Diabetes & Metabolic Syndrome: Clinical Research & Reviews 13 (2019) 890–893

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Original Article

Dose vitamin D supplementations improve peripheral diabetic neuropathy? A before-after clinical trial

Akram Ghadiri-Anari [a], Zohre Mozafari [a], Somaye Gholami [a], Seyed-Ali Khodaei [a], Marzieh Aboutorabi-zarchi [b], Fariba Sepehri [a], Azade Nadjarzade [c], Masoud Rahmanian [a], Nasim Namiranian [a,*]

[a] Diabetes Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[b] Assistant Professor of Neurology, Diabetes Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[c] Associate Professor of Nutritional Sciences, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

ARTICLE INFO

Article history:
Received 21 November 2018
Accepted 19 December 2018

Keywords:
Diabetes mellitus
Neuropathy
Vitamin D

ABSTRACT

Objective: Peripheral neuropathy is a common complication of diabetes mellitus. This study was set to assess the effect of vitamin D supplementation on peripheral neuropathy in patients with type 2 diabetes (T2DM).

Materials and methods: This study was a quasi-experimental trial in Yazd diabetic research center. Sixty T2DM subjects (30–65 years old) with painful diabetic neuropathy enrolled in this study from March 2017 till April 2018. Patients received weekly 50000 IU of vitamin D3 for 12 weeks orally. Evaluation of diabetic neuropathy was performed by using Michigan Neuropathy Screening Instrument (MNSI) before and after trial. Also fasting plasma glucose, HbA1c, calcium and vitamin D checked before and after the trial. SPSS version 20 software was used for statistical analysis. $P \leq 0.05$ was considered to be statistically significant.

Results: Among 60 T2DM patients, 58 completed the study. Most of them (53.4%) were male. At the end of study, HbA1c, vitamin D, MNSI (both questionnaire and physical examination) improved that is statistically significant (p-value: <0.001).

Conclusion: Oral supplementation of vitamin D 3 (50,000 IU) once weekly for 12 weeks was associated with improvement in the serum level of vitamin D and significant decrease in the symptoms and sign of diabetic neuropathy. So serum vitamin D level should be checked in persons with diabetic neuropathy and low levels of it should be corrected in order to reducing neuropathy severity.

1. Introduction

Diabetic neuropathy is one of the micro-vascular complications of diabetes, occurring in 30–50% of all diabetic patients [1].This complication is one of the major causes of morbidity and mortality in diabetic patients. Diabetic neuropathy decrease life expectancy and quality [2].

Pathogenesis of diabetic neuropathy is unclear, but hyperglycemia has been proposed as the major risk factor [3]. However, glycemic control was shown to have less effect in prevention of diabetic neuropathy [4].

Vitamin D deficiency is common in diabetic patients, and low level of vitamin D is correlated with the presence and severity of sensory neuropathy [5–10]. So it seems that hypovitaminosis D is an independent risk factor for diabetic peripheral neuropathy [5,7].

Several studies revealed that oral and topical vitamin D supplementation leads to improvement of the neuropathy symptoms [11–14].

The biological effect of vitamin D on the nervous system includes; synthesis of enzymes involved in neurotransmitter synthesis as well as substances involved in brain detoxification mechanisms. So vitamin D is a potent inducer of neurotrophins and neurotransmitters [15].

This study was set out due to high prevalence of diabetes (16.3%) in Yazd province [16] and no study on the effect of vitamin D

* Corresponding author. Yazd Diabetes Research Center, Shahid Sadoughi University of medical sciences, Yazd, Iran.
E-mail addresses: namiranian.nasim@gmail.com, N_namiranian@ssu.ac.ir (N. Namiranian).

https://doi.org/10.1016/j.dsx.2018.12.014
1871-4021/

supplementation on the sigh and symptoms of diabetic neuropathy in our region (Yazd, a city in the middle of IRAN). We hypothesized that supplementation of vitamin D may play a potential therapeutic role in decreasing the severity of diabetic neuropathy.

