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The benefits of add-on therapy of vitamin D to the quality of life in diabetic neuropathy patients: a randomized controlled trial

Kenzie Ongko Wijaya[1], Rizaldy Taslim Pinzon[1,2], Esdras Ardi Pramudita[1]

[1]Faculty of Medicine, Duta Wacana Christian University, Yogyakarta, Indonesia
[2]Department of Neurology, Bethesda Hospital, Yogyakarta, Indonesia

ABSTRACT

Background. Diabetic neuropathy mostly causes physical disabilities that will reduce social participation, medical/psychological rehabilitation, and enjoyable activities. These factors in turn create a cycle of depression, anxiety, and sleep disorders. Variables related to pain perception play an important role, pain catastrophizing will increase anxiety so that sufferers feel they have a disability that is worse than reality. In the end, patients will give up and reduce their self-efficacy.

Results. Data from 68 subjects was collected and analyzed. After eight weeks of treatment, the experimental group showed a more significant mood improvement (88.2% vs. 70.6%, p=0.031). There were no adverse events recorded in this study.

Conclusions. Vitamin D addition along with standard treatment significantly improve mood more effectively than standard treatment alone in diabetic neuropathy patients.

Keywords: diabetic neuropathy, diabetes, quality of life, vitamin D, supplementation

INTRODUCTION

Diabetic neuropathy is the most common complication of diabetes, it is estimated that 425 million people in the world suffer from this disease and 50% of them will experience diabetic neuropathy over time [1]. In 2019, researchers in Iran estimated quality of life, depression ranked first, pain catastrophizing second, and anxiety ranked last of the 27 items studied. Depression and physical disability will reduce social participation, medical/psychological rehabilitation, and enjoyable activities. This withdrawal, in turn, creates a cycle of depression, anxiety, and sleep disorders. The onset of pain will increase anxiety so that the patient feels that they have a disability that is worse than the reality of their illness. In the end the patient will give up and reduce self-efficacy [2].

Vitamin D deficiency has been associated with diabetic peripheral neuropathy rather than retinopathy or maculopathy. Previous study in Kuwait demonstrated vitamin D deficiency was found in 82% of patients with diabetic neuropathy and 61% of patients without neuropathy. Vitamin D therapy has been shown to significantly reduce the severity of diabetic neuropathy pain [3]. The provision of 5000 IU vitamin D therapy for diabetic neuropathy has not been widely used and its effect on the patient's quality of life is still limited. This research is an effort to develop better therapeutic strategies for diabetic neuropathy.

METHODS

Study design and setting

Designed as a randomized clinical trial, open-label, controlled study conducted at Bethesda Hospital, a large tertiary hospital in Yogyakarta, Indonesia. Enrollment of this study began in December 2020 and was completed in three months. The study group received an oral vitamin D 5000 IU once daily over eight weeks in addition to painful diabetic neuropathy standard treatment (pregabalin, gabapentin, or amitriptyline). The control group only received standard treatment over the same period of time.

Corresponding author:
Kenzie Ongko Wijaya
E-mail: kenzieowpersonal@gmail.com

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Participants

Participants were all patients with type 2 diabetes, aged >18 years, with a vitamin D status of <30 ng/ml) with complain of painful diabetic neuropathy symptoms (i.e., burning, tingling) and all subjects were assessed by a neurologist. The exclusion criteria were subject to significant renal and liver impairment, known hypersensitivity with vitamin D, pregnancy, breastfeeding patients, enrolled in any clinical trial within a month, and unwillingness to participate.

Randomization and blinding

Following written informed consent, participants were allocated to 1 of 2 groups using block randomization with a 1:1 ratio then assigned to the experimental (n = 34) or standard care (n = 34) trial group. A randomization list was generated by a statistician using blocks of 5 stratifications.

Ethical consideration

We confirm that all ongoing and related trials for this drug/intervention are registered and received ethical approval from the Bethesda Hospital Ethics Committee with the number 71/KEPK-RSB/XII/21. This research also registered in the Indonesian Clinical Trial Registry with the number INA-MEODDY6 and ClinicalTrials.gov with the number of NCT04689958. All subjects gave signed informed consent in accordance with the Declaration of Helsinki.

Assessment

The outcome was the percentage changes in the score on the Brief Pain Inventory (BPI) and Subjective Global Assessment (SGA), for pain impact on the interference on sleep quality, general activity, and mood. We measured the subjects BPI scores before and after the intervention and categorized it into: vastly improved: >50% improvement on their score; improved: 30-50% improvement on their score; slightly improved: 10-30% improvement on their score; no improvement: <10% improvement on their score from the baseline. SGA score measurement of the subject was also carried out before and after the intervention and was categorized into: vastly improved: >50% improvement on their score; improved: 30-50% improvement on their score; slightly improved: 10-30% improvement on their score no improvement: <10% improvement on their score from the baseline.

