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ORIGINAL ARTICLE

Vitamin D Therapy Attenuates Symptoms of Painful Diabetic Peripheral Neuropathy (PDPN) in T2DM patients

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ABSTRACT

Objective: To study the outcome of oral vitamin D therapy on symptoms of PDP Nin T2DM patients

Methods: This randomized double blind placebo controlled trial comprised 120 T2DMpatients with vitamin D deficiency and symptoms of PDPN on the basis of neuropathy symptoms score (NSS) and neuropathy disability score (NDS). Patients were randomly divided in to two groups. Patients in group A were given capsule vitamin D2, 00000IU/month over while patients in group B were given capsule placebo for a period of 03 months duration. The study outcomes of PDPN were assessed by NSS and NDS as primary endpoint while glycemic control and vitamin D level were secondary end point of study from baseline.

Results: After 12 weeks therapy of vitamin D, significant improvements were recorded in primary end points NSS score (from 5.9±2.0 to 4.7±1.5) vs placebo (6.5 ±2.0 to 6.4 ±3.2) with p-value (0.002) and NDS score (from 7.8±2.0 to 6.5± 2.5) vs placebo (7.7±1.8 to 7.9±2.5) with p-value (0.001). Similarly secondary endpoints were also improved significantly from baseline to end point after 12 weeks of vitamin D therapy vitamin D value (from 25.8±14 to 44.5±12.5) vs placebo group (from 28.5±14.5 to30.0±15.5) with p-value (0.002), HbA1c from 9.0±2.8 to 7.8±3.5) vs Placebo (from 9.8±2.0 to 9.5±2.2) with p-value 0.001 (table 2).

Conclusion: Vitamin D therapy attenuates symptoms of PDPN in T2DM patients

Keywords: Vitamin D, T2DM, PDPN, HbA1c

INTRODUCTION

There is increase risk of developing painful diabeticperipheral neuropathy (PDPN) in T2DM patients. PDPN prevalence reaches up to 50% in T2DM. [1] The actual cause of PDPN is not well understood as numbers of factors are contributing to its initiation to progression.[2] Most of the time symptoms of PDPN are associated with uncontrolled and long standing diabetes. The symptoms of PDPN are quite varies from patients to patients. Common symptoms of PDPN are burning, aching and tingling sensation in lowers extremities. The symptoms of PDPN are usually troublesome at night. These worsening symptoms have negative impact on sleep, mood and quality of life.[3] An integrated approach is required to prevent PDPN symptoms in T2DM patients in order to reduce its associated complications.

Lifestyle modification usually comes first in the prevention of PDPN. Lifestyle modification includes appropriate glycemic control with regular walk, healthy eating, avoidance of alcohol and maintenance of ideal body weight. Lifestyle modification usually slows down the progression of PDPN. The pharmacological management of PDPN involves multiple drugs with varying results. The most commonly prescribed drugs for PDPN are tricylicanti depressants (TCA), selective serotonin reuptake inhibitors (SSRI), serotonin nor-epinephrine reuptake inhibitors (SNRI), anti convulsant, GABA analogs, topical agents, narcotic andnon narcotic analgesic. Some patients cannot tolerate these drugs and some drugs have notorious adverse effects. So management of PDPN is challenge for the medical specialist, consultant and family physician. [4-5]

The role of vitamin D in various diseases is already well-established. Its adequate level in the body have a potential benefits in various diseases. Optimum level of vitamin D boosts immune system, fight against infections and maintain metabolic functions. Moreover vitamin D has potential role in various CNS, respiratory, endocrine and reproductive diseases. [6-7]

Various studies demonstrated that optimum level of vitamin D supplementation not only control blood sugar in T2DM patients but also prevent its associated micro and macrovascular complications. Vitamin D supplementation also prevents PDPN in T2DM patients in various studies.[8-9]Studies have shown that vitamin D deficiency predisposes to PDPN in diabetics as well as in non diabetics while vitamin D supplementation improves symptoms of neuropathic pain in both in diabetics as andnon diabetics. [10-12]

So the present study was conducted to evaluate the effects of vitamin D therapy on symptoms of PDPN in T2DM patients.

MATERIALS & METHODS

This multicentre double blind randomized placebo controlled trial was conducted at a government hospital as well as 02 private clinical set up of district Rahim Yar Khan over a period of 12 weeks from March to May 2021. A total of 420 T2DM patients were screened for vitamin D deficiency on the basis of clinical symptoms of vitamin D deficiency. Out of which 184 T2DM patients were enrolled and 120 patients were randomized for treatment on the basis of inclusion and exclusion criteria.

