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TYPE 2 DIABETIC PATIENTS;

TO STUDY THE EFFECT OF VITAMIN D SUPPLEMENTATION ON SYMPTOMS OF PERIPHERAL NEUROPATHIC PAIN IN TYPE 2 DIABETIC PATIENTS

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ABSTRACT... Background: Peripheral neuropathic pain is a devastating complication in type 2 diabetic patients with significant morbidity and mortality. **Objectives:** To investigate the effect of oral vitamin D supplementation on symptoms of peripheral neuropathic pain in type 2 diabetic patients. **Study Design:** Prospective randomized placebo controlled trial. **Setting:** Diabetic Clinic of Sheikh Zayed Medical College/Hospital Rahim Yar Khan. **Period:** Over a period of 6 months from Jan-July 2017. **Methods:** 116 vitamin D deficient type 2 diabetic patients with symptoms of peripheral neuropathic pain were divided in to two groups to prescribed either oral vitamin D_3 capsule 50000IU weekly or Placebo capsule for a period of 12 weeks. Symptoms of diabetic neuropathic pain were assessed by neuropathy symptoms score (NSS) and neuropathy disability score (NDS) while Vitamin D status was estimated by measuring the serum total 25(OH) D concentration. The primary end point was changes in NSS and NDS while secondary end point was changes in HbA1C and 25 (OH) D concentrations from baseline. **Results:** After 12 weeks of vitamin D therapy, vitamin D improved its own level in interventional group (28.5±12.5 to 48.2±15.6) vs placebo group (30.6±16.2 to31.5±12.6) with p-value (0.001). This rise was accompanied by improvement in HbAlc (8.2±1.8 to 7.5±2.2) vs Placebo (7.8±1.5 to 8.0±1.8) with p-value (0.004) and NSS score (6.02±1.5 to 4.52±0.8) vs placebo (5.82 ±1.8 to 5.65±1.5) with p-value (0.002). However no significant changes were seen in NDS in both study groups. **Conclusion:** Oral vitamin D_3 therapy has positive impact on its own status as well as symptoms of peripheral neuropathic pain in type 2 diabetic patients.

Key words: Vitamin D, Type 2 Diabetes, Peripheral Neuropathic Pain.

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INTRODUCTION

Peripheral diabetic neuropathic pain (PDNP) is one of the devastating conditions that can leads to significant morbidity as well as mortality in type 2 diabetic patients. Its etiology is poorly understood as numbers of pathways are involved in its pathogenesis.[1] Most of the time it is usually associated with aching, burning, and tingling sensation in feet and lower leg that is often worse at night. It often disturbs sleep, impairs the quality of life and has negative influence on mood.[2] Neuropathy prevalence increases as diabetes become more advance and it affects approximately 50% patients with type 2 diabetes. Therefore a holistic approach is required to prevent PDNP and its upcoming complications in order to reduce burden on health system.[3]

The mainstay in the prevention of diabetic neuropathic pain focus on tight glycemic control and life style modification in the form of regular exercise, weight loss, balanced diet in order to slow the progression of distal symmetric poly neuropathy. On the other hand pharmacological treatment compromises of multiple drugs with varying results such as tricylic anti- depressants, anti-convultants, opiods as well as various GABA analogues. However PDPN is difficult to manage and always become a clinical challenge for clinicians as patients are more concern about PDPN than other type of neuropathies. On the other hand patient's compliance and adverse effects are

others consequences of drug.[4-5]

In recent years a lot of research has been done on Vitamin D. Its optimum level in the body not only maintains bone mineral homeostasis but also plays a protective role in number of diseases. Vitamin D protects against autoimmune, metabolic, infective, inflammatory, respiratory, nervous system, endocrinal and reproductive diseases.[6-7]

Studies have shown that a strong relationship exists between vitamin D and glycemic control. Its inadequate level in the body predisposes to diabetes while its optimum level maintains blood sugar and prevents diabetes related complications in which PDNP is one of them.[8-9] Moreover pain threshold due to multiple etiologies have been increased by vitamin D supplementation and reduced by vitamin D deficiency. Low level of vitamin D itself predisposes to symptoms of peripheral neuropathic pain even in non diabetics.[10-12]

Keeping in view, we assume that vitamin D supplementation either directly or indirectly improve the symptoms of peripheral neuropathic pain symptoms in type 2 diabetic patients.

MATERIALS & METHODS

This 12 weeks randomized placebo controlled trial was conducted at diabetic clinic of Sheik Zayed Medical College/Hospital Rahim Yar Khan. Initially 560 type 2 diabetic patients were screened at diabetic clinic over a period of 6 months from Jan-July 2017. On the basis of clinical presentation such as burning, tingling and aching sensation in feet's and legs. Moreover patients with history of reduced pain, numbness, temperatures changes and loss of balance were screened. Out of which a total of 160 patients enrolled in the study based upon inclusion and exclusion criteria.