Statistical analysis

Categorical data were presented using frequency and percentage. The Chi-square test was used for categorical data and the independent t-test or Mann-Whitney test were used to compare the mean scores between the two study groups. Paired t-test or Wilcoxon signed-rank tests were also used to compare mean scores at week-4 and week-8 after intervention in each group. Statistical significance was set at $p<0.05$, and SPSS version 23 was used for statistical analysis. Missing data will be imputed and intention to treat analysis concept will be used for all the statistical analysis.

RESULTS

A total of 68 individuals who met the specified inclusion and exclusion criteria were allocated randomly into two groups: the experimental group and the control group, each comprising 34 participants. However, during the follow-up period, three participants from the experimental group and one participant from the control group were lost to follow-up and discontinued their participation in the study. Thus, data from a total of 68 participants were collected and subjected to analysis, as depicted in Figure 1 of the CONSORT flow chart for this study.

Subjects' baseline characteristics

Table 1. presents an overview of the baseline characteristics of the study participants. The study consisted of more female subjects, accounting for 60.3% of the participants, while male subjects made up the remaining 39.7%. On average, the participants in this study had an age of 64.96 ± 8.3 years. The average duration of diabetes among the participants was 9.74 ± 7.79 years, with hypertension being the most common comorbidity, affecting 58.8% of the subjects. The most frequently used co-medications were antihypertensive medications (60.3%), followed by vitamin B supplements (51.5%), antiplatelet agents (44.1%), and statins (19.1%).

The experimental group had mean baseline scores of 4.15 ± 0.93 for the Neuropathy Deficit Score (NDS) and 2.12 ± 1.01 for the Neuropathy Symptoms Score (NSS), whereas the control group had mean baseline NDS and NSS scores of 3.88 ± 0.88 and 2.5 ± 0.99, respectively. There were no significant differences in baseline characteristics or the type of burn between the two groups, except for marital status.

Sleep quality, general activity, and mood

Table 2. presents the analysis results of data collected using the SGA instrument at the study's conclusion, specifically during the 8th week. Improvements were determined based on increases in the "Vastly improved" and "Improved" categories. Upon analysis, it was discovered that a majority of participants in the experimental group exhibited a >30% increase in their SGA scores. Notably, the experimental group demonstrated higher levels of improvement in sleep

TABLE 1. Baseline characteristics

	Vitamin D 5000 IU + Standard Treatment (n=34)	Standard Treatment (n=34)	Total (n=68)	*p*-value
Age, mean ± SD (years)	65.41 ± 8.51	64.5 ± 8.2	64.96 ± 8.3	0.654
Heights, mean ± SD (centimeters)	157.24 ± 9.42	158.29 ± 9.2	157.76 ± 9.25	0.641
Weights, mean ± SD (kilograms)	62.69 ± 11.7	65.5 ± 7.36	64.10 ± 9.81	0.241
Gender				
Male	12 (35.3%)	15 (44.1%)	27 (39.7%)	0.621
Female	22 (64.7%)	19 (55.9%)	41 (60.3%)	
Marital Status				
Not Married	1 (2.9%)	1 (2.9%)	2 (2.9%)	0.043*
Married	25 (73.5%)	32 (94.1%)	57 (83.8%)	
Divorce	8 (23.5%)	1 (2.9%)	9 (13.2%)	
Education				
Elementary School	3 (8.8%)	4 (11.8%)	7 (10.3%)	0.610
Junior High School	4 (11.8%)	1 (2.9%)	5 (7.4%)	
Senior High School	15 (44.1%)	16 (47.1%)	31 (45.6%)	
Bachelor Degree	10 (29.4%)	9 (26.5%)	19 (27.9%)	
Others	2 (5.9%)	4 (11.8%)	6 (8.8%)	
Occupation				
Domestic worker	1 (2.9%)	2 (5.9%)	3 (4.4%)	0.639
Entrepreneur	3 (8.8%)	2 (5.9%)	5 (7.4%)	
Private Employee	4 (11.8%)	1 (2.9%)	5 (7.4%)	
Unemployment	3 (8.8%)	3 (8.8%)	6 (8.8%)	
Retired	12 (35.3%)	17 (50%)	29 (42.6%)	
Others	11 (32.4%)	9 (26.5%)	20 (29.4%)	
Type of Health Financing				
Public insure	28 (82.4%)	21 (61.8%)	49 (72.1%)	0.246
Private insure	0 (0%)	1 (2.9%)	1 (1.5%)	
Company insure	1 (2.9%)	3 (8.8%)	4 (5.9%)	
Others	5 (14.7%)	9 (26.5%)	14 (20.6%)	
Duration of diabetes, mean ± SD (years)	8.67 ± 7.83	10.82 ± 7.7	9.74 ± 7.79	0.160
Comorbidities				
Hypertension	18 (52.9%)	22 (64.7%)	40 (58.8%)	0.324
Cardiovascular disease	15 (44.1%)	21 (61.8%)	36 (52.9%)	0.145
Gastrointestinal disease	2 (5.9%)	5 (14.7%)	7 (10.3%)	0.231
Co-medications				
Antihypertensive	19 (55.9%)	22 (64.7%)	41 (60.3%)	0.457
Vitamin B	22 (62.9%)	13 (38.2%)	35 (51.5%)	0.051
Antiplatelet	13 (38.2%)	17 (50%)	30 (44.1%)	0.329
Statin	6 (17.6%)	7 (20.6%)	13 (19.1%)	0.758
Baseline NDS Scores, mean ± SD	4.15 ± 0.93	3.88 ± 0.88	4.01 (0.91)	0.244
Baseline NSS Scores, mean ± SD	2.12 ± 1.01	2.5 ± 0.99	2.31 (1.01)	0.097