2. Material and methods

2.1. Subjects

This study was a quasi-experimental (before − after) trial. One hundred-thirty type 2 diabetic patients with painful diabetic neuropathy were investigated at Yazd diabetic research center from March 2017 till April 2018. Inclusion criteria were type 2 diabetes, 30–65 years old, having a medical record at the Yazd diabetic research center, willingness to participate in this research, presence of diabetic neuropathy. Diabetic peripheral neuropathy was diagnosed in patients with a physical examination score ≥2.5 by using Michigan Neuropathy Screening Instrument [17]. In this study, Michigan Neuropathy Screening Instrument (MNSI) was accepted as a diagnostic test according to ADA recommendations (Table 1).

Maximum total score for each foot is 4 and for both feet are 8. Patients with no prospect of follow up (life in the other city), amputation of lower extremities, pregnancy and lactation, acute and severe lower extremities pain requiring injection of analgesics, other causes for pain in the feet (peripheral arterial disease or infections), current (during past 6 months) consumption of vitamin D and calcium or multivitamins orally and parenteral over the past 6 months excluded from study. Also subjects with the presence of the following disorders such as kidney failure, liver failure, heart failure, inflammatory arthritic diseases, hyperparathyroidism, alcoholism, malnutrition were excluded. Seventy persons excluded from the study due to some reasons.

In this study, 130 patients were evaluated that 62 patients did not meet the inclusion criteria and 8 patients did not want to participate in our study. Therefore, sixty participants enrolled in this trial. All patients attended regular follow-ups at the Yazd diabetic research center, Yazd, IRAN. A detailed history was recorded and a physical examination was conducted for all patients.

2.2. Study protocol

The duration of trial was 12 weeks or three months from the start of treatment. It should be noticed that all of the intervention period was done during autumn (October–December). Patients received weekly 50000 IU of vitamin D3 (Vitamin D3, Zahravi Pharm. Co. Tabriz, Iran) in the form of oral pearls. Before and after the intervention, the MNSI (both 15-item questionnaire and MNSI examination) completed. All of the neuropathy examination before and after the intervention was done by a neurologist who was blinded about the study. Blood samples were obtained after 8 h of fasting for fasting plasma glucose (FPG), HbA1C, calcium and 25 (OH) vitamins D.Blood chemistry tests such as FPG and calcium were analyzed using an auto analyser BA-400(Bio systems, European), and commercially available kits were used according to the manufacturer's instructions. Serum 25(OH) D was measured with the DiaSorin Liaison 25(OH) D chemiluminescent immunoassay system at Diasorin headquarters (Stillwater, MN). HbA1C was measured by high-performance liquid chromatography on a Diamat Analyser (Bio-Rad, München, Germany).

Table-1
Score assigned during MNSI procedure.

Appearance of feet (Abnormal: Presence of deformity, dry skin, callus, infection and fissures)	Normal = 0, Abnormal = 1
Ulceration	Absent = 0, Present = 1
Ankle reflexes	Absent = 1, Present with reinforcement = 0.5, Present = 0
Vibration perception	Absent = 1, Reduced = 0.5, Present = 0

2.3. Ethics statement

The study proposal was presented to the Ethics Committee of Shahid Sadoughi University of Medical Sciences and approved by the Internal Medicine Department. The Ethics Committee approved the study with the number IR.SSU.REC.1396.71 on June 25, 2017. The patients were informed about the objective of the study and each participant provided written consent prior to the study. Trial registration: IRCT2017102325266N2.

2.4. Statistical analysis

SPSS version 20 software was used for statistical analysis. Results were presented as mean ± standard deviation (SD). The Shapiro-Wilk test was done to check the normal distribution. The paired *t*-test was used to compare the continuous variables. Also the Pearson correlation was done. *P*-value of less than 0.05 was considered to be statistically significant. The study sample size was calculated according comparison two means formula, considering type one error: 0.05, power: 0.8.

