in activities of daily living [23].

In conclusion, one of the increasingly recognized complications of CKD is cognitive decline [1–3]. In this paper, we presented the first epidemiological evidence that this decline correlates with increased serum uric acid levels. If uric acid has a causal role in VCI via its ability to cause microvascular disease and hypertension, then this could be a significant problem in subjects with CKD as hyperuricemia occurs in approximately half of the subjects by the time the dialysis is initiated [34, 47]. We believe that extending these cross-sectional findings to longitudinal studies would be helpful to determine whether elevated uric acid increases the risk or rate of cognitive decline in CKD patients.

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Disclosure Statement

Dr. Johnson has several patent applications related to the lowering of uric acid as a means for preventing metabolic syndrome and hypertension.

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