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EFFECT OF VITAMIN D SUPPLEMENTATION ON ELECTROPHYSIOLOGICAL PARAMETERS OF PERONEAL AND TIBIAL NERVE IN DIABETIC POLYNEUROPATHY PATIENTS

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ABSTRACT

Background: Nerve conduction study is widely used for the assessment of diabetic polyneuropathy. Vitamin D help to reduce the risk of diabetes associated complications.

Objective: To evaluate the effect of vitamin D on latency, amplitude and conduction velocity of peroneal and tibial nerves bilaterally in diabetic polyneuropathy patients.

Materials and Methods: The randomized prospective study was conducted on 35 to 65 years old polyneuropathic type 2 diabetes mellitus patients posted for diabetic care. Sixty patients were divided into two groups of 30 each such as Group I (vitamin D supplemented) and Group II (placebo supplemented). A dose of vitamin D 60000IU/week was selected and treatment continued for 6 months. After treatment routine clinical investigations such as age, height, weight, body mass index, waist, systolic blood pressure and duration of disease were recorded. Electrophysiological parameters such as latency, amplitude and conduction velocity were evaluated.

Results: Group I patients showed no statistical significant difference in routine clinical investigation parameters except diastolic blood pressure when compared with Group II. Electrophysiological parameters of peroneal and tibial nerves bilaterally (right and left sides) analysis depicts statistically non significant in peroneal nerve and statistically significant in tibial nerve decrease in mean latency; whereas increase in amplitude and conduction velocity after vitamin D supplementation (Group I) when compared with placebo group (Group II). Data was analyzed using paired t test and percent change calculation.

Conclusion: Vitamin D supplementation may be a beneficial element in the complex treatment of type 2 diabetic polyneuropathy.

KEYWORDS : Vitamin D, diabetic polyneuropathy, nerve conduction study, peroneal nerve,tibial nerve

Introduction

Diabetic polyneuropathy (DPN) is the most common complication of diabetes and cause of morbidity and disability.1 It has been estimated that more than half of the diabetic patients suffer from polyneuropathy. 2 Despite some success, intervention of DPN remains a medical challenge. Symptoms of neuropathy affect 30-40% of diabetic patients and the prevalence of these symptoms increase with longer duration of diabetes and hypertension.3 The electro diagnostic assessments are sensitive, specific and reproducible measures of the presence and severity of polyneuropathy.4 Nerve conduction study is widely used for the assessment of diabetic polyneuropathy not only to evaluate the degree of abnormality but also to document serial changes in the clinical course of the disease.5 Multiple consensus panels recommend the inclusion of electrophysiological testing (Nerve conduction studies and electromyography) in the evaluation of diabetic neuropathy. In many instances if the diabetic peripheral neuropathy is diagnosed earlier, it can be treated, at least in the initial stages. The early and precise detection can help in better understanding the pattern of pathophysiological changes as well as in controlling crippling illness like peripheral neuropathy.6 Accumulating data have provided evidence that vitamin D is involved in brain function.7 A role of vitamin D on islet insulin release is either direct or indirectly through its effect on plasma calcium concentrations.8 Therefore, the relationship between vitamin D and diabetes is certainly worthy of further investigations. The effective treatment of diabetic polyneuropathy remains a major challenge and anticonvulsants and anti-depressants remain the mainstay of symptom relief, but provide no benefit for underlying nerve damage. However, increasing data suggest that vitamin D play a pivotal role in the peripheral nervous system and in particular diabetic neuropathy.9-11 Thus, this study is to evaluate the effect of vitamin D in the alteration of electrophy siological parameters (latency, amplitude and conduction velocity) of peroneal and tibial nerves bilaterally in polyneuropathic type 2 diabetes mellitus.

Materials and Methods

Study Design

The study protocol was approved by Institutional Ethics Committee of SN Medical College, Bagalkot before the study being started. The details of study were explained and informed consent was taken from each of the subjects. The duration of study was a year from October 2016 to October 2017. The study was carried out in the Department of Physiology, SN Medical College and HSK Hospital and Research Centre, Bagalkot, Karnataka in collaboration with Tulsigirish Diabetes Hospital and Diabetes Research Foundation Bagalkot, Karnataka and Department of Biophysics, Government Institute of Science, Aurangabad, Maharashtra. Male polyneuropathy type 2 diabetes mellitus patients (n=60) in the age range of 35 to 65 years were selected prospectively and randomized in the following 2 groups:

Group I: Out of 60 polyneuropathic type 2 diabetes mellitus patients, 30 patients were treated with vitamin D tablet supplement (San-D 60k, Vitamin D3 Chewable tablet composed of Cholecalciferol 60,000 IU, manufactured by Pure and Cure Healthcare Privet Limited, Uttarakhand, India). Group II: 30 patients were treated with placebo tablet (which do not contain vitamin D) supplement. The study subjects of both the groups were given a weekly dose with their respective tablet. Study parameters were evaluated after six months of treatment.