3. Results

Among 130 eligible type 2 diabetic patients, 60 participants enrolled in our study base on inclusion and exclusion criteria. Two patients left the study in 4th and 6th week of study because they did not used vitamin D. At the end of study, 58 diabetic patients completed the study.

The patients were 35–65 years old and most of them 53.4% were male. The baseline characteristics of patients were described in table-2.

The before and after intervention laboratory and clinical findings were presented in table-3.

As presented in Table 2 the mean score of the15-item self-administered questionnaire of Michigan Neuropathy Screening Instrument (MNSI) at the first of study was 6.05 (±1.45) which decreased to 4.63 (±2.10) after intervention (p: <0.001). Also the physical examination scores of MNSI which were done by the neurologist before and after vitamin D supplementation were 4.87 (±1.29) and 3.68 (±1.45) respectively (p: <0.001).

Table 2
The baseline characteristics of patients.

Baseline characteristics (Number)	Total (58)
Age (years)	56.89 (±5.53)
Duration of diabetes (years)	10.55 (±5.71)
BMI(kg/m2)	29.95 (±4.67)
Male gender, N (%)	31 (53.4%)
Smoking, N (%)	7 (12.1%)
Fasting plasma glucose (mg/dL)	164.65 (±55.43)
HbA1c (%)	8.13 (±1.60)
25 (OH) vitamin D3 (ng/mL)	26.69 (±17.26)
Calcium (mg/dL)	8.95 ± 0.86
MNSI[a]: Questionnaire (Score)	6.05 (±1.45)
MNSI: Physical Examination (Score)	4.87 (±1.29)

Data represented as N (%) or mean ± SD.
[a] Michigan Neuropathy Screening Instrument.

Table 3
The before and after intervention laboratory and clinical findings.

Variables	Before Trial Mean (±SD)	After Trial Mean (±SD)	*P*-value
Fasting plasma glucose (mg/dL)	164.65 (±55.43)	159.70 (±53.93)	0.522
HbA1c (%)	8.13 (±1.60)	7.69 (±1.31)	0.021
25 (OH) vitamin D3	26.69 (±17.26)	55.52 (±31.94)	0.001
Calcium (mg/dL)	8.95 ± 0.86	9.73 ± 0.52	0.14
MNSI: Questionnaire (Score)	6.05 (±1.45)	4.63 (±2.10)	0.001
MNSI: Physical Examination (Score)	4.87 (±1.29)	3.68 (±1.45)	0.001

4. Discussion

In this study, oral supplementation of a dose of vitamin D 3 (50,000 IU capsule) once weekly for 12 weeks was associated with a significant improvement in the 25(OH) vitamin D concentration as well as HbA1c after trial. Also improvement in diabetic peripheral neuropathy using Michigan Neuropathy Screening Instrument (questionnaire and lower extremity examination) was seen. Lower serum vitamin D level has been associated with a higher HbA1c [18]. However effects of vitamin D supplementation on the HbA1c level are controversial. In SUNNY Trial a large intermittent dose of vitamin D (50,000 IU monthly for 6 months) supplementation at a level optimizing vitamin D level did not improve glycemic control in patients with type 2 diabetes [19]. In our study, baseline HbA1c was higher than patients with well controlled type 2 diabetes in SUNNY trial. It may be possible that glycemic effect of vitamin D appear on patients with poor controlled type 2 diabetes [19].

In another study that is concordance with our study, high-dose vitamin D in patients with painful diabetic neuropathy was associated with a significant decrease in HbA1c and the symptoms of painful diabetic neuropathy [20]. Some difference of this article with our study were administration of single intramuscular dose of 600,000 IU vitamin D, normal baseline vitamin D status and evaluation of neuropathy symptoms but no neurologic examinations with other questionnaires (20).

Some studies revealed high prevalence of vitamin D deficiency in patients with diabetes compared to healthy individuals and low level of vitamin D are correlated with the severity of sensory neuropathy [5–10].

Topical application of vitamin D to the areas affected by neuropathy in humans has been reported to decrease neuropathic symptoms [11].

