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# An Overview of Peripheral Neuropathy in Type 2 Diabetic Patients

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**ABSTRACT**

**Background**: Elevated serum uric acid (SUA) level was associated with Diabetic Nephropathy (DN) in Previous recent studies. Diabetic neuropathy is one of the most common chronic complication of diabetes characterized by damage to nerve glial cells, axons, and endothelial cells, and the morbidity from 30% to 50% in T2DM Diabetic peripheral neuropathy (DPN) is the main clinical manifestation of sensory and autonomic nerve symptoms, distal symmetry polyneuropathy, and motor neuropathy are the most common types of DPN.

## Introduction

Type 2 diabetes mellitus (T2DM) is associated with long-term complications resulting in cardiovascular diseases, renal failure, and nephropathy [1, 2]. It has increased health problems and become a worldwide concern [3, 4]. Type 2 DM involves 90–95% of diabetics and is more prevalent among the elderly [5, 6]. Diabetic Peripheral Neuropathy (DPN) is one of the most common chronic microvascular complications in progressing of T2DM to diabetic foot ulcer [6]. It frequently leads to amputation and/or disability and death. DPN accounts for 30–50% of patients with diabetic leg and foot ulcers [7]. The main related factors included age > 40 years, obesity, and hypertension [8,9,10]. However, its prevalence and the risk factors on a global scale remain unclear especially in the low- and middle-income countries. Previous research revealed that hyperuricemia with hyperglycemia, insulin resistance, dyslipidemia, and metabolic syndrome, all are involved in the development of diabetic neuropathy [11,12,13].

According to the reports in 2020, serum uric acid (SUA) level ≥ 7.3 mg/dL was found to be associated with an increase in peripheral neuropathy [14]. The high SUA level was related to the incidence of macro and microvascular complications in patients with DM. An elevated level of SUA in T2DM was associated with metabolic syndrome and insulin resistance [15], as well as with a higher risk of developing diabetic polyneuropathy [16]. Previous research identified SUA as a sign of oxidative stress from hyperuricemia, which can cause insulin resistance, diabetes, and cardiovascular disease [17]. However, SUA -lowering therapy has a positive effect on reducing the incidence of T2DM and insulin resistance [18].

The presence of DPN affects the quality of life and increases death from cardiovascular disease. Unfortunately, there is no certain therapy definitively eliminating the symptoms of diabetic neuropathy. Therefore, identifying the relationship between diabetic polyneuropathy and its

associated risk factors is essential to determine appropriate treatment and provide prevention and screening measurements. Acceding to the previous studies, there is a significant relationship between SUA levels and diabetic peripheral polyneuropathy. However, there is still no agreement among them, and further studies are recommended in this area. This study aimed to investigate the relationship between SUA levels and diabetic peripheral polyneuropathy in patients with type 2 diabetes referring to RAZI Clinic in Rasht during 2019–2020.

In recent years, human intake of foods such as those with the umami flavor (rich in purines), high added sugar (sucrose), and high fructose corn syrup have increased dramatically [1]. Fructose is the main component of added sugar. Unlike other sugars, fructose can cause mitochondrial oxidative stress [2, 3] and inhibits AMPK [4], and the subsequent intracellular ATP depletion [5] and nucleotide turnover lead to a significant increase in serum uric acid [6]. In addition to causing gout, many studies have shown that hyperuricemia is also closely related to cardiovascular diseases, metabolic syndrome, insulin resistance, and diabetes [7, 8]. However, its function is a matter of debate [9]. Here, we reviewed the effects of hyperuricemia on diabetes and its complications and concluded that high levels of uric acid is closely related to diabetes and its chronic complications.

