BMJ Open Diabetes Research & Care

Vitamin D for the treatment of painful diabetic neuropathy

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To cite: Basit A, Basit KA, Fawwad A, *et al*. Vitamin D for the treatment of painful diabetic neuropathy. *BMJ Open Diabetes Research and Care* 2016;**4**:e000148. doi:10.1136/bmjdrc-2015-000148

▸ Additional material is available. To view please visit the journal online (http://dx.doi.org/10.1136/bmjdrc-2015-000148).

Received 8 August 2015
Revised 12 October 2015
Accepted 13 November 2015

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ABSTRACT

Objective: To assess the effect of high-dose vitamin D in patients with painful diabetic neuropathy.

Methods: A single intramuscular dose of 600 000 IU vitamin D was administered, and the effects on metabolic parameters and neuropathic pain assessed over 20 weeks.

Results: 143 participants with predominantly type 2 diabetes, aged 52.31±11.48 years, with a Douleur Neuropathique 4 (DN4) score (3.0±1.8), total McGill pain score (21.2±14.9), and Short Form McGill Pain Questionnaire (SFMPQ) score (2.1±0.9), were enrolled. The baseline 25-hydroxyvitamin D (25(OH)D) level was 31.7±23.3 ng/mL and 58 (40.5%) patients showed evidence of vitamin D deficiency (25(OH)D<20 ng/mL). Intramuscular administration of vitamin D resulted in a significant increase in 25(OH)D (46.2±10.2 ng/mL, p<0.0001) and a reduction in positive symptoms on the DN4 (p<0.0001), total pain score (p<0.0001), and SFMPQ (p<0.0001).

Conclusions: Treatment with a single intramuscular dose of 600 000 IU of vitamin D in patients with painful diabetic neuropathy is associated with a significant decrease in the symptoms of painful diabetic neuropathy.

Trial registration number BIDE-12/2014.

Key message

- Vitamin D may play an important role in the treatment of painful diabetic neuropathy.
- A single high-dose intramuscular injection of vitamin D_3 provides significant relief in painful diabetic neuropathy.
- The benefits of vitamin D were maximal at 10 weeks and lasted for the period of the 20-week study.

INTRODUCTION

A large population-based study has recently shown that the prevalence of painful diabetic neuropathy (PDN) is ∼21%, and painful symptoms are more prevalent in patients with type 2 diabetes, females, and South Asians.[1] PDN is characterized by symmetrical lower limb paresthesiae, dysesthesiae, lancinating pains and allodynia, with nocturnal exacerbation[2] and significant sleep disturbance, with a reduced quality of life.[3] National and international guidelines advocate a range of therapies for symptom relief.[4,5] However, the therapeutic efficacy for all recommended medications is at best ∼50% pain relief and is limited due to unwanted side effects.[2,6] Apart from peripheral and central alterations,[7] metabolic alterations such as increased glycemic flux[8] and elevated plasma methylglyoxal levels have been implicated in the pathogenesis of PDN.[9]

Several recent observational studies in patients with diabetes have demonstrated a significant association between vitamin D deficiency, and paraesthesiae and numbness,[10] but also between neurological deficits and electrophysiology[11,12] as well as parasympathetic dysfunction.[13] Furthermore, a recent systematic review and meta-analysis of 1484 patients with type 2 diabetes has demonstrated a highly significant association (OR −2.68) between vitamin D deficiency and the development of diabetic peripheral neuropathy.[14] A more detailed study using electrophysiology and Douleur Neuropathique 4 (DN4) scores has shown that serum levels of vitamin D are significantly reduced while serum vitamin D-binding protein (VDBP) and vitamin D receptor (VDR) levels are comparable between diabetic patients with and without peripheral neuropathy.[15] Recently, the FIELD study, a multinational undertaking, has shown that vitamin D deficiency was present in 50% of 9795 patients with type 2 diabetes and it predicted microvascular outcomes.[16]

There is, of course, an association between vitamin D deficiency and painful symptoms in the general population.[17] In relation to a mechanistic link between vitamin D and pain, a recent study has shown that nociceptive calcitonin gene-related peptide-positive neurons have a distinct vitamin D phenotype with hormonally regulated ligand and receptor levels.[18] Vitamin D deficiency results in increased numbers of axons containing CGRP and, in culture, VDR expression is increased in growth cones and sprouting appears to be regulated by VDR-mediated rapid response signaling pathways.[19] Nerve Growth Factor (NGF) is known to be depleted in experimental diabetes[20] and, in a study of patients with diabetic neuropathy, NGF immunostaining on skin keratinocytes correlated with skin axon-reflex vasodilation, a measure of small fiber neuropathy.[21] In an experimental study, NGF expression was maintained in sciatic nerves of diabetic animals treated with a vitamin D analog (CB1093). Similarly, tacalcitol, active vitamin D_3, induces NGF production in human epidermal keratinocytes.[22] Treatment with vitamin D_3 has been shown to reduce demyelination in a cuprizone experimental model of demyelination[23] and, in a separate spinal cord compression model, it has been shown to induce axonal regeneration.[24]

