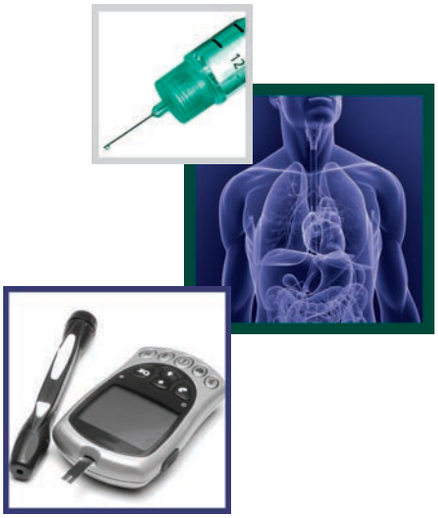
EDITORIAL

Vitamin D and painful diabetic neuropathy: missing link or innocent bystander?



Uazman Alam[1]

Rayaz A Malik*[1]

"There is a significant need for novel medication in the treatment of painful diabetic neuropathy ... there is a growing body of evidence that vitamin D deficiency may be related to diabetic neuropathy."

Painful diabetic neuropathy is an extremely disabling condition that may be present in at least a fifth of diabetic patients [1]. The etiology of painful diabetic neuropathy is complex with peripheral somatic [2,3], autonomic [4] and central thalamic perfusion defects identified in these patients [5]. The characteristic symptoms include symmetrical paresthesia, dysesthesia, electric shock-like pains and allodynia in the feet with nocturnal exacerbation. The treatment of this condition has remained unsatisfactory with a 'good' response to conventional medication rated at between 30–50% pain relief [6]. There are many available treatments, all are at best moderately effective, and their use is limited by side effects. Currently, there are only two US FDA-approved treatments, duloxetine and pregabalin, based on proven efficacy in randomized placebo-controlled trials; however, neither are entirely effective, particularly as patients can have a poor response and/or tolerability to both medications [7]. Furthermore, recent studies of novel drugs in the treatment of painful diabetic neuropathy have dramatically failed [8,9], with active treatment being barely superior to placebo. Therefore, there is a need to establish potential new mechanisms and, hence, treatments for painful diabetic neuropathy. It is, therefore, intriguing that a recent study has shown elevated levels of methylglyoxal in diabetic patients with painful neuropathy, and has shown that it mediates its effects by depolarizing sensory neurons and inducing post-translational modification of the voltage-gated sodium channel $Na_v1.8$, which is associated with increased electrical excitability, facilitating firing of nociceptive neurons [10]. Gain-of-function variants of the sodium channel $Na_v1.7$ and, more recently, $Na_v1.8$ have been found in a significant proportion of patients with painful neuropathy [11]. While these observations are of potential relevance, translation to clinically effective therapies is likely to take several years.

Vitamin D deficiency is highly prevalent in diabetic populations [12] and those with deficiencies are likely to have common characteristics to those with painful diabetic neuropathy. Three recent studies have found an association between vitamin D deficiency and diabetic neuropathy [13–15]; however, all have failed to assess the differences between positive (hyperalgesia and allodynia) and negative (paresthesia and

"The treatment of this condition has remained unsatisfactory with a 'good' response to conventional medication rated at between 30–50% pain relief."

[1]Centre for Endocrinology & Diabetes, Institute of Human Development, University of Manchester & The Manchester Royal Infirmary, Central Manchester Hospital Foundation Trust, 46 Grafton Street, Manchester, M13 9NT, UK
*Author for correspondence: Tel.: +44 161 275 1196; Fax: +44 161 275 1183; rayaz.a.malik@manchester.ac.uk

Future Medicine part of fsg

numbness) symptoms in these cohorts. Previous epidemiological studies have shown a higher prevalence of painful diabetic neuropathy and painful symptoms *per se* in south Asians despite a lower prevalence of neuropathy compared with other ethnic groups [1]. South Asians are at the highest risk of vitamin D deficiency [12]. In our previous study [12], 55% of the south Asian patients were severely deficient in vitamin D, with 25-hydroxyvitamin D levels <10 ng/ml, and there is probably a considerable overlap with those who suffer from painful diabetic neuropathy. We are not aware of a seasonal variation of pain in neuropathic states, and if painful diabetic neuropathy may, in part, be attributed to vitamin D deficiency then there should be a theoretical excess of pain in winter in the northern hemisphere. Our previous prevalence data show minimal seasonal variation in white Europeans, while there is no variation in south Asians in the north west of England [12]. Of further clinical relevance, a recent study from India has shown that vitamin D deficiency is significantly associated (odds ratio: ~4.0) with infected foot ulcers [16]. This suggests an added detrimental effect of vitamin D deficiency as a consequence of reduced immunity, and a consequent increased risk of infection in diabetic patients who have developed an ulcer due to neuropathy.