Inclusion criteria

Male individuals suffering from type 2 diabetic polyneuropathy and age 30 to 65 years were included in this study.

Exclusion criteria

Patients who had physical deformities, individual suffering from any chronic illnesses other than diabetes, individual with history of chronic exposure to substances which result in altered neuronal functions and individuals suffering from any neurological disease other than diabetic polyneuropathy were excluded from this study.

Routine Clinical Investigations

Anthropometric measurements (height and weight) were taken by using scales on bare foot. Waist circumference was measured such as midway between lateral lower ribs and iliac crest after gentle expiration while patient was standing (in centimeters). Body mass index (BMI) was calculated by using Quetelet's Index.12 Blood pressure was recorded using a mercury sphygmomanometer with consideration of 120 / 80 mmHg as cut off normal value with standard protocol of measurement according to the American Heart Association guidelines.

Electrophysiological Parameters

Nerve conduction study of peroneal and tibial nerve was performed with exact location of nerves in an environment with room temperature ranging from 23°C to 25°C using computerized RMS EMG EP MK II machine and surface electrodes. During the test, the nerve was stimulated, with surface electrode patches attached to the skin. Two

electrodes were placed on the skin over the nerve. One electrode stimulated the nerve with a very mild electrical impulse Resulting electrical activity was recorded by another electrode as amplitude. This was repeated for each nerve being tested. The nerve conduction velocity (NCV) was then calculated by measuring the distance between electrodes and the time taken for electrical impulses to travel between electrodes. Measurement of latency was conducted with sweep duration of 100 ms (frequency 5–500 Hz, repetition rate 0.5Hz). At least 10 consecutive stimuli were given and the minimum latency values observed were considered for evaluation.13

Statistical Analysis

Analysis of data was done using Microsoft Excel and EPI INFO 2002. Standard statistical methods were used to determine the mean and standard deviation (SD). Paired t-test was used to compare the results of various study parameters in the two groups. All the values were quoted as the mean ± SD. The P value of <0.05 was considered statistically significant difference and represented y asterisk '*' between two groups.

Results

There was no statistical significant difference found between mean age (52.80 vs 50.27 years, p=0.2994), height (170.27 vs 169.40 cm, p=0.3021), weight (61.53 vs 62.46 kg, p=0.6994), waist circumference (33.07 vs 32.33 cm, p=0.5279), body mass index (21.29 vs 21.83 kg/m2, p=0.4346), systolic blood pressure (135.20 vs 136.93 mmHg, p=0.3603) and duration of disease (7.00 vs 7.40 years, p=0.5140) in vitamin D supplemented (Group I) patients when compared with placebo supplemented (Group II) patients. Only mean diastolic blood pressure (85.73 vs 88.40 mmHg, p=0.5140) showed statistically significant difference, when Group I compared with Group II patients (Table 1).

In vitamin D supplemented (Group I) patients, mean latency (3.25 vs 3.48 mSec, p = 0.1320) of right peroneal nerves and mean latency (3.30 vs 3.54 mSec, p = 0.1219) of left peroneal nerves showed statistically not significant difference after six months of treatment when compared with placebo supplemented patients (Group II). Whereas, mean amplitude (6.33 vs 4.90 mV, p = 0.0047) and mean conduction velocity (54.76 vs 42.27 m/s, p = 0.0001) of right peroneal nerve and mean amplitude (7.21 vs 5.05 mV, p = 0.0005) and mean conduction velocity (52.06 vs 40.03 m/s, p = 0.0001) of left peroneal nerve showed statistically significant difference (Table 2). In Figure 1, right peroneal nerve of Group I showed -7.08% reduction in latency, 22.59% elevation in amplitude and 22.81% elevation in conduction velocity; whereas left peroneal nerve of Group I showed -7.27% reduction in latency, 29.96% elevation in amplitude and 23.11% elevation in conduction velocity with respect to Group II.

