Uric acid in the balance — neuropathy

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Welcome to another Diabetes Digest commentary on a recent paper, as well as several short abstracts of other papers that you may find interesting or useful to your clinical or research practice.

The paper I have chosen to focus upon is from a group in Quanzhou, China, led by Zhuang et al. This group looked at Serum uric acid (SUA) levels in relation to diabetic peripheral neuropathy (DPN). As we all know, the aetiological jigsaw puzzle for peripheral neuropathy pathogenesis is incomplete, with many factors identified and accepted. One of these, although having limited recent data, is the effect of hyperuricaemia and DPN. This study by Zhang et al hypothesised that perhaps low serum uric acid may also play a similar role. The rationale for this hypothesis was that a high SUA may cause vascular smooth muscle cells migration and inhibit endothelial cell release of nitric oxide; whereby resulting in vascular dysfunction and irreversible damage and thus tissue ischaemia and impaired peripheral nerve function.

Therefore, due to the important antioxidant effect of SUA, maintaining a too-low SUA level over the long-term may conversely expose people with diabetes to increased oxidative stress and, thus, nerve pathologies. This was a prospective observational study that enrolled 525 type 2 diabetes mellitus (T2DM) subjects without hyperuricemia, into those with symptomatic neuropathy (SDPN; n=150), asymptomatic neuropathy (ASDPN; n=125) and no neuropathy (NDPN; n=250).

Exclusion criteria were extensive, including <20 or >75 years old, hyperuricemia, gout, medication influencing SUA, malnutrition, severe liver or kidney damage, acute infection, alcohol abuse, non-diabetic neuropathies, etc. Neuropathy was determined by deficits in 10g monofilament, vibration, temperature pain sensations and neurogenic symptoms. Additionally, bilateral motor and sensory nerve conduction studies were performed at the median nerve, ulnar nerve, tibial nerve and common peroneal nerves. Retinol examinations included retinal photographs, optical coherence tomography and fluorescein angiography.

Venous blood samples were obtained for SUA, fasting plasma glucose, HbA_{1c}, creatinine, lipids, liver and renal function, and these were recorded.

There were no significant differences between the groups for: age, sex ratio, BMI, blood pressure, blood lipids, liver and kidney function, vitamin B12 and PLT. The incidence of diabetic retinopathy was found to be higher in those with diabetes with symptomatic neuropathy.

In all three groups, SUA was less than 420 (313.7±73.1) umol/L. It was more reduced in ASDPN compared with NDPN (P< 0.001) but even further decreased in SDPN group (P<0.001). Nerve conduction in SDPN showed the greatest impairment. In a multivariate model controlling for other covariables and after adjustment, the low SUA was independently associated with diabetic neuropathy (odds ratio 0.985 [0.981 ~ 0.988], P<0.001). Similarly, low SUA level was positively correlated with the mean of values in all nerve conduction parameters: Motor and sensory action potentials and conduction velocities (r=0.470, P<0.001; r = 0.396, P<0.001, respectively). The SUA level was shown to distinguish between patients with and without diabetic neuropathy.

The study has shown that low SUA appears to have detrimental adverse effects on nerve function and may equally contribute to the pathogenesis of DP regarding uric acid and nerve damage. It appears it is a balance — not too high and not too low. ■

Zhuang Y, Huang H, Hu X et al (2022) Serum uric acid and diabetic peripheral neuropathy: a double-edged sword. Acta Neurol Belg doi: 10.1007/s13760-022-01978-1. [Online ahead of print]

PLoS One

Masticatory dysfunction in patients with diabetic neuropathy: A cross-sectional study

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓✓

1 Chewing well is beneficial for both effective diet therapy and control of blood glucose level in individuals with diabetes. Meanwhile, long-term hyperglycaemia is a risk factor for microvascular complications, which are the main cause of morbidity and mortality in these patients.

2 The authors set out to determine whether or not masticatory disorders are relevant to diabetic microvascular complications. A cross-sectional study included 172 patients with type 2 diabetes who underwent educational between April 2016 and March 2020.

3 According to the bivariable analysis, masticatory efficiency was significantly correlated with diabetes duration, number of remaining teeth, the number of moving teeth and condition of diabetic neuropathy.

4 Multivariable linear regression models were constructed to examine which factors were related to masticatory efficiency. Statistical significance was defined as a two-sided ***P*** value of < 0.05.

5 The authors demonstrated that patients with type 2 diabetes who developed diabetic neuropathy had significantly reduced masticatory efficiency.