"Vitamin D deficiency is highly prevalent in diabetic populations and those with deficiencies are likely to have common characteristics to those with painful diabetic neuropathy."

Treatment

Studies of the therapeutic use of vitamin D in patients with painful diabetic neuropathy are limited. Vitamin D is thought to exert an effect on the peripheral nerve through NGF [17,18] and calbindin-D (a calcium-binding protein in the peripheral axon) [19]. A recent study of a rodent neuropathic pain model has shown an antinociceptive effect of 1,25-dihydroxyvitamin D3 in a dose-dependent manner [20]. To date, we know of only two interventional studies. The first by Valensi *et al.*, who assessed the effects of a topical compound (QR-333) containing quercetin (which has aldose reductase inhibitor effects), ascorbyl palmitate and vitamin D3 [21]. Although this study was a double-blind placebo-controlled trial, with three distinct compounds that may induce active effects, it is difficult to define the relative effectiveness of vitamin D3. The second study by Lee *et al.* showed that oral cholecalciferol resulted in an approximate 50% reduction in painful neuropathic symptoms; however, this study had neither a placebo group nor was it randomized, leaving it open to considerable bias [22]. Vitamin D supplementation has been used effectively to treat other conditions of pain, particularly in rheumatological conditions [23,24]. However, a Cochrane review by Straube *et al.* concluded that there was a poor evidence base for the use of vitamin D in chronic pain, because studies were of variable quality with variable outcomes due to methodological differences [25]. There is a significant need for novel medication in the treatment of painful diabetic neuropathy. Furthermore, there is a growing body of evidence that vitamin D deficiency may be related to diabetic neuropathy. A well-constructed controlled trial of vitamin D supplementation in painful diabetic neuropathy is required in order to truly assess the effectiveness of this treatment. While awaiting the results of such studies, our current replacement regimen consists of an initial bolus of 40,000 U of vitamin D3 daily with the evening meal for 21 days, followed by a long-term maintenance dose of 20,000–40,000 U once weekly.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

1 Abbott CA, Malik RA, van Ross ER, Kulkarni J, Boulton AJ. Prevalence and characteristics of painful diabetic neuropathy in a large community-based diabetic population in the U.K. *Diabetes Care* 34(10), 2220–2224 (2011).

2 Quattrini C, Tavakoli M, Jeziorska M *et al.* Surrogate markers of small fiber damage in human diabetic neuropathy. *Diabetes* 56(8), 2148–2154 (2007).

3 Karlsson P, Porretta-Serapiglia C, Lombardi R, Jensen TS, Lauria G. Dermal innervation in healthy subjects and small fiber neuropathy patients: a stereological reappraisal. *J. Peripher. Nerv. Syst.* 18(1), 48–53 (2013).

4 Gandhi RA, Marques JL, Selvarajah D, Emery CJ, Tesfaye S. Painful diabetic neuropathy is associated with greater autonomic dysfunction than painless diabetic neuropathy. *Diabetes Care* 33(7), 1585–1590 (2010).

5 Selvarajah D, Wilkinson ID, Gandhi R, Griffiths PD, Tesfaye S. Microvascular perfusion abnormalities of the thalamus in painful but not painless diabetic polyneuropathy: a clue to the pathogenesis of pain in Type 1 diabetes. *Diabetes Care* 34(3), 718–720 (2011).

6 Bril V, England J, Franklin GM *et al.*; American Academy of Neurology; American Association of Neuromuscular and Electrodiagnostic Medicine; American Academy of Physical Medicine and Rehabilitation. Evidence-based guideline: treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *Neurology* 3(4), 345–352 (2011).

7 Tesfaye S, Vileikyte L, Rayman G *et al.*; on behalf of the Toronto Expert Panel on Diabetic Neuropathy. Painful diabetic peripheral neuropathy: consensus recommendations on diagnosis, assessment and management. *Diabetes Metab. Res. Rev.* doi:10.1002/dmrr.1225 (2011) (Epub ahead of print).