In vitamin D supplemented (Group I) patients, mean latency (3.38 vs 3.74 mSec, p = 0.0421), mean amplitude (18.68 vs 12.54 mV, p = 0.0002) and mean conduction velocity (53.74 vs 42.64 m/s, p = 0.0001) of right tibial nerve showed statistically significant difference after six months of treatment when compared with placebo supplemented patients (Group II). Mean latency (3.42 vs 3.80 mSec, p = 0.0134), mean amplitude (19.54 vs 13.14 mV, p = 0.0001) and mean conduction velocity (50.34 vs 41.44 m/s, p = 0.0001) of left tibial nerve also showed statistically significant difference when compared Group I with Group II (Table 3). In Figure 2, right tibial nerve of Group I showed -10.65% reduction in latency, 32.87% elevation in amplitude and 22.66% elevation in conduction velocity; whereas left tibial nerve of Group I showed -11.11% reduction in latency, 32.75% elevation in amplitude and 17.68% elevation in conduction velocity with respect to Group II.

Discussion

Polyneuropathy is a common complication in diabetic patients.2 The physiological properties of nerve and muscle are modified due to pathophysiological changes resulting from diabetes.14 Nerve conduction studies are simple, sensitive and objective technique for evaluating impulse conduction along the peripheral nerves.4 The present study deals with the abnormalities in nerve conduction in polyneuropathic type 2 diabetes mellitus patients.

Routine clinical investigations in our study were comparable between Group I and Group II. Only diastolic blood pressure values in Group I were reduced significantly as compared to Group II. From these findings, it may be inferred that age, duration of disease and anthropometric indices do not influence in treatment of polyneuropathic type 2 diabetic patients with vitamin D.

Further, we studied electrophysiological parameters such as latency, amplitude and conduction velocity bilaterally (right and left side) in peroneal and tibial nerve. After six months of vitamin D supplementation in Group I, polyneuropathic diabetic patients showed reduced latency and elevated amplitude and conduction velocity bilaterally in both peroneal and tibial nerves as compared to placebo group (Group II). This study revealed that polyneuropathic type 2 diabetic patients were ameliorated following treatment with the vitamin D supplementation (60,000 IU/week). Our results in this study also agree with following previous work on vitamin D as a beneficial element in complex treatment of polyneuropathic diabetic patients. Vitamin D has important actions on glucose metabolism; these include improved insulin exocytosis, direct stimulation of insulin receptor, improved uptake of glucose by peripheral tissues and improving insulin resistance.15 Pietschmann et al.16 and Isaia et al.17 showed in their respective studies that an association exists between low circulating concentrations of vitamin D and the prevalence of diabetes and impaired glucose tolerance. Vitamin D has not only comparable analgesic but also play a pivotal role in the peripheral nervous system and in particular diabetic neuropathy.8,10,18-20 Nerve Growth Factor (NGF) and neuronal Ca2+ homeostasis, both play a neuroprotective role in the peripheral nerve have been linked to vitamin D experimental studies through the regulation of neurotrophins.21 Observational studies have demonstrated a significant link between vitamin D deficiency and polyneuropathic diabetes.10,22 The data supporting a benefit of vitamin D treatment in painful polyneuropathic diabetes is as yet limited. However, in a non-randomisednon-placebo controlled but prospective study with cholecalciferol (vitamin D3) at a mean dose of 2059 IU daily for 3 months in painful polyneuropathic diabetes an improvement of ~50% on the Visual Analogue (pain) Scores (VAS) was observed.23 The largest observational study of patients within the community in north west England (n = 15,692) has shown that the prevalence of painful symptoms and painful polyneuropathic diabetes was 34 and 21% respectively.24 Additionally, despite a lower prevalence of neuropathy in South Asians compared to Europeans and Afro-Caribbeans, painful symptoms were greater in South Asians.24 These differences may partly be explained in relation to vitamin D deficiency as these groups have been shown to have excess vitamin D deficiency.25

Despite above reports linking vitamin D deficiency with increased risk of diabetes mellitus and complications, there is limited data on patients with polyneuropathic diabetes and electrophysiological studies. We aimed to evaluate the electrophysiological parameters in vitamin D supplemented polyneuropthic diabetic patients with placebo group. Our comparative and percent change analysis showed that polyneuropathic diabetic patients were significantly associated with vitamin D supplementation. In a cross sectional study, assessed using the clinical and electrophysiological measures by Shebab et al,10 vitamin D deficiency is an independent risk factor for polyneuropathic diabetic patients, therefore further studies are required to confirm vitamin D supplementation to prevent or delay the onset also demands good quality randomized controlled trials.

Conclusion

Our findings suggest that the vitamin D supplementation could be an element in the complex treatment of polyneuropathic type 2 diabetes mellitus. Treatment with Vitamin D may alter the development or progression of neuropathy complications of diabetes. This preliminary study has been conducted on a relatively small population and provides evidence of a link between vitamin D and diabetic polyneuropathy.