Data are presented as mean ± standard deviation (SD) and n(%). Abbreviations: NDS: Neuropathy Deficit Score; NSS: Neuropathy Symptoms Score

quality (76.5% vs. 73.5%), daily activities (88.2% vs. 70.6%), and mood (88.2% vs. 70.6%) compared to the control group, a significant difference was observed only in the improvement of mood (p=0.031), whereas sleep quality (p=0.885) and daily activities (p=0.096) did not show statistically significant differences.

In Table 3. the results obtained using the Brief Pain Inventory (BPI) instrument are displayed. These

TABLE 2. Comparison of sleep quality, daily activity, and mood using Subjective Global Assessment (SGA)

	Vitamin D 5000 IU + Standard Treatment (n=34)	Standard Treatment (n=34)	Total (n=68)	*p*-value
Sleep Quality				
Vastly improved	13 (38.2%)	13 (38.2%)	26 (38.2%)	0.885
Improved	13 (38.2%)	12 (35.3%)	25 (36.8%)	
Slightly improved	3 (8.8%)	5 (14.7%)	8 (11.8%)	
No improvement	5 (14.7%)	4 (11.8%)	9 (13.2%)	
General Activity				
Vastly improved	12 (35.3%)	9 (26.5%)	21 (30.9%)	0.096
Improved	18 (52.9%)	15 (44.1%)	33(48.5%)	
Slightly improved	1 (2.9%)	8 (23.5%)	9 (13.2%)	
No improvement	3 (8.8%)	2 (5.9%)	5 (7.4%)	
Mood				
Vastly improved	9 (26.5%)	12 (35.3%)	21 (61.8%)	0.031*
Improved	21 (61.8%)	12 (35.3%)	33 (48.5%)	
Slightly improved	0 (0%)	6 (17.6%)	6 (8.8%)	
No improvement	4 (11.8%)	4 (11.8%)	8 (11.8%)	

Vastly improved: >50% improvement on their score;
Improved: 30-50% improvement on their score;
Slightly improved: 10-30% improvement on their score;
No improvement: <10% improvement on their score

TABLE 3. Comparison of sleep quality, daily activity, and mood using Brief Pain Inventory (BPI)

	Vitamin D 5000 IU + Standard Treatment (n=34)	Standard Treatment (n=34)	Total (n=68)	*p*-value
Sleep Quality (0-100)				
Week 4	7.94 ± 17.88	17.64 ± 24.37	12.79 ± 21.77	0.109
Week 8	5.58 ± 15.80	12.35 ± 21.18	8.97 ± 18.85	0.091
Week 4 - 8	-2.35 ± 14.78	-5.29 ± 17.44	-3.82 ± 16.11	0.504
p^b Value	0.168	0.084		
Daily Activity (0-100)				
Week 4	1.76 ± 7.16	13.82 ± 22.96	7.79 ± 17.94	0.003*
Week 8	2.35 ± 7.80	8.82 ± 16.47	5.58 ± 13.20	0.022*
Week 4 - 8	-0.59 ± 3.42	-5.00 ± 15.81	-2.20 ± 11.69	0.112
p^b Value	0.317	0.055		
Mood (0-100)				
Week 4	5.00 ± 12.85	16.17 ± 23.61	10.58 ± 19.69	0.013*
Week 8	3.82 ± 9.85	12.05 ± 19.96	7.94 ± 16.16	0.095
Week 4 - 8	-1.17 ± 9.77	-4.11 ± 18.76	-2.65 ± 14.92	0.311
p^b Value	0.470	0.155		