Results of studies in type 1 diabetic subjects with painful diabetic neuropathy showed decrease in pain scores with vitamin D supplementation [12,13].

In a prospective, placebo-controlled trial study, oral vitamin D supplementation improved vitamin D level and the symptoms of neuropathy by using neuropathy symptom score (NSS) in patients with type 2 diabetes than control group (14). No improvement was observed for neuropathy disability score (NDS) and nerve conduction study (NCS) between the two groups after trial in this study. Evaluation of neuropathy in this study performed by other tools: a neuropathy symptom score (NSS), a neuropathy disability score (NDS) and nerve conduction study (NCS). In our study, diabetic peripheral neuropathy assess by using Michigan Neuropathy Screening Instrument. Another reason for no significant changes in NDS (ankle reflex, vibration, pinprick and temperature) maybe short term (8 weeks) duration of supplementation [14].

Neuropathy severity was significantly improved after vitamin D normalization using the Toronto Clinical Neuropathy Scoring System (Symptom scores, Reflex scores, Sensory test scores) in another study. However, there was improvement of nerve conduction studies in mild diabetic peripheral neuropathy after vitamin D correction but no effect in moderate and severe cases. Duration of this trial was three months similar to our study and with no control group [21]. Also evaluation of symptoms and physical examination performed in this Toronto Clinical Neuropathy Scoring System. So it is concordance with our research due to improvement of both symptoms and signs [21].

Another multicenter, randomised, double-blind trial evaluated efficacy and safety of intramuscular vitamin D2 supplementation in type 2 diabetic with peripheral neuropathy. In this trial improvement in clinical symptoms and nerve conduction velocity were seen after one year of follow-up [22].

The main limitation of this study was the absence of control group. In conclusion, this study showed that correction of hypovitaminosis D improved symptoms and signs of peripheral neuropathy in patients with type 2 diabetes. Therefore it is recommended to check vitamin D level in diabetic patients as a possible cause for diabetic neuropathy and that if the vitamin D level is low, therapy with vitamin D is initiated. Current medication of diabetic neuropathy had many side effects especially narcotics. Vitamin D therapy appears to be a safe, cheap and effective treatment for painful diabetic neuropathy. We recommend conducting randomised, controlled trials in order to confirm the efficacy and clinical benefits of vitaminD supplementation on painful diabetic neuropathy. Also future studies by using nerve conduction studies is recommended.

Funding

This study was conducted with financial support that was provided by Shahid Sadoughi University of Medical Sciences.

Conflicts of interest

None of the authors have any potential conflict of interests associated with this research.

Acknowledgments

Great thanks of patients that participated in this study and personnels of diabetes research center in Yazd, Iran involved in collecting and processing the data.

References

[1] Deshpande AD, Harris-Hayes M, Schootman M. Epidemiology of diabetes and diabetes-related complications. Phys Ther 2008 Nov 1;88(11):1254–64.
[2] Argoff CE, Cole BE, Fishbain DA, Irving GA. Diabetic peripheral neuropathic pain: clinical and quality-of-life issues. InMayo Clinic Proceedings 2006 Apr 1;81(4):S3–11 [Elsevier].
[3] DCCT Research Group, Box NDIC/DCCT, Bethesda MD. 20892. Effect of intensive diabetes treatment on nerve conduction in the Diabetes Control and Complications Trial. Ann Neurol 1995 Dec;38(6):869–80.
[4] Peltier A, Goutman SA, Callaghan BC. Painful Diabetic Neuropathy BMJ 2014;348:g1799.
[5] 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 2012;29(1):43–9.
[6] Chaychi L, Mackenzie T, Bilotta D, Lynch M, Cohen J, Comi R. Association of serumvitamin D level with diabetic polyneuropathy. Med Pract Rev

