Association between serum uric acid and large-nerve fiber dysfunction in type 2 diabetes: a cross-sectional study

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Abstract

Background: Large-nerve fiber dysfunction, as assessed by vibration perception threshold (VPT) predicts risks of ulceration, amputation, and mortality in diabetes. Serum uric acid (UA) is closely associated with various metabolic disorders, especially diabetes. Thus, we sought to investigate the clinical relevance of UA to large-nerve fiber dysfunction, among patients with type 2 diabetes (T2D).

Methods: Medical records of consecutive patients with T2D who were admitted to Beijing Friendship Hospital Pinggu Campus between May 2014 and December 2016 were collected. Data for the 824 eligible patients included in the final analysis were extracted using a structured form. A VPT value ≥15 in either foot was defined as abnormal. We compared the clinical characteristics between patients with abnormal VPT and those with normal VPT (VPT value < 15 in both feet) in the overall population and in gender subgroups. Logistic regression analysis was performed to explore the association of abnormal VPT with UA level. One-way analysis of variance was used to compare VPT values across four UA quartiles.

Results: UA levels were significantly lower in T2D patients with abnormal VPT than in those with normal VPT (294.5 ± 84.0 vs. 314.9 ± 92.8 μmol/L, P < 0.01), especially among male patients (311.7 ± 85.2 vs. 336.9 ± 89.6 μmol/L, P < 0.01). From the logistic regression analysis, hyperuricemia (males > 420 μmol/L; females > 360 μmol/L) was associated with a reduced risk of abnormal VPT (odds ratio [OR], 0.60; 95% confidence interval [CI], 0.39–0.91; P < 0.05). This association was robust in male patients (OR, 0.43; 95% CI, 0.24–0.76; P < 0.01) but not in female patients (OR, 0.92; 95% CI, 0.47–1.82; P = 0.816), even after adjustment for confounding factors. For the younger male subgroup (age < 65 years), VPT values decreased as the UA level increased (P for trend = 0.002), but this trend was not significant in older male subgroup (age ≥ 65 years; P for trend = 0.400).

Conclusions: Low serum UA levels showed a significant association with an increased risk of large-nerve fiber dysfunction in male patients with T2D, but not in female patients with T2D. In addition, in only the younger subgroup of male patients (< 65 years), lower levels of UA also correlated with higher VPT values.

Keywords: Peripheral neuropathy; Uric acid; Type 2 diabetes

Introduction

An abnormal vibration perception threshold (VPT), which represents large-nerve fiber dysfunction, plays an important role in the progression of diabetic peripheral neuropathy (DPN). DPN affects include pain and foot ulceration, which can lead to the need for amputation, severe disability, and reduced quality of life. Thus, early detection of at-risk patients is crucial to prevent progression to complex stages in patients with type 2 diabetes (T2D). In the early stages of neuropathy, the vibratory sensory system is the first affected component. Studies have indicated a relationship between the loss of vibration sensation and progression of DPN. Furthermore, the VPT has been demonstrated to be a quick, accurate, and quantitative screening instrument for evaluating vibration dysfunction in patients with DPN. An elevated VPT value is correlated with higher risks of foot ulcerations, amputations, and mortality in patients with diabetes.

Serum uric acid (UA) is an end product of purine synthesis. It is being investigated as a marker of various metabolic conditions, including diabetes. The current study sought to investigate the clinical relevance of UA to large-nerve fiber dysfunction, among patients with T2D.

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disturbances.\textsuperscript{[10]} In T2D, UA has been reported to be correlated not only with macro-vascular diseases, such as stroke\textsuperscript{[11-13]} and peripheral arterial disease (PAD),\textsuperscript{[14,15]} but also with some micro-vascular diseases, such as nephropathy\textsuperscript{[16]} and retinopathy.\textsuperscript{[17]} In addition, a previous study on large-nerve fiber dysfunction, represented by the VPT, demonstrated a significant relationship between abnormal VPT and hypertension (HT), an increased level of low-density lipoprotein (LDL) cholesterol, smoking, a higher level of glycated hemoglobin A1c, and a longer duration of diabetes.\textsuperscript{[1,18]} However, the association of large-nerve fiber dysfunction with UA is unclear.

In the present study, we aimed to investigate the relationship between serum UA levels and abnormal VPT, as an indicator of large-nerve fiber dysfunction, by testing vibration perception in patients with T2D.