Data are presented as mean ± standard deviation (SD)
Comparison between experimental and control groups: p^a
Comparisons within groups under the same conditions: p^b
** the p-value is statistically significant*

results indicate that there was no significant decrease in scores from week 4 to week 8 in both groups concerning sleep quality (-5.29 ± 17.44 vs. -2.35 ± 14.78), daily activity (-5.00 ± 15.81 vs. -0.59 ± 3.42), and mood (-4.11 ± 18.76 vs. -1.17 ± 9.77). However, significant score differences were observed between the groups at both week 4 (p=0.003) and week 8 (p=0.022). Furthermore, significant differences were found in mood scores between the two groups at week 4 (p=0.013). There was no significant difference observed in sleep quality. Ultimately, it's noteworthy that the experimental group achieved the lower BPI score.

DISCUSSION

Low levels of vitamin D are considered one of the risk factors for diabetic neuropathy, and several pre-

vious studies have shown that supplementing with vitamin D can alleviate symptoms in diabetic neuropathy patients. Biologically, vitamin D plays a role in the nervous system by facilitating enzyme synthesis used in neurotransmitter production and brain detoxification. Therefore, it acts as a potent inducer of neurotropin and neurotransmitter functions [4]. Vitamin D deficiency occurs when the serum level of 25(OH) D is less than 20 ng/mL, and to fully harness its medical benefits, a serum level of more than 30 ng/mL is recommended [5]. At the start of the study, both groups had vitamin D levels below 20 ng/mL. After the intervention, the experimental group achieved vitamin D levels above 30 ng/mL, optimizing the potential medical benefits of vitamin D, while the control group remained deficient.

The administration of vitamin D was found to improve pain symptoms in diabetic neuropathy patients, supported by a 2022 study conducted by Pinzon. The severity of pain was assessed using the Visual Analog Scale (VAS), ranging from 0 to 10. Before the intervention, the mean VAS scores in the experimental and control groups were 5.82 ± 2.037 and 5.69 ± 2.27, respectively. After supplementation, the experimental group exhibited a significantly greater reduction in VAS scores compared to the control group (-3.84 ± 1.93 vs. -2.10 ± 2.39, p=0.010). In conclusion, vitamin D supplementation led to a more pronounced reduction in pain intensity compared to symptomatic therapy alone.

A 2017 study by Akyuz investigated the effects of vitamin D supplementation on pain, quality of life (QoL), and nerve conduction studies in women with chronic pain and vitamin D deficiency. Pain scores significantly decreased after 8 weeks of supplementation (P = 0.000), and QoL improved significantly (P=0.001). Vitamin D supplementation not only reduced pain severity but also improved overall QoL and various health-related domains. Changes in pain severity were correlated with improvements in QoL and overall well-being [6].

Vitamin D supplementation in chronic pain patients not only reduces pain but also offers benefits such as improved sleep, mood, and physical activity [6]. In 2012, Huang administered vitamin D supplementation to subjects with chronic pain and measured their pain levels, sleep quality, physical activity, mental health, emotional well-being, and social functioning. The results revealed a significant reduction in pain, improvements in sleep quality, and enhancements in various aspects of QoL (physical activity, body pain, general health, vitality, social activity, mental health, physical and emotional well-being), except for emotional functioning. These improvements across multiple domains support the notion that vitamin D supplementation is associated with a reduction in pain symptoms [7].

This study found that administering 5000 IU of vitamin D supplementation alongside standard therapy resulted in increased scores and improved mood, as evidenced by the BPI and SGA instruments. However, other aspects of quality of life did not show significant improvement. It's important to note that this study had an open-label design, which may have influenced the results. Additionally, the potential adjustment of vitamin D doses was not analyzed and compared beforehand. Future double-blind studies comparing various doses and adjusting vitamin D supplements are needed to determine the optimal therapeutic approach.

CONCLUSIONS

Supplementing standard therapy with an additional 5000 IU of vitamin D did not yield superior improvements in the quality of life for diabetic neuropathy patients when compared to standard therapy alone.

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