The inclusion criteria were vitamin D deficient type 2 diabetic patients, aged 25-55years , (HbA1c) ≤11%, BMI ≤ 27, duration of diabetes<10 years with neuropathic symptomatic score (NSS) > 5 and neuropathic disability score (NDS) >6.

Patients were excluded if they had any other causes of peripheral neuropathic pain such as inflammatory, malignant, autoimmune, thyroid disorders, AIDS, viral hepatitis, nutritional (vitamin B12 & B6). In addition smoking, alcohol and drug history was taken that causes peripheral neuropathic pain such as amiodarone, colchicine and dapsone. Patients who were taking drug for peripheral neuropathic pain were excluded from the study such as SSRI, SNRI, GABA, tricylic and opiods analogs. In addition patients with history of thyroid, renal and hepatic disorder were also excluded from the study. An ethical committee approval was taken from institutional board review and perspectives of study were clearly explained to all patients before taking informed consent.

Patients were randomly allocated in interventional and placebo group. Randomization was done by allocation of random number to each patient by computed generated software. The interventional group was given vitamin D capsule at a dose of 50,000IU weekly for a period of 12 weeks. On the other hand placebo group were given placebo capsule with same size, color and packing but it contained starch as an active ingredients for same time period. Researcher and study groups were blinded to study plan.

A detailed general physical examination was conducted for every patient Neuropathic pain was assessed by neuropathic symptomatic score (NSS) and neuropathic disability score (NDS) .NSS assessed pain in terms of its (location, nature, intensity, relieving maneuvers). NSS value extent from 0-9 and more than 5 is termed as neuropathy. While assessment of temperature, vibration, pin prick sensation and ankle reflex was done by NDS. NDS value extent from 0-10 and more than 6 is termed as neuropathy. The primary end point was change in NSS and NDS while secondary end point was change in HbA1c and vitamin D level from baseline.

Serum sugar and lipid profiles were analyzed by routine method to all patients at start of study. HbA1c and Vitamin D status was checked at start as well as the end of study. Vitamin D status was

assessed by measuring Serum 25-hydroxyvitamin D 25(OHD) concentrations by radioimmunoassay. Regular follow up were maintained for all patients to check the compliance of drug as well any drop out.

Data Analysis

All numeric data was analyzed by using statistical package for social sciences (SPSS-16). Values were expressed as mean ± standard deviation. A t-test was used to access any change in values at baseline. Paired t-test was used for the comparison of the changes from 0 to 12 weeks with in each group while t-test or Mann-Whitney U-test was used for the comparison of changes between groups from baseline to end point. A p- value less than 0.05 were deemed to be statistically significant.

RESULTS

A total of 160 patients were enrolled in the study, out of which 116 were randomized for treatment, 58 in each group. Compliance of vitamin D is good and all patients tolerated vitamin D quite well with no adverse effects. However 4 patients in the interventional group and 5 patients in the placebo group were dropped out due to loss of follow up. So, 54 patients in vitamin D group and 53 patients in placebo group completed the clinical trial shown in flow chart (Table-I). The baseline demographic characteristics in terms of age, body mass index (BMI), gender, blood pressure, duration of diabetes and lipid profile showed no significant differences among two groups at baseline (Table-II). However after 12 weeks of vitamin D supplementation, vitamin D improved its own level in interventional group (28.5±12.5 to 48.2±15.6) vs placebo group (30.6±16.2 to31.5±12.6) with p-value (0.001). This rise in Vitamin D status was accompanied by improvement in HbAlc (8.2±1.8 to 7.5±2.2) vs Placebo (7.8±1.5 to 8.0±1.8) with p-value (0.004) and NSS score (6.02±1.5 to 4.52±0.8) vs placebo (5.82 ±1.8 to 5.65±1.5) with p-value (0.002). However no significant changes were seen in NDS in both study groups (Table-III).