2011;2(1):11–5.
[7] Soderstrom LH, Johnson SP, Diaz VA, Mainous Iii AG. Association between vitamin D and diabetic neuropathy in a nationally representative sample: results from 2001–2004 NHANES. Diabet Med 2012;29(1):50–5.
[8] Bajaj S, Singh RP, Dwivedi NC, Singh K, Gupta A, Mathur M. Vitamin D levels and microvascular complications in type 2 diabetes. Ind J Endocrinol Metabol 2014;18(4):537.
[9] Alamdari A, Mozafari R, Tafakhori A, Faghihi-Kashani S, Hafezi-Nejad N, Sheikhbahaei S, Naderi N, Ebadi M, Esteghamati A. An inverse association between serum vitamin D levels with the presence and severity of impaired nerve conduction velocity and large fiber peripheral neuropathy in diabetic subjects. Neurol Sci 2015;36(7):1121–6.
[10] Qu GB, Wang LL, Tang X, Wu W, Sun YH. The association between vitamin D level and diabetic peripheral neuropathy in patients with type 2 diabetes mellitus: an update systematic review and meta-analysis. J Clin Translational Endocrinol 2017;9:25–31.
[11] Valensi P, Le Devehat C, Richard JL, Farez C, Khodabandehlou T, Rosenbloom RA, LeFante C. A multicenter, double-blind, safety study of QR-333 for the treatment of symptomatic diabetic peripheral neuropathy: a preliminary report. J Diabetes Complicat 2005;19(5):247–53.
[12] Bell DS. Reversal of the symptoms of diabetic neuropathy through correction of vitamin D deficiency in a type 1 diabetic patient. Case Reports Endocrinol 2012;2012.
[13] Lee P, Chen R. Vitamin D as an analgesic for patients with type 2 diabetes and neuropathic pain. Arch Intern Med 2008;168(7):771–2.
[14] Shehab D, Al-Jarallah K, Abdella N, Mojiminiyi OA, Al Mohamedy H. Prospective evaluation of the effect of short-term oral vitamin D supplementation on peripheral neuropathy in type 2 diabetes mellitus. Med Princ Pract 2015;24(3):250–6.
[15] Kiraly SJ, Kiraly MA, Hawe RD, Makhani N. Vitamin D as a neuroactive substance. Sci World J 2006;6:125–39.
[16] Lotfi MH, Saadati H, Afzali M. Prevalence of diabetes in people aged≥ 30 years: the results of screen-ing program of Yazd Province, Iran, in 2012. J Res Health Sci 2013;14(1):88–92.
[17] Feldman EL, Stevens MJ, Thomas PK, Brown MB, Canal N, Greene DA. A practical two-step quantitative clinical and electrophysiological assessment for the diagnosis and staging of diabetic neuropathy. Diabetes Care 1994;17(11):1281–9.
[18] Dalgård C, Petersen MS, Weihe P, Grandjean P. Vitamin D status in relation to glucose metabolism and type 2 diabetes in septuagenarians. Diabetes Care 2011;34:1284–8.
[19] Krul-Poel YH, Westra S, ten Boekel E, ter Wee MM, van Schoor NM, van Wijland H, Stam F, Lips PT, Simsek S. Effect of vitamin D supplementation on glycemic control in patients with type 2 diabetes (SUNNY trial): a randomized placebo-controlled trial. Diabetes Care 2015;38:1420–6.
[20] Basit A, Basit KA, Fawwad A, Shaheen F, Fatima N, Petropoulos IN, Alam U, Malik RA. Vitamin D for the treatment of painful diabetic neuropathy. BMJ Open Diabet Res Care 2016;4(1), e000148.
[21] Saad M, Gabr WM, Barakat E, Enein AF. The effect of hypovitaminosis D normalization on diabetic neuropathy. Egypt J Neurol Psychiatr Neurosurgery 2016 Apr 1;53(2):102–6.
[22] Yueyue Z, Xiaoxia S, Dexue L, Ruige L. Efficacy and safety of vitamin D2 supplementation on diabetic peripheral neuropathy: a multicentre, randomised, double-blind trial. Lancet Diabet Endocrinol 2016;4:S29.