Declarations

Funding: None

Conflict of interest: None Declared

Ethical approval: Approved by Institutional Ethics Committee

Table 1: Routine clinical investigations in both the study groups (n=60)

	Group I	Group II		
Clinical data	(Vitamin D)	(Placebo)	p-value	Significance
	n=30	n=30		
Age (years)	52.80±9.60	50.27±9.11	0.2994	Not significant

Height (cm)	170.27±3.33	169.40±3.14	0.3021	Not significant
Weight (kg)	61.53±8.35	62.46±10.13	0.6994	Not significant
Waist (cm)	33.07±5.69	32.33±2.89	0.5279	Not significant
BMI (Kg/m2)	21.29±2.53	21.83±2.78	0.4346	Not significant
Systolic BP (mmHg)	135.20±5.12	136.93±8.91	0.3603	Not significant
Diastolic BP (mmHg)	85.73±3.99	88.40±4.97*	0.0254	Significant
Duration of disease (years)	7.00±2.64	7.40±2.04	0.5140	Not significant

BMI: Body mass index; BP: Blood pressure. All the values quoted as the Mean ± Standard deviation. Paired t-testwas used to compare the results between two groups. The p value of <0.05 was considered statistically significant different and represented by asterisk '*'.

Table 2: Electrophysiological parameters of peroneal nerve after treatment in both the study groups (n=60)

Peroneal Nerve	Electro-physiological Parameters	**Group I (Vitamin D) n=30**	**Group II (Placebo) n=30**	**p-value**	**Significance**
Right	Latency (mSec)	3.25±0.64	3.48±0.52	0.1320	Not significant
	Amplitude (mV)	6.33±1.56	4.90±2.16*	0.0047	Significant
	Conduction Velocity (m/s)	54.76±3.36	42.27±5.76*	0.0001	Significant
Left	Latency (mSec)	3.30±0.64	3.54±0.54	0.1219	Not significant
	Amplitude (mV)	7.21±2.06	5.05±2.49*	0.0005	Significant
	Conduction Velocity (m/s)	52.06±4.50	40.03±6.38*	0.0001	Significant

mSec: Milli second; mV: Milli volt; m/s: Meter/second. All the values quoted as the Mean ± Standard deviation. Paired t-test was used to compare the results between two groups. The p value of <0.05 was considered statistically significant different and represented by asterisk '*'.

Table 3: Electrophysiological parameters of tibial nerve after treatment in both the study groups (n=60)

Tibial Nerve	Electro-physiological Parameters	Group I (Vitamin D) n=30	Group II (Placebo) n=30	p-value	Significance
Right	Latency (mSec)	3.38±0.54	3.74±0.78*	0.0421	Significant
	Amplitude (mV)	18.68±5.48	12.54±6.52*	0.0002	Significant
	Conduction Velocity (m/s)	53.74±2.66	42.64±5.12*	0.0001	Significant
Left	Latency (mSec)	3.42±0.53	3.80±0.62*	0.0134	Significant
	Amplitude (mV)	19.54±5.05	13.14±6.85*	0.0001	Significant
	Conduction Velocity (m/s)	50.34±1.64	41.44±4.43*	0.0001	Significant

mSec: Milli second; mV: Milli volt; m/s: Meter/second. All the values quoted as the Mean ± Standard deviation. Paired t-test was used to compare the results between two groups. The p value of <0.05 was considered statistically significant different and represented by asterisk '*'.

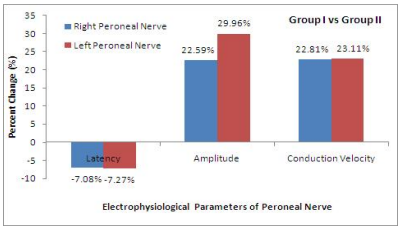

Figure 1: Percent change of electrophysiological parameters of peroneal nerve in Group I with respect to Group II

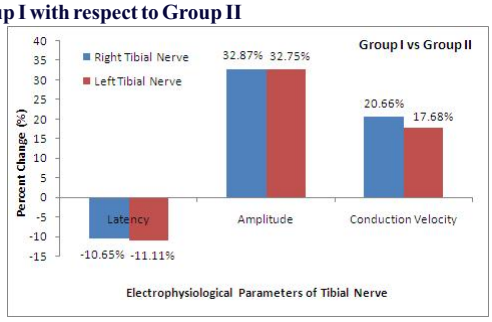

Figure 2: Percent change of electrophysiological parameters of tibial nerve in Group I with respect to Group II

