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Effect of Replacement of Vit-D in Diabetic Painful Neuropathy among Chronic Type 2 Diabetic Patients

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ABSTRACT

Background: Painful symptoms of diabetic neuropathy are more common in patients having type 2 diabetes. The objective in this trial was assessment of mean change in pain score upon giving Vit-D supplementation in patients with diabetic painful neuropathy.

Methodology: This study was conducted from December 2019 to June 2020 in OPD of Fauji Foundation Hospital, Rawalpindi after the ethical approval. A total of 251 diagnosed cases of diabetes (both male and female patients), with high HbA1c and low Vit-D levels were included in the study. Patients having Vit-D deficiency and chronic diabetic neuropathy were given Vitamin supplementation and results were assessed after 1 month through change in pain score according to Douleur Neuropathique 4. A document of consent form was filled by patients who were recruited for this study. Data analysis was done on SPSS version 16.Paired sample t- test, was used to compare pain score where p value less than 0.05 was considered statistically significant.

Results: Among the participants mean age was 48.22+17.06. There were 106 (42.2%) males and 145 (57.8%) female patients. A statistically significant ($p<0.05$)mean reduction in pain score of 2.20±1.19 was observed, upon giving Vit-D supplementation in Vit-D deficient patients having painful diabetic neuropathy.

Conclusion: Vit-D supplementation significantly reduced pain in patients having diabetic painful neuropathy.

Keywords: Diabetes Mellitus, Diabetic Neuropathy, Vitamin D3

Authors' Contribution:
[1]Conception; Literature research; manuscript design and drafting; [2,3] Critical analysis and manuscript review; [4,5]Data analysis; Manuscript Editing.

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Introduction

Patients with type 2 diabetes are having lot of complications including microvascular triopathy i.e retinopathy, neuropathy and nephropathy. The recent studies according to International Diabetes Federation, estimated that diabetes is 8.3% prevalent worldwide and estimated increase by 2030 will be around 69% in adults.[1] Diabetic Painful Neuropathy (DPN) is considered as most devastating

complication in diabetes, affecting around 50% of patients with diabetes during their lifetime.[2] It becomes a distress for the patients by affecting their everyday physical activities, leading to psychiatric manifestations and disability.[3] Generally, they are categorized into focal or multi-focal neuropathies like amyotrophy or polyneuropathies including diabetic sensori-motor polyneuropathy (DSPN). One of most common microvascular complications of diabetes is painful diabetic neuropathy, with having symptoms of burning feet especially at night and often under diagnosed and mismanaged.[4]

Vit-D is a hormone that is produced in skin and is dependent on exposure to sunlight. Several observational studies on diabetes have shown association of Vit-D deficiency with paresthesia and numbness.[5] A pro-form of Vit-D i.e., 25-hydroxy Vit-D has half life of almost three weeks and is much more active and stable than 1-25 hydroxy Vit-D which has half life of only 4 hours. Hence, Vit-D status is evaluated by using 25-hydroxy Vit-D as per Institute of Medicine in United States.[6] Worldwide in international literature, levels of 25-OHD in body below 50 nmol/L are taken as insufficient.[7] Several studies are available internationally considering the role and replacement of Vit D in painful diabetic neuropathy but in our Pakistani population, very less data is availableand this aspect needs further research.Thereforethisresearchwas planned to evaluate the role of Vit-D in diabetic polyneuropathy in our local population and make guidelines that can be implemented in favor of patients in future.