In relation to the potential therapeutic benefits of vitamin D therapy, studies are limited. An open-label prospective study in 51 patients with type 2 diabetes and painful neuropathy showed that ~2000 IU of cholecalciferol daily for 3 months resulted in an ~50% decrease in the visual analog scale (VAS).[25] Recently, in a placebo controlled study of 112 patients with type 2 diabetes randomized to 50 000 IU of cholecalciferol once weekly for 8 weeks, there was a significant increase in 25(OH)D and an improvement in the Neuropathy Disability Score (NDS), but no change in NDS nor in neurophysiology.[26]

Given the mechanistic link between vitamin D and neuropathy, and the known prevalence of vitamin D deficiency, particularly in South Asians with diabetes, we have now undertaken a single-center open-label clinical trial to determine the effects of a single high-dose administration of intramuscular vitamin D on symptoms of PDN.

MATERIALS AND METHODS

Study design and participants

This prospective open-labeled study was conducted between June 2012 and April 2013, in the Baqai Institute of Diabetology and Endocrinology (BIDE) in Karachi, Pakistan.

Ethics statement

Ethical approval for the study was obtained from the Institutional Review Board (IRB) of BIDE. Study participants gave signed informed consent, in keeping with the Declaration of Helsinki.

Inclusion criteria

All patients with type 1 or type 2 diabetes, aged 18–80 years, with a glycated hemoglobin (HbA1c) level ≤11% at the screening visit, were considered eligible to participate in the study.

Exclusion criteria

Patients with renal impairment, or hypothyroidism or hyperthyroidism; patients currently taking vitamin D supplementation, or antiepileptic or antituberculous medication; patients with a previous or current problem of primary or tertiary hyperparathyroidism, hypercalcemia, psychiatric disorder, alcohol dependency, Hepatitis B or C, HIV infection or peripheral neuropathy due to a non-diabetic cause; pregnant or breastfeeding female patients; patients allergic to nuts or any nut products and patients participating in any other interventional research trial, were excluded from the study.

Assessment

Patients underwent assessment at baseline and on four subsequent visits every 5±1 week, such that the second, third, fourth, and fifth visits occurred at 4–6; 8–12; 14–16 and 18–20 weeks, respectively.

Data collection

Blood pressure, weight, and height were recorded at all visits. The 25-hydroxyvitamin D (25(OH)D) serum calcium (Ca), HbA1c, fasting blood glucose, and creatinine, were assessed at the screening (visit 1, V1) and the last visit (V5) of the study. Medications for PDN were not changed throughout the study.

PDN assessment

Six questions that reflected positive symptoms for pain on the DN4 Neuropathic Pain Diagnostic Questionnaire, those being questions 1, 2, 3, 4, 5, and 10 (sensations of burning, painful cold, electric shocks, tingling, pins and needles, and brushing, respectively), were assessed in all participants at each visit. The Short Form McGill Pain Questionnaire (SFMPQ) was evaluated to establish the sensory dimensions of pain, which included pain sensations such as throbbing, shooting, stabbing, sharp, cramping, gnawing, hot, burning, aching, heavy, tender, and splitting; and affective dimensions of the pain experience, which included sensations such as tiring-exhausting, sickening, fearful, and punishing-cruel.[27] The primary efficacy parameter was the change in total McGill pain location (higher numbers indicating more severe pain) and McGill pain score.

Administration of vitamin D_3 injection and measurement of 25(OH)D

A single intramuscular dose of 600 000 IU of vitamin D_3 was administered at V1 by paramedical staff in accord with the results of a recent study indicating a good therapeutic effect with this dose.[28] The laboratory used internal quality controls for the measurement of 25 (OH) vitamin D. Serum 25(OH)D was measured using an immunoenzymometric assay, based on a solid phase ELISA performed on microtiter plates, and was performed exactly per the manufacturer's instructions.

The cross-reactivity for vitamin D_2 (of the assay) as per manufacturer's assertion was 100% (relative to vitamin D_3) and the assay has excellent correlation to existing globally recognized assays, in combination with good sensitivity and precision (EP17-A Protocols for

Determination of Limits of Detection and Limits of Quantitation; Approved Guideline, STANDARD published by Clinical and Laboratory Standards Institute). The linear range of the assay is 7.7–122.9 ng/mL. Interassay and intra-assay variation of the in-house control was 2.5% and 9.2%, respectively.