Methods

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Beijing Friendship Hospital Pinggu Campus of Capital Medical University (No. 2018-project 001-01). The informed consent in this study had been exempted.

Patients and study design

Adult patients (aged 18–80 years) with T2D were selected from 2063 consecutive inpatients treated in the Department of Endocrinology, Beijing Friendship Hospital Pinggu Campus of Capital Medical University, Beijing, between May 2014 and December 2016 [Figure 1]. Patients were excluded if they had acute diabetic complications, acute and chronic infectious diseases, angina, myocardial infarction, a history of percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG) therapy within the previous 1 year, heart failure (NYHA class III or IV), a diagnosis of hepatic dysfunction, an estimated glomerular filtration rate (eGFR) <60 ml-min\textsuperscript{-1}·1.73 m\textsuperscript{2}, other causes of neuropathy (eg, peripheral nerve lesions), PAD, or use of any medication that might influence UA (eg, allopurinol, levodopa, thiazide diuretics, furosemide, thambutol, pyrazinamide, salicylate, niacin or cyclosporine, or glucocorticoids\textsuperscript{[19]}) in the previous 1 month. In addition, patients with an ankle brachial index score >1.2 were excluded from the analysis because of possible arterial stiffness. Lists of medications used within the last 1 month were obtained from selected patients. HT was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or use of anti-hypertensive treatment. Dyslipidemia was defined as serum triglyceride (TG) ≥1.7 mmol/L, LDL-C ≥2.6 mmol/L, or HDL-C <1.0 mmol/L for men and <1.3 mmol/L for women, or treatment with anti-dyslipidemia drugs. Cardiovascular disease (CVD) was defined as a history of angina, myocardial infarction, or treatment with any CVD-related medication, PCI, or CABG.

VPT measurements

VPT values were assessed using a digital biothesiometer (OERHUATAI Technology, Beijing, China), and average values of five measurements for each foot were calculated. Patients were divided into two groups by vibration perception: a normal vibration group with a VPT value <15 V for both feet and an abnormal VPT group with a vibration perception of ≥15 V for at least one foot.

Medical information extraction, UA assessment, and eGFR calculation

All electronic medical records of eligible patients were reviewed, and information was extracted using a structured form. Details of medicine use were obtained from the outpatient medical records of Pinggu District Hospital and Community Health Center. Medicine use was defined as consecutive use in the last 1 month before this onset. Furthermore, we extracted information on blood sample testing within 3 days before or after admission. All the blood samples were tested using an auto-analyzer (Beckman Coulter AU 5821, Indianapolis, IN, USA). The UA concentration was measured by the uricase method. eGFR was calculated by the equation of the Chronic Kidney Disease Epidemiology Collaboration.\textsuperscript{[20]}

Statistical analysis

Data were presented as mean ± standard deviation (SD), median (Q\textsubscript{1}, Q\textsubscript{3}), or proportions. Differences between the abnormal VPT group and normal vibration group were compared using chi-square χ\textsuperscript{2}, Student t test, and Wilcoxon analyses as appropriate. Logistic regression analysis was used to explore the relationship between serum UA level and abnormal VPT in the overall patient population and in the two gender subgroups. Only those characteristics that showed a significant difference between the two groups (P < 0.05 on univariate analysis) and that were considered clinically relevant to DPN were included in the model. All statistical analyses were performed using SPSS (version 20.0, SPSS, Inc, Chicago, IL, USA). Two-sided P-values <0.05 were considered statistically significant. For logistic regression, continuous variables were transformed into grade variables as: age (<65 years and ≥65 years), diabetes duration (<10 years and ≥10 years), body mass index (BMI) (<24, ≥24 and <28, ≥28 kg/m\textsuperscript{2}), HbA1c (<7.0% and ≥7.0%), and eGFR (<90 and ≥90 ml·min\textsuperscript{-1}·1.73 m\textsuperscript{2}).