*Uric Acid.* In the human body, uric acid is the ultimate product of purine metabolism. It is generated in the liver. Purine nucleotides decompose to hy- poxanthine and guanine, some of which can be recycled and phosphorylated into hypoxanthine nucleotides, while the remaining part is metabolized by xanthine dehydrogenase oxidase (XDH/XO) enzymatic reaction to the terminal product uric acid. XDH/XO is mainly expressed in the pa- renchymal cells of the liver and small intestine. XDH has low reactivity and can be converted to XO. Uric acid production primarily depends on the amount of substrate and the activity of XO [10-11]. In the end, XDH/XO promotes the final steps in purine metabolism which convert hypoxanthine to xanthine and xanthine to UA [11]. The kidney also plays an important role in the regulation of blood uric acid levels. The circulating uric acid is easily filtered from the glomeruli into the renal tubule. About 90% of filtered UA is reabsorbed by the middle of the proximal convoluted tubule mainly by urate transporter 1 (URAT1) and glucose transporter 9 (GLUT9) [12], and the remaining excreted 10% is responsible for 60–70% of total body uric acid excretion [13, 14]. A small amount of uric acid secreted in the intestine is responsible for 30–40% [14]. The production and excretion rate of uric acid is relatively constant in healthy people. Changes in the uric acid content in body fluids can reflect the state of metabolism, immunity, and other functions of the human body. If the body produces too much uric acid or the excretion mechanism is degraded, the body will retain excessive uric acid. Hyperuricemia was defined as the circulating uric acid levels of more than 5.7 mg/dl for women and 7.0 mg/dl for men [15]. When the blood uric acid concentration exceeds the norm, the human body fluid.

**Pathological Mechanism of Uric Acid on Diabetes and Its Chronic Complications**

1.1. *Uric Acid and Diabetes.* At present, many studies have shown that the relevant pathological mechanisms include some aspects as follows :

(1) *Inflammation*. Increased uric acid levels in the blood promoted the expression of interleukin-1$\beta$ (IL-1$\beta$), interleukin-6 (IL-6), tumor necrosis factor-$\alpha$ (TNF- $\alpha$) [19], and CRP production [20]. In animal studies, the activation of inflammation induced by UA decreases insulin sensitivity in mice [21], and infusion of UA into mice can increase TNF-$\alpha$ levels and activate the classical inflammatory pathway [22]. In human studies, serum UA was positively associated with TNF-$\alpha$, interleukin-6 and C-reactive protein in healthy people [23].

(2) *Oxidative Stress*. Excessive uric acid will lead to an increase in reactive oxygen species (ROS) pro- duction, which leads to inflammation and dys- function in the vessel [24]. UA is a powerful antioxidant that can remove superoxide and hy- droxyl radicals in plasma, and UA has prooxidant effects in vascular tissue by increasing ROS pro- duction, such as H2O2 [24]. UA-mediated oxidative stress-induced lipid peroxidation, DNA damage, and activation of inflammatory factors finally lead to cellular damage [24]. Oxidative stress also can affect the expression of insulin gene, causing a decrease in insulin secretion [25].

n a seemingly paradoxical relationship, both poor glucose control and rapid treatment of hyperglycemia can be associated with an increased risk of neuropathy. A clinically distinct form of neuropathy that deserves mention is treatment-induced neuropathy in diabetes (TIND). This underdiagnosed iatrogenic small-fiber neuropathy is defined as the “acute onset of neuropathic pain and/or autonomic dysfunction within 8 weeks of a large improvement in glycemic control specified as a decrease in glycosylated HbA1c of more than 2% points over 3 months” 15. TIND was first recognized soon after the introduction of insulin and named “insulin neuritis” 16. For many decades, “insulin neuritis” was considered a rare cause for acute neuropathy. However, recently published data suggest that it is much more common and clinically relevant. It is most common in type 1 diabetes mellitus (DM) treated with insulin, although rapid glucose correction can occur in both types of diabetes as a result of either insulin, or less frequently, oral agents. In a study by Gibbons and Freeman, a surprising 10.9% of 954 subjects with diabetes met criteria for TIND, and the risk of developing TIND was associated with the magnitude and rate of HbA1c change 15. Similar to DPN, the neuropathy of TIND generally follows a length-dependent pattern, but, in contrast, the pain and autonomic symptoms are more extensive and less responsive to opioids. The underlying pathophysiology is poorly understood, although it has been suggested that rapid glycemic control both with and without insulin leads to hemodynamic changes (arteriovenous shunting) resulting in endoneurial hypoxia of small fibers 17, 18.