Vitamin D levels were categorized as deficient (25(OH)D<20 ng/mL), insufficient (25(OH)D 20–30 ng/mL), and sufficient (25(OH)D>30 ng/mL).[29]

STATISTICAL ANALYSIS

Data analyses were conducted on StatsDirect (Altrincham, Cheshire, UK). All continuous variables, namely, age, weight, height, body mass index, systolic and diastolic blood pressure, and biochemical variables, are presented as mean±SD. Analysis of variance (ANOVA) and paired Student t test or non-parametric counterpart were used depending on the normality of the data. All participants enrolled into the study were included in subsequent analyses with missing data handled by using the last observation carried forward (LOCF) for pain scores. Regression analyses were undertaken between baseline 25(OH)D status and total McGill pain location, McGill pain score, DN4, and positive symptoms at baseline. p Value <0.05 was considered statistically significant and maintained for multiple comparison tests.

Table 1 Baseline characteristics of patients

Baseline characteristics	Total
n	143
Age (years)	52.3±11.50
Male gender n (%)	59 (41)
Type of diabetes	
Type 1	7 (4.9%)
Type 2	136 (95.1%)
Duration of diabetes (years)	12.1±7.60
Body mass index (kg/m²)	29.7±5.8
Systolic BP (mm Hg)	126±16
Diastolic BP (mm Hg)	80±9
Hypertension (BP≥130/85 mm Hg)	73 (51.0%)
Fasting plasma glucose (mg/dL)	158.5±71.2
Serum creatinine (mg/dL)	0.98±0.30
Calcium (mg/dL)	8.7±0.6
Serum cholesterol (mg/dL)	169±41
Triglyceride (mg/dL)	134±80
High-density lipoprotein (mg/dL)	39±10
Low-density lipoprotein (mg/dL)	106±34
HbA1c (%)	8.6±1.5
HbA1c (mmol/mol)	70.2±16.4
25(OH)D (ng/mL)	31.7±23.2
Deficient (<20 ng/mL)	58 (40.6%)
Insufficient (20–30 ng/mL)	24 (16.8%)
Sufficient (>30 ng/mL)	61 (42.7%)

Data represented as n (%) or mean±SD.
25(OH)D, 25-hydroxyvitamin D; BP, blood pressure; HbA1c, glycated hemoglobin.

RESULTS

Table 1 shows the baseline demographic, clinical, anthropometric, and biochemical variables of the study population. In total, 143 participants with predominantly type 2 diabetes aged 52.31±11.48 years with a DN4 score (3.0±1.8), total McGill pain score (21.2±14.9), and SFMPQ score (2.1±0.9), were enrolled. The baseline 25(OH)D level was 31.7±23.3 ng/mL and 58 (40.5%) patients had evidence of vitamin D deficiency (25(OH)D<20 ng/mL).

Loss to follow-up

Seven participants did not complete to V5. The final visit before dropout is as follows: two participants at V4, one participant at V3, one participant at V2, and three participants had been seen only at V1. All participants enrolled into the study were included in subsequent analyses with LOCF used for pain scores.

Biochemistry

Comparing V1 with V5, 25(OH)D levels increased significantly (31.7±23.3 ng/mL to 46.2±10.2 ng/mL, p<0.0001). There was also a significant reduction in HbA1c (8.6±1.5% vs 8.2±1.5%, p=0.02) and increase in high-density lipoprotein (HDL) (39±10 vs 43±11 mg/dL, p=0.03), with no change in total cholesterol and no change in triglycerides. There was a small but significant increase in serum Ca levels (p=0.009) (table 2).

Total McGill pain location

Total McGill pain location changed significantly between V1 and V2 (p=0.001), with a further significant reduction at V3 (p<0.0001), V4 (p<0.0001) and V5 (p<0.0001) compared with V1 (table 3, supplementary fig 1).

McGill pain score

The McGill pain score did not change between V1 and V2 (p=not significant (NS)), however, there was a significant reduction at V3 (p<0.0001), V4 (p<0.0001), and V5 (p<0.0001), compared with V1 (table 3, supplementary fig 1).

Douleur Neuropathique 4

There was no significant change in the DN4 score between V1 compared with V2, V3, V4, and V5. However, when the positive symptoms of the DN4 score were compared, there was no change between V1 and V2 (p=NS), but there was a significant reduction at V3 (p=0.0005), V4 (p=0.001), and V5 (p=0.0003), compared with V1 (table 3, supplementary fig 1).