An inclusion criteria was T2DM with inadequate glycemic control (HbA1c 7-11%) and documented vitamin D deficiency. The symptoms of PDPN were diagnosed on the basis of two important scores, i.eneuropathic symptomatic score (NSS) and neuropathic disability score (NDS). Pain location, intensity, nature and reliving and aggravating techniques were assessed by NSS. The score more than 5 was classified as neuropathy. On the other hand sensation regarding temperature, vibration, pin prick and reflexes were assessed by NDS and score more than 06 were characterized as neuropathy. A detailed history and clinical examination was undertaken about symptoms of PDPN such as burning, numbness and aching sensation in upper and lower limb**.**

An exclusion criterion was primary and secondary causes of PDPN such as nutritional, autoimmune, cancerous, inflammatory, AIDS and drugs related. Patients who were taking any drugs for PDPN were also excluded from study. Moreover patients with history of kidney dysfunction, liver disease and thyroid disorder were excluded from the study. Study approval was got from ethical committee of institutional board review of this institute. All participants gave informed consent before the start of clinical trial.

Patients were randomly divided in to two groups. The process of randomization was done by computed generated software by allocating odd and even number to each group. Patients in group A were taken capsule vitamin D capsule 2, 00000IU/month while patients in group B were takencapsule

placebo for the 03 months duration. The capsule placebo look similar to vitamin D capsule in physical appearance but it contains cellulose as active principle. Researcher and patients were blinded to the treatment plan in both study groups.

The study outcomes of PDPN were assessed by NSS and NDS as primary endpoint while glycemic control and vitamin D level were secondary end point of study from baseline.

Blood sugar was analyzed by accu check glucometer (Rosch). Lipid profile was done by enzymatic end point method using standard kits (Randox). HbA1c level was analyzed through high performance liquid chromatography (HPLC) while serum level of 25-hydroxyvitamin D 25 (OHD) was analyzed by radioimmunoassay.

Data Analysis: Statistical package for social sciences (SPSS-21) was used to analyze numeric data. The values of data were expressed as mean± standard deviation. The difference in comparison from start to end points within group was done by paired t-test while difference between groups was assessed by paired t-test and Whitney U-test as appropriate. A p-value <0.05 were considered to be statistically significant.

RESULTS

The tolerability and safety profile of vitamin D was quite good and no major and minor adverse effects were reported in this clinical trial. All participants finished this clinical trial and no patients were dropped out from the study. These have shown in study flow chart (figure 1). The baseline demographic characteristics of both study groups have shown in (table 1) which did not show any significant statistical difference. However after 12 weeks therapy of vitamin D, Significant improvement was recorded in primary end points NSS score (from 5.9±2.0 to 4.7±1.5) vs placebo (6.5 ±2.0 to 6.4 ±3.2) with p-value (0.002) and NDS score (from 7.8±2.0 to 6.5± 2.5) vs placebo (7.7±1.8 to 7.9±2.5) with p-value (0.001). Similarly secondary endpoints were also improved significantly from baseline to end point after 12 weeks of vitamin D therapy vitamin D value (from 25.8±14 to 44.5±12.5) vs placebo group (from 28.5±14.5 to30.0±15.5) with p-value (0.002), HbA1c from 9.0±2.8 to 7.8±3.5) vs Placebo (from 9.8±2.0 to 9.5±2.2) with p-value 0.001(table 2).

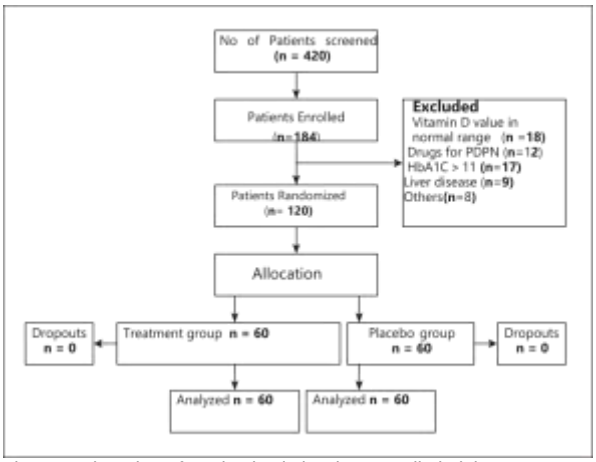

Figure: 1 Flow chartof randomized placebo controlled trial

Table-1: Baseline characteristicsof T2DM patients in both study groups (N=120)

Baseline parameters	Treatment Group A (n=60)	Placebo Group B(n=60)	P-value
Age(years)	43±12	38±11	0.42
Sex Male/Female	40/20	41/19	0.55
Body weight(kg)	84±9.5	87±11.5	0.34
BMI (Body Mass index kg/m^2)	28.5±3.5	29 ±2.5	0.65
Systolic Blood Pressure(SBP)	115±10.5	110±8.5	0.44
Diastolic Blood Pressure(DBP)	75± 8.5	82±6.5	0.72
Blood sugar fasting(mg/dl)	160 ±17	170±20.2	0.012
HbA1c	9.0±2.8	9.8±2.0	0.42
Serum Cholesterol(mg/dl)	185±20,5	165±22.0	0.82
Serum Triglycerides(mg/dl)	175±20.5	190±22.4	0.43
Serum low density lipoprotein LDL(mg/dl)	130±10	125±13.5	0.33
Serum high density lipoprotein HDL(mg/dl)	45±4.0	44.5±3.5	0.66
Duration of Diabetes(years)	7.5±2.5	7.2±2.8	0.32

t-test between two groups

Table-2: Baseline and endpoint comparison of differences within and between groups