Hamamoto Y, Ouhara K, Miyagawa T et al (2022) Masticatory dysfunction in patients with diabetic neuropathy: A cross-sectional study. PLoS One 17(6): e0269594

Diabetes Metab Res Rev

Weight-bearing physical activity in people with diabetes-related foot disease: A systematic review

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓✓

1 People with diabetes-related foot disease can benefit from weight-bearing physical activity, but it may also contribute to ulceration or delayed ulcer healing.

2 The authors systematically searched peer-reviewed literature for studies reporting objectively measured weight-bearing activity in people with diabetes-related foot disease. Daily step counts' means (over studies) and weighted means (over participants) were calculated.

3 A total of 27 publications were included from a potential 1,247. The mean steps/day in people with International Working Group of the Diabetic Foot risk 1/2: 6,125 (12 studies; 345 participants; weighted mean: 5,384). In IWGDF risk 3: 6,167 (eight studies; 291 participants; weighted mean: 6,239). In those with a foot ulcer: 4,248 (six studies; 186 participants; weighted mean: 4,484).

4 Levels of weight-bearing physical activity were found to be similar between people with diabetes at various risk levels for foot ulceration but lower for those with a foot ulcer. Weight-bearing activity differs depending on the climatological environment and is higher indoors than outdoors. These results provide reference for intervention studies or for clinicians aiming to provide mobility advice in this population.

van Netten JJ, Fijen VM, Bus SA (2022) Weight-bearing physical activity in people with diabetes-related foot disease: A systematic review. Diabetes Metab Res Rev e3552 [Online ahead of print]

BMJ Open Diabetes Res Care

Efficacy and safety of the combined metabolic medication, containing inosine, nicotinamide, riboflavin and succinic acid, for the treatment of diabetic neuropathy: a multicenter randomized, double-blind, placebo-controlled parallel group clinical trial

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓

1 Antioxidants may have a positive impact on diabetic polyneuropathy (DPN), likely due to alleviation of oxidative stress. We aimed to evaluate the efficacy and safety of combination of antioxidants: succinic acid, inosine, nicotinamide and riboflavin (SINR) in the treatment of DPN.

2 Men and women (aged 45-74) with type 2 diabetes and symptomatic DPN, with initial Total Symptom Score (TSS) 5, were randomised into experimental (n=109) or placebo (n=107) group.

3 In the SINR group, mean TSS change after 12 weeks was -2.65 (±1.46) vs -1.73 (±1.51) in the placebo group (P<0.0001; t-test). Reduction of symptoms in the SINR group was achieved regardless of haemoglobin A1c levels, but better results were observed in patients with initial TSS <7.5.

4 The combination of SINR effectively alleviates DPN symptoms in patients with type 2 diabetes.

Kharitonova T, Shvarts YG, Verbovoy AF et al (2022) Efficacy and safety of the combined metabolic medication, containing inosine, nicotinamide, riboflavin and succinic acid, for the treatment of diabetic neuropathy: a multicenter randomized, double-blind, placebo-controlled parallel group clinical trial (CYLINDER). BMJ Open Diabetes Res Care10(3):e002785

Diabetes Res Clin Pract

Association between plasma apolipoprotein M and cardiac autonomic neuropathy in type 1 diabetes

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓

1 Cardiac autonomic neuropathy (CAN) is characterised by an increased risk of cardiovascular mortality. CAN is diagnosed by a decreased heart rate viability (HRV). This study aimed to investigate if plasma apoM was associated with an increased risk of CAN.

2 A total of 278 individuals with type 1 diabetes were recruited from Steno Diabetes Center in Copenhagen, Denmark, from 2010 to 2012.

3 A change of 0.1 µM plasma apoM was associated with the diagnosis of CAN. ApoM plasma levels were also positively associated with CAN when adjusted for age and gender, as well as lipids, beta-blockers, blood pressure, alcohol and Hba_{1c}, and time with diabetes.

4 Increased plasma apoM was associated with an increased risk of CAN and a significant reduction in HRV indices. Further studies are needed to explore additional molecular alterations behind such observations.

Safi M, Borup A, Stevns Hansen C et al (2022) Association between plasma apolipoprotein M and cardiac autonomic neuropathy in type 1 diabetes. Diabetes Res Clin Pract 189:109943

> "As we all know, the aetiological jigsaw puzzle for peripheral neuropathy pathogenesis is incomplete, with many factors identified and accepted."