Questionnaire scores stratified on vitamin D status

There was an improvement in pain scores that was independent of baseline vitamin D status. Comparing patients based on deficient/insufficient vitamin D status (25(OH)D≤30 ng/mL) and sufficient vitamin D status (25(OH)D>30 ng/mL), there were no differences

Table 2 Change in anthropometric and metabolic parameters after administration of vitamin D

Parameters (n=143)	Pretreatment baseline	Post-treatment week 20	p Value
Body mass index (kg/m^2)	29.7±5.8	30.2±7.1	NS
Systolic blood pressure (mm Hg)	126±16	123±15	NS
Diastolic blood pressure (mm Hg)	80±9	78±7	NS
HbA1c (%)	8.6±1.5	8.2±1.5	0.02
HbA1c (mmol/mol)	70.2±16.4	66.1±16.6	
Creatinine (mg/dL)	0.98±0.30	1.01±0.35	NS
Calcium (mg/dL)	8.7±0.60	8.9±1.0	0.009
Serum cholesterol (mg/dL)	169±41	162±43	NS
Triglycerides (mg/dL)	134±80	136±78	NS
High-density lipoprotein (mg/dL)	39±10	43±11	0.03
Low-density lipoprotein (mg/dL)	106±34	100±34	NS
25(OH)D (ng/mL)	31.7±23.2	46.2±10.2	<0.0001

Data are represented as mean±SD.
25(OH)D, 25-hydroxyvitamin D; HbA1c, glycated hemoglobin; NS, not significant.

between pretreatment baseline scores and V5 scores for total McGill pain location, McGill pain score, DN4, and positive symptoms. However, there was a significant reduction in total McGill pain location (p<0.0001 and p<0.0001), McGill pain score (p=0.002 and p=0.0002), and positive symptoms (p=0.05 and p=0.002), when comparing pretreatment baseline scores to V5 scores within the stratified groups (deficient/insufficient vitamin D status (25(OH)D≤30 ng/mL) and sufficient vitamin D status (25(OH)D>30 ng/mL) (table 4).

Regression analyses

There were no significant correlations between 25(OH) D status with either total McGill pain location, McGill pain score, DN4 or positive symptoms at baseline.

DISCUSSION

The present study adds to the limited data on the potential benefits of vitamin D therapy on PDN. While this study shows that a significant proportion of patients with diabetes in Karachi have vitamin D deficiency, the overall level of vitamin D in this population is higher than previous studies from Pakistan, indicating that a significant proportion had previously received vitamin D replacement from their primary physician.[30–34] This may explain the relatively weak but significant association between the levels of vitamin D and the severity of PDN, confirming the findings from the National Health and Nutrition Examination Survey,[10] and a study from Kuwait.[11]

The administration of 600 000 IU of vitamin D results in a modest but significant increase in 25(OH)D levels measured at 20 weeks. This improvement in 25(OH)D levels was associated with an improvement in several independent measures of PDN, which became significant at V3, approximately 10 weeks after administration of vitamin D. This would argue against a placebo effect, as this would have been expected to manifest immediately or at least at V2. Furthermore, a maximal placebo response from baseline of 33–36% has been shown in double-blind randomized controlled trials[35] and our data show improvement of pain far in excess of a placebo response. However, we cannot exclude a placebo response particularly as patients received regular follow-up after a known active intervention. Previously, a prospective study of 51 patients with type 2 diabetes from Australia reported a significant reduction in VAS from 3.3 to 1.7 and SFMPQ score from 32.1 to 19.4.[25] Similarly, in a randomized, placebo controlled, double-blind trial of QR-333, a topical compound (containing vitamin D_3), reduced numbness, jolting pain, and irritation from baseline values, with an overall

Table 3 Pain and neuropathic pain measures from baseline to final visit with significance at each visit

Pain and neuropathy measures	Pretreatment baseline	V2	V3	V4	V5
Total McGill pain location	21.3±15.0	19.1±15.9	7.5±7.5*	6.5±6.4*	5.9±5.3*
Median (IQR) (–/45)	23 (7–36)	13 (5–36)	5 (2–11)*	5 (2–9)*	5 (3–8)*
McGill pain score (–/5)	2.1±0.9	1.9±1.0	1.7±1.1^a	1.5±1.0*	1.5±1.0*
DN4	3.0±1.8	2.8±2.1	2.6±1.9	2.8±2.1	2.8±2.1
Median (IQR) (–/10)	3 (2–4)	3 (1–4)	2 (1–4)	3 (1–4)	3 (1–4)
Positive symptoms (DN4)	2.0±1.4	1.7±1.5	1.5±1.4#	1.4±1.4^	1.4±1.2**
Median (IQR) (–/6)	2 (1–3)	1 (1–3)	1 (0–2)	1 (0–2)	1 (0–2)

*p<0.0001, ^{a}p=0.007, #p=0.03, ^p=0.006, **p=0.004.
DN4, Douleur Neuropathique 4; V2, visit 2.