Results

Baseline characteristics of the study population

A total of 824 patients with T2D (461 males and 363 females) were included in the analysis. The demographic and clinical characteristics of all patients and in the two gender subgroups are presented in Table 1. Patients in the abnormal VPT group were older (59.8 ± 9.5 years vs. 46.1 ± 11.8 years), were more often female (50.3% vs. 34.3%), had a longer diabetes duration (9 years vs. 3 years), and had a lower BMI (25.8 ± 3.9 vs.
26.6 ± 4.2 kg/m²) as compared to patients in the normal vibration group (all P-values < 0.05). Patients with abnormal VPT also showed a higher prevalence of CVD (14.1%), cerebral infarction (18.3%), HT (63.2%), dyslipidemia (86.9%), and diabetic retinopathy (46.7%); reduced levels of TG (1.6 mmol/L), total cholesterol (4.9 ± 1.3 mmol/L), and UA (294.5 ± 84.0 μmol/L); a lower eGFR (98.0 ± 14.8 ml/min-1·1.73 m²); and more frequent treatment with anti-dyslipidemia drugs (22.7%) (all P < 0.05). Among male patients with T2D, those with abnormal VPT had a significantly lower level of UA than those with normal VPT (P = 0.002). However, there was no significant difference in the UA level between women in the normal and abnormal VPT groups (P = 0.616).

Association between UA and abnormal VPT in all patients and in gender subgroups

On univariate logistic regression analysis, a lower UA level (male: ≤420 μmol/L, female: ≤360 μmol/L) was significantly associated with abnormal VPT (odds ratio [OR], 0.60; 95% confidence interval [CI], 0.39–0.91; P = 0.015) [Table 2]. This association was significant only in males (OR, 0.43; 95% CI, 0.24–0.76; P < 0.01) and not in females (OR, 0.92; 95% CI, 0.47–1.82; P = 0.816), even after adjustment for confounding factors [Tables 2 and 3]. In addition, multivariate logistic regression analysis showed that age, diabetes duration, and HT were significantly associated with abnormal VPT in male patients (all P < 0.05) [Table 2].
Association between quartiles of UA and VPT values in male patients with T2D of different age subgroups

To further explore the association between UA and VPT values, male patients were divided into four quartiles based on their UA level. In the younger subgroup (age <65 years), the VPT values (mean ± SD) in the Q1, Q2, Q3, and Q4 groups were 20.8 ± 12.4, 19.9 ± 13.0, 17.9 ± 12.0, and 16.0 ± 11.6, respectively. The VPT values decreased as the UA level increased (P for trend < 0.002) [Table 4]. For patients 65 years or older, the VPT values in the Q1, Q2, Q3, and Q4 groups were 35.0 ± 12.1, 37.2 ± 11.1, 39.1 ± 11.3, and 44.0 ± 11.9, respectively.

Table 1: Comparison of clinical variables between patients with and without abnormal VPT.

| Characteristics | All patients | Male patients | Female patients |
|-----------------|--------------|---------------|----------------|
|                 | Normal vibration (n = 321) | Abnormal VPT (n = 503) | Statistics | P values | Normal vibration (n = 211) | Abnormal VPT (n = 250) | Statistics | P values |
| Male, n (%)     | 211 (65.7) | 250 (49.7) | 20.430 | <0.001 | 3.0 (0.2, 7.0) | 8.0 (2.0, 11.0) | -6.767 | <0.001 |
| Diabetes duration (years) | 4.0 (5.0, 10.0) | 10.0 (4.0, 13.0) | -5.677 | <0.001 |
| Age (years)     | 46.1 ± 11.8 | 93.9 ± 9.5 | -17.388 | <0.001 | 43.3 ± 10.9 | 58.3 ± 10.2 | -15.253 | <0.001 |
| BMI (kg/m²)     | 26.6 ± 4.2 | 25.3 ± 3.9 | 2.671 | 0.008 | 26.8 ± 4.0 | 25.6 ± 3.5 | 3.339 | <0.001 |
| TC (mmol/L)     | 5.1 ± 1.1 | 4.9 ± 1.3 | 2.523 | 0.012 | 5.1 ± 1.2 | 4.9 ± 1.3 | 3.956 | <0.001 |
| TG (mmol/L)     | 2.2 (1.4, 3.5) | 1.6 (1.1, 2.5) | 4.615 | 0.011 | 2.4 (1.5, 4.2) | 1.5 (1.1, 2.4) | 5.060 | <0.001 |
| HDL-C (mmol/L)  | 1.2 ± 0.3 | 1.2 ± 0.3 | -1.492 | 0.135 | 1.1 ± 0.3 | 1.2 ± 0.3 | -1.862 | 0.063 |
| LDL-C (mmol/L)  | 2.7 ± 0.8 | 2.6 ± 0.9 | 0.229 | 0.819 | 2.6 ± 0.9 | 2.5 ± 0.8 | 0.554 | 0.580 |
| HbA1c (%)       | 10.1 ± 1.1 | 9.9 ± 2.3 | 0.620 | 0.535 | 10.3 ± 8.7 | 10.0 ± 2.3 | 0.562 | 0.574 |
| UA (µmol/L)     | 314.9 ± 92.8 | 294.5 ± 84.0 | 3.274 | 0.001 | 336.9 ± 89.6 | 311.7 ± 85.2 | 3.089 | <0.001 |
| eGFR (ml·min⁻¹·1.73 m⁻²) | 111.9 ± 5.1 | 98.0 ± 14.8 | 13.033 | <0.001 | 113.7 ± 15.0 | 99.6 ± 15.8 | 9.762 | <0.001 |