Methodology

The Quasi experimental study was conducted in Diabetes clinic of Fauji Foundation Hospital from December 2019 to June 2020.Minimum sample size of 242was calculated by using WHO calculator using formula 2.1 and absolute precision value of 0.07.

$$n=\frac{z^2_{1-\alpha/2}[P_1(1-P_1)+P_2(1-P_2)]}{d^2}$$

Consecutive non-probability sampling strategy was used to include 251 patients and approval from the ethical review committee was taken before collecting the data. Diabetic Patients from both genders of age 25-70 years, with duration of diabetes more than five years, patients having HbA1C levels more than 9 and vitamin D levels less than 27 ng/ml were included. Patients who were already taking treatment for Vitamin D, tuberculosis or epilepsy, patients with advanced renal disease, severe co-morbid diseases like chronic liver disease, advanced cardiac failure, cancer or renal implant were excluded. Patients having either of thyroid disease, active hepatitis B and C or any peripheral neuropathies due to some other non-diabetic pathology were also not included. After taking written consent, both male and female patients presenting to OPD were evaluated. Subjects diagnosed with diabetes were tested for HbA1c and Vit-D levels at initial visit and those diagnosed with vitamin D deficiency and having chronic diabetic neuropathy were given Vitamin D supplementation. Results were assessed after 1 month through change in pain score according to Douleur Neuropathique 4. Data was analyzed on SPSS 16 version. Standard deviation as well as mean calculation was done for the quantitative variables i.e., pain score. Percentage along with frequency calculation was done for qualitative variables like gender and age. Paired sample t- test, was used to compare mean of pain score considering P-value of less than 0.05 taken as significant statistically. Control of effect modifiers like age and gender was done by stratification and post stratification paired sample t-test.

Results

Out of 251 patients, mean age (years) in the study was 48.22$\pm$17.06. There were 106 (42.2%) males and 145 (57.8%) female patients. The mean pain score at baseline visit, according to Douleur Neuropathique 4 Questions (DN4) was 5.06$\pm$1.14 and at 1 month after

treatment was 2.87±0.33. There was a mean reduction in pain score of 2.20±1.19 upon giving vitamin D supplementation in vitamin D deficient patients having painful diabetic neuropathy.

Pre-treatment and Post-treatment mean of pain score was compared according to age, gender, level of Glycosylated Hb, vitamin D levels and duration of diabetes as it is seen in Table 1. A significant improvement in intensity of pain was seen ($p<0.05$) with respect to all parameters, upon giving vitamin D supplementation in V-it-D deficient patients.

Table. Comparison of pre and post treatment diabetic neuropathic pain score according to different parameters

Parameters	Sub-parameter	Pre-Treatment Diabetic neuropathic pain score	Post-Treatment Diabetic neuropathic pain score	P-value
Age Group	25-50 years	5.00±1.06	2.87±0.33	<0.05
	51-70 years	5.13±1.22	2.87±0.33	<0.05
Gender	Male	5.07±1.11	2.88±0.31	<0.05
	Female	5.06±1.17	2.86±0.34	<0.05
HbA1c	< 9	5.05±1.14	2.87±0.32	<0.05
	> 9	5.09±1.14	2.86±0.34	<0.05
Vit D Levels	< 27	5.05±1.16	2.87±0.33	<0.05
	> 27	5.18±1.04	2.84±0.36	<0.05
Duration of Diabetes	< 8 years	5.07±1.12	2.87±0.33	<0.05
	> 8 years	5.05±1.12	2.86±0.34	<0.05

Discussion

Painful diabetic polyneuropathy is an extremely disabling presentation of diabetes and affects every 5th patient having type 2 Diabetes Mellitus.[8] The pathophysiology of diabetic painful neuropathy is very complicated with peripheral sensiomoter, autonomic and central thalamic perfusion abnormalities seen in chronic diabetic patients. Typical presentation of these symptoms is dysesthesia, symmetrical paraesthesias and electric shocks-like pain especially in the feet with night time exacerbations.[9] Prevalence of Vit-D deficiency is very high in these patients with diabetes and replacement of adequate dose of 25-hydroxy Vit D (40,000 IU/week) for 24 weeks was found to be very effective in improving the clinical manifestations.[10] Recently there are studies which have found an strong link between Vit-D deficiency and painful diabetic neuropathy. However, all of these trials have proven the differences between positive symptoms like hyperalgesia and allodynia and negative symptoms like paresthesia and numbness. In literature various epidemiological trials have concluded a much higher prevalence of diabetic painful neuropathy in south Asian population despite of having a low overall prevalence of neuropathy in comparison with other ethnic groups.[1] In our previous study, almost half of overall subjects were having deficiency of Vit-D, with levels <27ng/ml, and there was a significant overlap with the patients suffering from diabetic painful neuropathy. The current study provides useful data on vitamin D therapy as a potential treatment for painful diabetic neuropathy (PDN). A few recent trials have shown a significant association between diabetes and Vit-D deficiency.[11] To establish the role of Vit-D supplementation for decreasing pain due to diabetic neuropathy, we administered Vit-D in diabetic patients having painful diabetic polyneuropathy (PDN). There are several therapies given for symptom relief and enhancing quality of