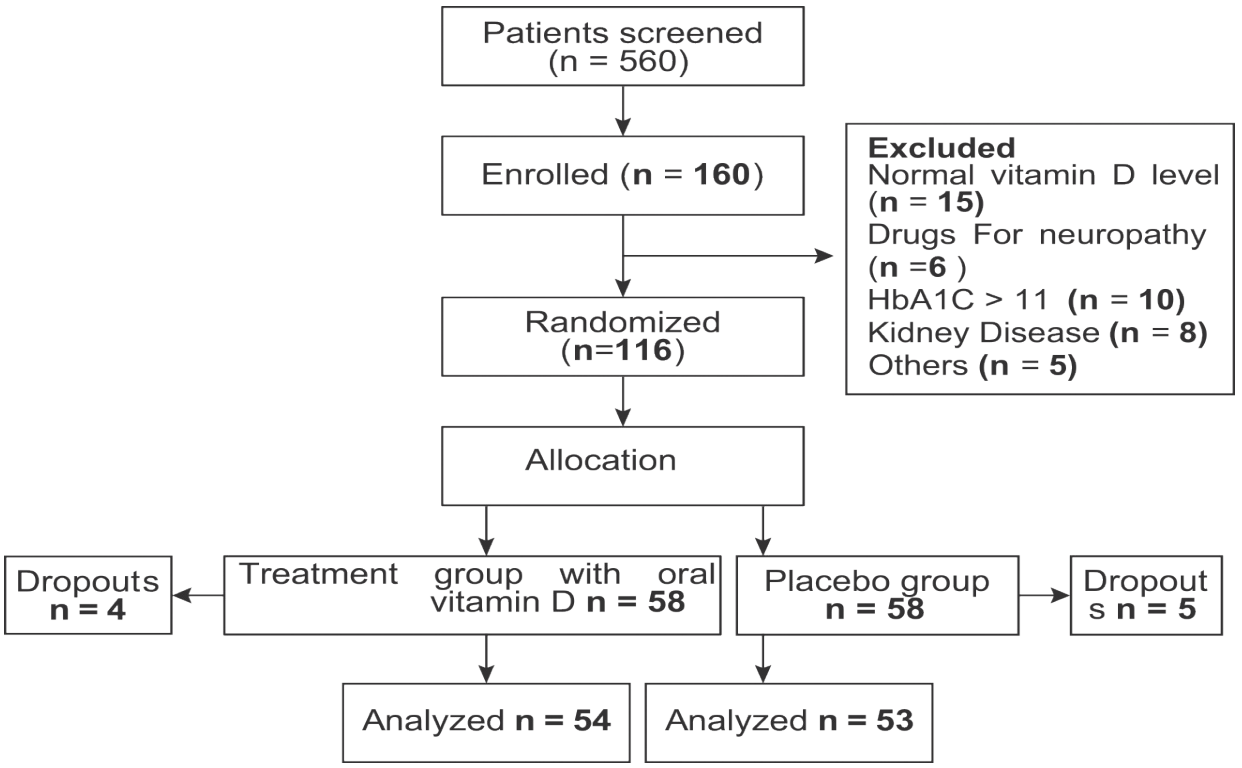

Table-I. Flow chart of patient's recruitments for placebo controlled trial

Baseline parameters	Vitamin D (n=54)	Placebo (n=53)	P-value
Age(years)	31±18	28±17	0.366
Sex Male/Female	36/18	33/20	0.745
Body weight(kg)	78±12.5	85±14.2	0.643
BMI (Body Mass index kg/m^2)	27.5±2.2	28.6 ±1.8	0.440
Systolic Blood Pressure(SBP)	110±15.24	125±12.5	0.032
Diastolic Blood Pressure(DBP)	85± 10.8	80±8.8	0.045
Blood sugar fasting(mg/dl)	92 ±20.5	98±18.2	0.055
HbA1c	8.2±1.8	7.8±1.5	0.034
Serum Cholesterol(mg/dl)	190±18.2	178±25.5	0.772
Serum Triglycerides(mg/dl)	170±20.2	185±18.6	0.050
Serum LDL(mg/dl)	140±12.5	135±15.2	0.068
Serum HDL(mg/dl)	44.5±3.2	46.8±2.8	0.421
Duration of Diabetes(years)	8.2±2.8	7.8±3.2	0.065

Table-II. Baseline characteristics of patients (N= 116) with symptoms of Neuropathy
LDL: High density lipoprotein Cholesterol, LDL: High density lipoprotein Cholesterol
Values are presented ± standard deviation, t-test between two groups

Variables	Vitamin D (n-54)		P value*	Placebo (n-53)		P value*	P value$^+$
	Baseline	End Point		Baseline	End Point		
HbA1c	8.2±1.8	7.5±2.2	0.002	7.8±1.5	8.0±1.8	0.056	0.004
NSS	6.02±1.5	4.52±0.8	0.001	5.82 ±1.8	5.65±1.5	0.425	0.002
NDS	7.5±1.6	7.3± 1.6	0.45	8.2±2.1	8.0±1.8	0.26	0.345
25(OH)D, mmol/l	28.5±12.5	48.2±15.6	0.001	30.6±16.2	31.5±12.6	0.64	0.001

Table-III. Comparison of the changes from baseline to end point within and between groups' after treatment with Vitamin D and Placebo
NSS: Neuropathic symptomatic score, NDS: Neuropathic disability score
P value* (comparison within groups) P value$^+$ (comparison of changes of each variable between the two groups)

DISCUSSION

During recent years a lot of work has been on vitamin D. Its inadequate level in body involve in the pathogenesis of various diseases, in which diabetes mellitus and its related complications are being one of them. Moreover vitamin D deficiency is more prevalent in Asian population and is often exaggerated in type 2 diabetic patients.[13] In this study vitamin D3 capsule at a dose of 50,000IU weekly over a period of 12 weeks not only improved its own status but also symptoms of peripheral neuropathic pain. This was the second randomized trials in Pakistan to observe the effect of vitamin D supplementation on symptoms of peripheral neuropathic pain.