Data were presented as mean ± standard deviation, median (Q1, Q3), or proportions. *Student t test, †Chi-square test, ‡Mann-Whitney U test, BMI: Body mass index; CVD: Cardiovascular disease; DR: Diabetic retinopathy; eGFR: Estimated glomerular filtration rate; HbA1c: Glycated hemoglobin A1C; HDL-C: High-density lipoprotein cholesterol; HT: Hypertension; LDL-C: Low-density lipoprotein cholesterol; TC: Total cholesterol; TG: Triglyceride; UA: Uric acid.
The present cross-sectional study, we found that lower UA level (UA ≤ 6.0 μmol/L for men, ≤ 2.0 μmol/L for women) was associated with poor outcome in patients with acute cerebral infarction. Furthermore, men with acute cerebral infarction who had good clinical outcome had higher UA levels. Amato et al also confirmed that an increased UA level correlated with a better outcome in patients with acute stroke. In the ACROSS-China study, a lower level of UA (≤ 22 μmol/L) was reported to be an independent and strong predictor of acute stroke.

Importantly, this association was significant in the older male subgroup (age ≥ 65 years). Overall, the relationship between UA and the risk of acute stroke was not significant in the younger male subgroup (age < 65 years). The association of reduced UA with increased risk of acute stroke has been demonstrated in several studies. Zhang et al observed that patients with acute cerebral infarction who had good clinical outcome had higher UA levels. Amato et al also confirmed that an increased UA level correlated with a better outcome in patients with acute stroke.

In our study, we observed a reverse association of UA with abnormal VPT, an indicator of large-nerve dysfunction. Indeed, gender is known to have an impact on the UA level and the risk of abnormal VPT, but there is no significant relationship between UA and vibration perception in female patients. Thus, our findings indicate that premenopausal levels of estrogen in females may lead to greater renal clearance of UA in this study. Indeed, the urinary UA excretion rate was significantly higher in women than in men. However, the difference in estrogen levels is a cause for the difference in the levels of UA in men and women.

Estrogens have been demonstrated to increase UA processing in the renal tubules, thereby reducing UA levels. Thus, one possible explanation for this association was observed in men but not in women. Indeed, estrogen has been shown to reduce UA levels, which could be the impact of estrogen on the serum UA level in the two gender subgroups. Our data show that a lower level of UA was associated with increased risk of abnormal VPT values decreased with increasing UA level, but this trend was not significant in the older male subgroup (age ≥ 65 years). Overall, the relationship between UA and VPT values decreased with increasing UA level, but this trend was not significant in the older male subgroup (age ≥ 65 years).

Table 2: Assessment of affected factors in patients with T2D with abnormal VPT by univariate logistic regression.

| Variables                              | All T2D patients | Male T2D patients | Female T2D patients |
|----------------------------------------|-------------------|-------------------|---------------------|
| Sex (female vs. male)                  | <0.001            | 1.94 (1.45–2.59) | 0.004               |
| UA (hyperuricemia vs. normal uric acid)| 0.015             | 0.60 (0.39–0.91) | 0.816               |
| Age (≥65 years vs. <65 years)          | <0.001            | 11.18 (5.78–21.63)| 0.001               |
| Diabetes duration (≥10 years vs. <10 years) | <0.001            | 3.46 (2.37–5.06) | 0.001               |
| BMI (kg/m²)                            | 0.135             | 0.77 (0.55–1.09) | 0.179               |
| eGFR (≥90 vs. <90 ml/min·1.73 m⁻²)     | 0.011             | 0.61 (0.42–0.89) | 0.004               |
| HbA1c (control vs. uncontrolled)       | 0.726             | 1.10 (0.65–1.86) | 0.585               |
| Dyslipidemia (yes vs. no)              | <0.001            | 0.59 (0.43–0.87) | 0.232               |
| Hypertension (yes vs. no)              | 0.023             | 0.75 (0.48–1.17) | 0.005               |