8 Selvarajah D, Gandhi R, Emery CJ, Tesfaye S. Randomized placebo-controlled double-blind clinical trial of cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: depression is a major confounding factor. *Diabetes Care* 33(1), 128–130 (2010).

9 Ziegler D, Hidvégi T, Gurieva I *et al.*; Lacosamide SP743 Study Group. Efficacy and safety of lacosamide in painful diabetic neuropathy. *Diabetes Care* 33(4), 839–841 (2010).

10 Bierhaus A, Fleming T, Stoyanov S *et al.* Methylglyoxal modification of $Na_v1.8$ facilitates nociceptive neuron firing and causes hyperalgesia in diabetic neuropathy. *Nat. Med.* 18(6), 926–933 (2012).

11 Faber CG, Lauria G, Merkies ISJ *et al.* Gain-of-function $Na_v1.8$ mutations in painful neuropathy. *Proc. Natl Acad. Sci. USA* 109(47), 19444–19449 (2012).

12 Alam U, Najam O, Al-Himdani S *et al.* Marked vitamin D deficiency in patients with diabetes in the UK: ethnic and seasonal differences and an association with dyslipidaemia. *Diabet. Med.* 29(10), 1343–1345 (2012).

13 Soderstrom LH, Johnson SP, Diaz VA, Mainous AG 3rd. Association between vitamin D and diabetic neuropathy in a nationally representative sample: results from 2001–2004 NHANES. *Diabet. Med.* 29(1), 50–55 (2012).

14 Shehab D, Al-Jarallah K, Mojiminiyi OA, Al Mohamedy H, Abdella NA. Does vitamin D deficiency play a role in peripheral neuropathy in Type 2 diabetes? *Diabet. Med.* 29(1), 43–49 (2012).

15 Skalli S, Muller M, Pradines S, Halimi S, Wion-Barbot N. Vitamin D deficiency and peripheral diabetic neuropathy. *Eur. J. Intern. Med.* 23(2), e67–e68 (2012).

16 Tiwari S, Pratyush DD, Gupta B *et al.* Prevalence and severity of vitamin D deficiency in patients with diabetic foot infection. *Br. J. Nutr.* 109(1), 99–102 (2013).

17 Riaz S, Malcangio M, Miller M, Tomlinson DR. A vitamin D(3) derivative (CB1093) induces nerve growth factor and prevents neurotrophic deficits in streptozotocin-diabetic rats. *Diabetologia* 42(11), 1308–1313 (1999).

18 Wion D, MacGrogan D, Neveu I, Jehan F, Houlgatte R, Brachet P. 1,25-dihydroxyvitamin D3 is a potent inducer of nerve growth factor synthesis. *J. Neurosci. Res.* 28(1), 110–114 (1991).

19 Lee YS, Taylor AN, Reimers TJ, Edelstein S, Fullmer CS, Wasserman RH. Calbindin-D in peripheral nerve cells is vitamin D and calcium dependent. *Proc. Natl Acad. Sci. USA* 84(20), 7344–7348 (1987).

20 Nasirinezhad F, Ramezanian E, Sadeghi M. Concentration-effect relationship of intrapritoneal administration of 1,25 (OH) 2-vitamin D in a chronic constriction model of neuropathic pain. *Basic Clin. Neurosci.* 2(3), 43–50 (2011).

21 Valensi P, Le Devehat C, Richard JL *et al.* A multicenter, double-blind, safety study of QR-333 for the treatment of symptomatic diabetic peripheral neuropathy. A preliminary report. *J. Diabetes Complications* 19(5), 247–253 (2005).

22 Lee P, Chen R. Vitamin D as an analgesic for patients with Type 2 diabetes and neuropathic pain. *Arch. Intern. Med.* 168(7), 771–772 (2008).

23 Khan QJ, Reddy PS, Kimler BF *et al.* Effect of vitamin D supplementation on serum 25-hydroxy vitamin D levels, joint pain, and fatigue in women starting adjuvant letrozole treatment for breast cancer. *Breast Cancer Res. Treat.* 119(1), 111–118 (2010).

24 Catalano A, Morabito N, Atteritano M, Basile G, Cucinotta D, Lasco A. Vitamin D reduces musculoskeletal pain after infusion of zoledronic acid for postmenopausal osteoporosis. *Calcif. Tissue. Int.* 90(4), 279–285 (2012).

25 Straube S, Andrew Moore R, Derry S, McQuay HJ. Vitamin D and chronic pain. *Pain* 141(1–2), 10–13 (2009).