References

1. Boulton AJM, Vinik AI, Arezzo JC, Bril V, Feldman EL, Freeman R, et al. Diabetic Neuropathies. Diabetes Care 2005;28:956-62.
2. Pasnoor M, Dimachkie MM, Kluding P, Barohn RJ.Diabetic neuropathy part 1: overview and symmetric phenotypes. Neurol Clin.2013;31:425-45.
3. Javed S, Alam U, Malik RA.Treating Diabetic Neuropathy: Present Strategies and Emerging Solutions. Rev Diabet Stud.2015;12:63-83.
4. Zilliox LA, Ruby SK, Singh S, Zhan M, Russell JW. Clinical Neuropathy Scales in Neuropathy Associated with Impaired Glucose Tolerance. J Diabetes Complications. 2015;29:372-7.
5. Graham WA, Goldstein R, Keith M, Nesathurai S. Serial nerve conduction studies of the tail of rhesus monkey (Macacamulatta) and potential implications for interpretation of human neurophysiological studies. Ann Indian Acad Neuro. 2007;10:252-4.
6. Dobretsov M, Romanovsky D, Stimers JR. Early diabetic neuropathy: triggers and mechanisms. World J Gastroenterol 2007;13:175-91.7. Garcion E,Wion-Barbot N,Montero-Menei CN,Berger F,Wion D.New clues about vitamin D functions inthe nervous system.TrendsEndocrinol Metab.2002;13:100-5. 8. Penckofer S, Kouba J, Wallis DE, Emanuele MA.Vitamin D and diabetes: let the sunshine in. Diabetes Educ.2008;34:939-40.
9. Holmoy T, Moen SM. Assessing vitamin D in the central nervous system. Acta Neurol Scand Suppl 2010;190:88-92.
10. 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;29:43-9.
11. Alam U, Asghar O, Malik RA. Are vitamin D and B deficiency relevant to the pathogenesis and treatment of diabetic neuropathy? Future Neurology 2012;7:235-8.
12. Deurenberg P, Weststrate JA, Seidell JC.Body mass index as a measure of body fatness: age- and sex-specific prediction formulas. Br J Nutr 1991;65:105-14.
13. Mishra UK, Kalita J. Clinical Neuophysiology. 2nd Ed. New Delhi; B. I. Churchill Livingstone Pvt Ltd.1999.
14. Krishnan AV, Kiernan MC. Altered nerve excitability properties in established diabetic neuropathy. Brain 2005;128:1178-87.
15. El-Fakhri N, McDevitt H, Shaikh MG, Halsey C, Ahmed SF. Vitamin D and Its Effects on Glucose Homeostasis, Cardiovascular Function and Immune Function. Horm Res Paediatr. 2014;81:363-78.
16. Pietschmann P, Schernthaner G, Woloszczuk W. Serum osteocalcin levels in diabetesmellitus:Analysisofthetypeofdiabetesandmicrovascularcomplications. Diabetologia. 1988;31:892-5.
17. Isaia GC, Ardissone P, Di Stefano M, Ferrari D, Martina V, Porta M, et al. Bone metabolism in type 2 diabetes mellitus. Acta Diabetol. 1999;36:35-8.
18. Shipton EA, Shipton EE. Vitamin D and Pain: Vitamin D and Its Role in the Aetiology and Maintenance of Chronic Pain States and Associated Comorbidities. Pain Res Treat.2015;2015:904-67.
19. Alam U, Arul-Devah V, Javed S, Malik RA. Vitamin D and Diabetic Complications: True or False Prophet? Diabetes Ther. 2016;7:11-26.
20. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. BMJ.2003;326:469.
21. Riaz S, Malcangio M, Miller M, Tomlinson DR. A vitamin D(3) derivative (CB1093) induces nerve growth factor and prevents neurotrophic deficits in streptozotocin-diabeticrats. Diabetologia.1999;42:1308-13.
22. Soderstrom LH, Johnson SP, Diaz VA, Mainous AG. 3rd: Association between vitamin D and diabetic neuropathy in a nationally representative sample: results from 2001-2004NHANES. Diabet Med. 2012;29:50-55.
23. Lee P, Chen R. Vitamin D as an analgesic for patients with type 2 diabetes and neuropathic pain. Arch Intern Med. 2008;168:771-772.
24. 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 2011;34:2220-4.
25. Tahrani AA, Ball A, Shepherd L, Rahim A, Jones AF, Bates A. The prevalence of vitamin D abnormalities in South Asians with type 2 diabetes mellitus in the UK. Int J Clin Pract.2010;64:351-5.