he diagnosis of a DPN is most often made on clinical grounds with a suggestive clinical history and neurologic exam. The Toronto consensus criteria define probable neuropathy as the presence of two or more of the following: neuropathic symptoms, decreased distal sensation, or decreased or absent ankle reflexes. Confirmed neuropathy requires abnormality of nerve conduction study (NCS) or a validated measure of small-fiber function [19]. However, the diagnostic value of NCS in routine clinical practice has been called into question. Whereas patients with warning signs for an atypical neuropathy (e.g., acute onset, asymmetry, proximal involvement, and unexpected severity) clearly need electrodiagnostic testing, those with typical DPN likely do not need NCS to confirm diagnosis [20– 22]. Early diabetic neuropathy often preferentially involves small-diameter axons; thus, skin biopsy with assessment of intraepidermal nerve fiber density (IENFD) may be useful in confirming the diagnosis when clinically warranted. In our practice, we use skin biopsies when we suspect a predominately small-fiber neuropathy in patients with an atypical course or a paucity of risk factors. Corneal confocal microscopy provides a non-invasive quantitative method of detecting neuropathy, and has been found to be more sensitive in assessing nerve repair than other standard measures such as IENFD and NCS [23]. Patients with suspected DPN should have a basic workup, including a blood glucose or hemoglobin A1c to confirm diabetes (fasting plasma glucose of more than 126 mg/dL or A1c of more than 6.5%) or pre-diabetes (fasting plasma glucose of more than 100 mg/dL or A1c of 5.7 to 6.4%), vitamin $B_{12}$ deficiency, paraproteinemia (serum protein electrophoresis and immunofixation), and (when appropriate) evaluation for alcohol use [24, 25]. When routine blood glucose testing is normal, the glucose tolerance test should be considered [24]. An important cause of vitamin $B_{12}$ deficiency is iatrogenic, linked to cumulative doses of metformin.

*Uric Acid and Diabetic Peripheral Neuropathy*. Diabetic neuropathy is one of the most common chronic complication of diabetes characterized by damage to nerve glial cells, axons, and endothelial cells, and the morbidity from 30% to 50% in T2DM. Diabetic pe- ripheral neuropathy (DPN) is the main clinical manifesta- tion of sensory and autonomic nerve symptoms, distal symmetry polyneuropathy, and motor neuropathy are the most common types of DPN. The pathophysiology changes conclude polyol pathway, PKC activity, increased AGEs, oxidative stress (ROS), inflammation (IL-1$\beta$, IL-6, TNF$\alpha$, and COX-2), microvascular alterations (endothelial dysfunction), nerve degeneration and regrowth (MMPs, Schwann cells and ECM), and the changes of the blood- nerve barrier  Lin et al. observed sig- nificant differences in the ratio of motor and sensory nerve amplitude and conduction velocity (CV) parameters be- tween groups with different blood UA levels (both $P < 0.05$). Blood UA levels were negatively correlated with the ratio of motor and sensory nerve amplitude and CV. Blood UA at 9 mg/dl and total cholesterol of 5.2 mmol/l were significantly associated with DPN in patients who had suffered from T2DM for more than 10 years. Yu et al. [25] performed a meta-analysis of 1388 patients with T2DM with peripheral neuropathy and in 4746 patients without peripheral neu- ropathy and showed that SUA levels were significantly el- evated in patients with diabetes complicated with peripheral

neuropathy and that increased hyperuricemia was related with increased risk of peripheral neuropathy.

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