Table 4 Pain and neuropathic pain measures for baseline and final visit stratified on vitamin D status with significance at each visit

Baseline vitamin D status	Total McGill pain location Median (IQR) (–/45) Pretreatment baseline	V5	McGill pain score Median (IQR) (–/5) Pretreatment baseline	V5	DN4 Median (IQR) (–/10) Pretreatment baseline	V5	Positive symptoms (DN4) Median (IQR) (–/6) Pretreatment baseline	V5
<30 ng/mL	21.9±15.0	6.2±6.3*	2.0±0.9	1.5±1.0**	2.8±1.8	2.8±2.0	1.9±1.5	1.4±1.2[a]
(n=80)	23.5 (6–37)	5 (3–8)	2 (1–3)	1.5 (1–2)	3 (1–4)	3 (1–4)	2 (1–3)	1 (0–2)
≥30 ng/mL	20.6±15.1	5.6±3.8*	2.2±1.0	1.6±0.9σ	3.3±1.7	3.1±1.8	2.1±1.4	1.4±1.1**
(n=63)	19 (7–36)	5 (3–8)	2 (2–3)	1 (1–2)	3 (2–4)	3 (2–4)	2 (1–3)	1 (0–2)

*p<0.0001, **p=0.002, [a]p=0.05, σp=0.0002.
DN4, Douleur Neuropathique 4.

improvement in measures of quality of life.[36] A recent case report on a patient with PDN who had been refractory to treatment with tricyclic's, gabapentin, pregabalin, and oxycodone, showed a dramatic improvement in neuropathic symptoms after treatment with 50 000 IU of vitamin D_2 weekly.[37] Furthermore, recently, a placebo controlled trial of oral vitamin D in type 2 diabetes has shown a significant reduction in the Neuropathy Symptom Score with no change in the NDS or neurophysiology.[26] The improvement in pain in our study seems to be independent of the baseline vitamin D status, with no difference in pretreatment and V5 pain scores in those with adequate vitamin D status (≥30 ng/mL) compared with those who have insufficient/deficient vitamin D status (<30 ng/mL). The exact reason for this effect, independent of vitamin D status, remains to be elucidated, however, possible rationale for it may include changes in Ca signaling, neurotrophic factors, and production of active metabolites.[22 38–39] While in vitro and in vivo studies have shown that vitamin D is neurotrophic, and regulates neuronal growth and differentiation,[22 39] the doses and duration of treatment in the previous study may be insufficient to improve neuropathic deficits, per se.

Lower serum vitamin D level have been associated with a higher HbA1c[40] and lower HDL levels.[41] In the current study, we show small but significant improvements in HbA1c and HDL. Thus an additional potential mechanism of benefit may be via the reduction in HbA1c and increase in HDL, observed in this study. Of note, there was a small increase in serum Ca, which was not clinically significant.

Treatment options for PDN are currently limited due to side effects from many of the current therapies. We acknowledge that a major limitation of the current study is the lack of a placebo group. However, a single high-dose of intramuscular vitamin D appears to be a safe and effective treatment for PDN. A longer placebo controlled study with more frequent assessment of vitamin D levels and objective measures of neuropathy is required to assess the optimal frequency, dose safety, and overall efficacy of vitamin D in PDN, and, perhaps, in diabetic neuropathy.

CONCLUSION

A single intramuscular dose of 600 000 IU of vitamin D appears to be a safe and efficacious treatment for PDN over 20 weeks.

Contributors AB contributed to the concept and design, and clinical and neurological assessment, and reviewed the manuscript. KAB was the study coordinator, researched the data and wrote the manuscript. AF contributed to the concept and design, supervised the project, researched and analyzed the data, and wrote and reviewed the manuscript. FS analyzed the data, and wrote and reviewed the manuscript. NF was the study coordinator, researched the data and wrote the manuscript. INP, UA and RAM contributed to the concept and design, analyzed the data and wrote the manuscript. AB is the guarantor.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Ethics approval Baqai Institute of Diabetology and Endocrinology IRB.

Provenance and peer review Not commissioned; internally peer reviewed.

Data sharing statement Patient level data and full data set are available from the first author at abdulbasit@bideonline.com.

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