life [12] but so far in literature, its estimated that all the medications have proven to relieve only50% of the pain and their dose can't be increased due to undesirable side effects.[13]

A study done at Baqai Institute of Diabetology and Endocrinology (BIDE) assessed the effect of vitamin D replacement in chronic diabetic painful neuropathy[14] The mean pain score at baseline according to DN4 was 3.0 ± 1.8 and 2.6 ± 1.9 at 8-12 weeks . Single dose of vitamin D (600,000 IU) showed decrease in positive symptoms regarding DN4 ($p<0.0001$), a total pain score of ($p<0.0001$), and SFMPQ of ($p<0.0001$) in patients with diabetic painful neuropathy. In our trial, mean age in years was 48.22+17.06 and in a study done locally by Basit et al, [12] mean age in years was 52.31±11.48 with similar results. Another study published in 2019established that oral replacement of Vit-D3 in dose of 50,000 units weekly for about 12 week time, resulted in a marked increase in Vit D levels and a reduction in diabetic painful neuropathy. They recommend regular check on Vit D levels in chronicdiabetic patients, with replacement if found low, to improve the quality of life.[15] Asystemic review and meta-analysis published in 2021, evaluated the benefits of add-on therapy of Vit D replacement and PDN in type 2 diabetic patients.[16] It provided the evidence that Vit-D deficiency was related to augmented risk of diabetic painful neuropathy in chronic type 2 diabetic patients (OR of 2.68, 95 % CI of 1.67–4.30, P value < 0.0001). In the current study, we observed mean pain score at baseline according to Douleur Neuroopahtique 4 (DN4) at 5.06±1.14 and 2.87±0.33 after 1 month post treatment.

A study conducted in 2016 observed mean pain score at baseline according to DN4 at 3.0 ± 1.8 and 2.6 ± 1.9 at 8-12 weeks. Hence vitamin D supplementation has shown too beneficial for treating DPN as depicted from our data and several previous studies. Traditionally Vit-D is being used very effectively for treatment of pain in other conditions, specially certain rheumatologic diseases.[17] However, a study done by Abdelsadek *et al.* demonstrated that there was no significant relationship between Vit-D replacement in chronic pain, as these trials studies were having variable quality along with variable outcomes due to difference in methodology used.[18] Based on these findings there is a strong need in use of novel medications in treatment of diabetic painful neuropathy. Furthermore, there is emerging evidence that Vit-D deficiency is related to diabetic painful neuropathy. There is a strong need of well constructed controlled clinical trials of replacement of Vit-D in diabetic painful neuropathy in order to assess the exact effectiveness of this kind of treatment. While the results of these trials are awaited, we recommend the of an initial bolus of 40,000 IU of Vit-D3 taken daily with evening meal for about 21 days, followed by a long term maintenance dose of between 20,000 to 40,000 IU once weekly.

Conclusion

Vit-D supplementation significantly reduced pain in patients with diabetic neuropathy.

Recommendation

We strongly recommend the measurement of serum 25-OH vitamin D levels of in all diabetic patients and vit D replacement should be done in patients having deficiency.

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