BMI: Body mass index; CI: Confidence interval; eGFR: Estimated glomerular filtration rate; HbA1c: Glycated hemoglobin A1c; OR: Odds ratio; UA: Uric acid.
Several reports have shed light on the protective role of UA. UA is the end product of purine synthesis and well known as an anti-oxidant and anti-inflammatory agent.[33-36] A reduction in UA reduces oxidant and peroxynitrite scavenging capacity, which may contribute to the occurrence of Alzheimer disease.[37] Furthermore, UA was shown to be effective in suppressing the Fenton reaction and detoxifying oxidants, indicating its critical role in membrane stabilization. In addition, UA protected cultured rat hippocampal neurons from glutamate-induced cell death.[38] Another possible mechanism underlying the protective role of UA might be the slowing of the degradation rate of extracellular superoxide dismutase-3[39] and acting as a negative feedback in counterbalancing the increase in reactive oxygen species.[40] Last, increased UA concentrations have been reported in rat models of focal ischemia, owing to the conversion of xanthine dehydrogenase to xanthine oxidase that occurs in ischemic areas or endothelial cells.[41,42] Reports suggest that hyperuricemia might play an important role in counteracting oxidative damage.[35,36] With regard to the association of UA and large-nerve fiber dysfunction in our study, studies on the effects of suppression of UA in peripheral nerve dysfunction in diabetes might help to further illustrate the underlying mechanisms.[43,44] The overproduction of nitric oxide might play a central role in renal mechanisms. Nitric oxide overproduction mediates hyperfiltration.[43] Increased glomerular filtration and filtration fraction of UA result in uricosuria.[44] Nitrosative stress coupled with oxidative stress contribute to peroxynitrite formation and lipid peroxidation, which damage adenosine triphosphate and mitochondria.[45] decrease cellular viability,[46] and induce apoptosis.[47] Moreover, the loss of antioxidant coupled and peroxynitrite scavenger might exacerbate various diabetic complications, even peripheral nerve dysfunction.[48] Unfortunately, hyperglycemia promotes the synthesis of reactive oxygen intermediates and suppresses levels of antioxidants.[49] This might be an explanation for the association between UA and large-nerve fiber dysfunction observed in our study, although further research is needed to confirm this.

Consistent with other studies, we also observed traditional risk factors for abnormal VPT as a marker of large-nerve fiber dysfunction including age, diabetes duration, and HT. Previous reports have shown that patients with abnormal VPT tended to be older and had a longer duration of diabetes.[1,49] This may, in part, explain why VPT values did not differ significantly among the UA quartiles for elderly patients (age ≥ 65 years). In addition, patients who developed an abnormal VPT were more likely to have other comorbidities (eg, HT). Thus, our results further corroborate the relationship between these risk factors and the occurrence of large-nerve fiber dysfunction.[11]

There are a few limitations to this study. First, information on nerve conduction and/or tissue biopsies is lacking, which can be used to formally measure neural dysfunction. Although such methods are different from VPT, a non-invasive test in detecting loss of protective sensation, they are impractical for routine screening. Second, the levels of UA were tested within the nearest 3 days before or after hospitalization rather than at a fixed time with restricted low-purine diet, which might confound its concentration. Third, all the information was extracted from electronic records, hence information on smoking, drinking, food, and exercise are not available. However, we attempted to adjust for all confounders that were collected from the medical records. Fourth, since this was a single-centered study, caution is recommended when generalizing these results to other populations. Indeed, our study did involve analysis of a large pool of patients with T2D. Last, attention should be paid to the prevalence of abnormal vibration in clinical practice when patients with T2D show a decreased serum UA level. However, this cross-sectional study was not powered to prove a causal relationship between UA levels and large-nerve fiber dysfunction. Therefore, well-designed prospective multi-center studies are warranted to better understand the cause-and-effect relationship between serum UA levels and large-fiber dysfunction.
In conclusion, lower serum levels of UA correlated with an abnormal VPT, an indicator of large-nerve fiber dysfunction, in male patients but not in females. Moreover, only in the younger subgroup of male patients (<65 years), lower levels of UA were also associated with higher values of VPT.

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Conflicts of interest

None.

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