Variables	Treatment Group A (n=60)		P value*	Placebo Group B(n=60)		P value* (within groups)	P value$^+$ (between groups)
	Baseline	End Point		Baseline	End Point		
HbA1c	9.0±2.8	7.8±3.5	0.001	9.8±2.0	9.5±2.2	0.33	0.001
NSS	5.9±2.0	4.7±1.5	0.001	6.5 ±2.0	6.4±3.2	0.88	0.002
NDS	7.8±2.0	6.5± 2.5	0.001	7.7±1.8	7.9±2.5	0.65	0.001
25(OH)D, mmol/l	25.8±14	44.5±12.5	0.002	28.5±14.5	30±15.5	0.55	0.002

NSS: Neuropathic symptomatic score, NDS: Neuropathic disability score

DISCUSSION

Vitamin D plays a vital role in regulation of bone mineral homeostasis. Its role in various diseases is already well established. Inadequate status of vitamin D has robust affiliation with T2DM as well as its related complications. Diabetes is called the disease of Asians and they are more prone to develop vitamin D deficiency. The symptoms of vitamin D deficiency are often exaggerated in T2DM patients. [13] This randomized trial showed that vitamin D therapy at a dose of 2, 00000 IU/ monthly not only improved its own level significantly but also improved symptoms of PDPN.

Studies have shown that PDPN has strong association with vitamin D deficiency in T2DM patients as well as in non diabetics. They concluded that vitamin D deficiency is an independent risk factor for diabetic peripheral neuropathy. [14-15] A study revealed that vitamin D therapy for 08 weeks duration augmented its level with significant improvement in symptoms of PDPN in T2DM patients similar to our study. There was significant improvement in NSS score similar to our study .However no significant improvement were recorded NCS and NDS score. Moreover we did not analyze nerve conduction study (NCS) in our study. [16]

In our study two symptoms of PDPN (burning sensation, and pain) were significantly improved after 12 weeks vitamin D supplementation. The mechanism by which vitamin D supplementation attenuates pain includes induction of neurotransmitters and nerve growth factors (NGF). The pain threshold may also be increased due to anti-inflammatory and antioxidant properties of vitamin D. Moreover vitamin D also reduces reactive oxygen species (ROS) products and expression of toll like receptors (2 & 4) that can contribute further in improving symptoms of PDPN. [17-19]

A study conducted in Baqai Institute of diabetes and endocrinology by Basit et al [20] revealed that single intramuscular injection vitamin D at a dose of 6, 00000 IU over a period of 20 weeks significantly reduced symptoms of painful diabetic neuropathy. They assessed diabetic neuropathy on the basis of Douleur Neuropathique 4 (DN4) score, total McGill pain score, and Short Form McGill Pain Questionnaire (SFMPQ) score while we

emphasize upon neuropathic symptomatic score (NSS) and neuropathic disability score (NDS).

Similarly in a systematic review of 4 studies comprising 374 patients suggested that adequate level of vitamin D is necessary for prevention of symptoms of peripheral neuropathic pain.[21] A study conducted in Chinese population revealed that vitamin D deficiency is a risk factor of diabetic peripheral neuropathy. Vitamin D levels are important prognostic biomarkers for assessment of PDPN in T2DM patients. [22.] Similar type of study was conducted in Turkey yield identical results.[23]

A study pointed out that even with a topical application of vitamin D cream there was significant improvement in symptoms of PDPN and quality of life in T2DM patients.[24] A clinical trial by Pinzon et al in Indonesia postulated that addition of oral vitamin D 5000IU daily for a period of 08 weeks to standard treatment significantly improves mood and pain in patients with diabetic neuropathy.[25] A study showed that vitamin D at a dose of 3, 00000 IU over a period of 12 weeks significantly improved symptoms of peripheral neuropathic pain similar to our study. However in contrast to our study symptoms of neuropathic pain was assessed by Douleur Neuropathique 4 (DN4) questionnaires. [26.] A study showed that high dose of vitamin D (40,000IU/week) for a period of 24 significantly improved microcirculation, inflammatory status and symptoms of neuropathic pain in T2DM patients.[27] Vitamin D supplementation not improve symptoms of PDNP in T2DM patients but also has a potential role in chronic low back pain syndrome and improve fibromyalgia in both diabetics as well as non diabetic.[28-29]

CONCLUSION

Vitamin D therapy attenuates symptoms of PDPN in T2DM patients

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