In spite of strong relationship between vitamin D deficiency and development of peripheral neuropathic pain,[14] very little work has been done on this subject so far. In study, Shehab et al [15] concluded that vitamin D deficiency is one of the important risk factor that leads to neuropathy in diabetic patients. Oral Vitamin D supplementation significantly improved symptoms of peripheral neuropathic pain and improved vitamin D status similar to our study. In another study vitamin D therapy yield similar results to our study, but the main difference between is the lack of improvement in nerve conduction study (NCS) value after 08 weeks of vitamin D therapy. However we did not access peripheral neuropathic pain by NCS as we mainly emphasize on NSS and NDS score.[16]

Burning sensation in feet and hyperesthesia were the two most important symptoms which were improved in all patients in our study. A number of mechanisms are involved in elevation of pain threshold and improvement in the function of affected nerves. Induction of neurotransmitters and nerve growth factors (NGF) by vitamin D in various experimental and clinical studies are main mechanism. Moreover antioxidant and anti

inflammatory effect of vitamin D are additional benefits in pain relieving. Furthermore decrease expression of toll like receptors (2 & 4) and reactive oxygen species are other possible mechanisms.[17-19]

Our results were consistent with two other studies, which were separately conducted in type 1 and type 2 diabetic patients. They pointed out that oral vitamin D therapy for a period of 12 weeks significantly improved symptoms of neuropathic pain in vitamin D deficient patients.[20,21] Similarly a study conducted by He et al[22] in china revealed that low level of vitamin D is an independent risk factors as well as valuable marker of peripheral neuropathy in type 2 diabetic patients. Another study demonstrated that topical application of Vitamin D cream on skin in both type 1 and 2 diabetic patients significantly improved symptoms of neuropathy and quality of life.[23] A study conducted in Turkey demonstrated that decreased level of vitamin D in diabetic patients is associated with peripheral neuropathy in its rural areas.[24]

In spite of strong relationship between vitamin D and symptoms of neuropathy in various clinical studies, limited work has been done so far in Pakistan to observe the effect of vitamin D supplementation on neuropathic pain. A study conducted at Baqai Institute of Diabetology and Endocrinology (BIDE) in Karachi demonstrated that high dose of vitamin D3 6,00000 IU intramuscularly at once significantly improved symptoms of diabetic peripheral neuropathic pain in diabetic patients.[25] In our study vitamin D improved glycemic control which is consistent with meta analysis of other clinical studies.[8,9] It might be possible that improvement in glycemic control by vitamin D in our study reduce symptoms of neuropathy and improved quality of life as observed in many above mentioned clinical trials. On the contrary vitamin D supplementation also improved symptoms of chronic low back pain and fibromyalgia even in non diabetic in various studies. These might its direct anti inflammatory and antioxidant effects.[26,27] These beneficial effects may reduce ongoing cardiovascular and others diabetes related complications as observed in another study.[28]

The result of our study showed that vitamin D either directly or through glycemic control improved symptoms of peripheral neuropathic pain. The main strength of our study we tried to adjust confounding factors for diabetic neuropathy such as smoking, alcohol, increase BMI, duration of diabetes (< 10 years), hypertension, dyslipidemia and HbA1C <10mg/dl.

LIMITATION OF STUDY

The main limitation of our study is that we mainly depended on NSS and NDS. However it was much better those we also used nerve conduction study (NCS) for better results. Second limitation of our study we did not adjusted potential confounders such as sun exposure, physical activity and diet.

CONCLUSION

Vitamin D supplementation not only improved its own status but also symptoms of peripheral neuropathic pain.

RECOMMENDATION

Further clinical trials of large sample size should be recommended after adjusting confounders in both diabetic and non-diabetic patients in order to observe its direct and indirect effects.

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Declaration of Interest

There is no conflict of interest in this study.

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When the roots are deep.
There is no reason to fear the wind.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author-s Full Name	Contribution to the paper	Author=s Signature
1	Mazhar Hussain	Conceived the idea, Manuscript review and statistical analysis.	
2	M. Arshad Qureshi	Designed the study, preparing the manuscript and data analysis.	
3	Abdul Qudoos Arain	Search the literature, collected the clinical data, Manuscript editing and drafting of the manuscript.	
4	Habib-Ur-Rehman	Final editing, plagiarism and drafting of manuscript.	