FAKULTAS FARMASI
UNIVERSITAS MUHAMMADIYAH PURWOKERTO

PHARMACY: Jurnal Farmasi Indonesia
(Pharmaceutical Journal of Indonesia)

Journal homepage: https://jurnalnasional.ump.ac.id/index.php/PHARMACY

Received 27-03-2023 Accepted 21-12-2023 Available online 07-08-2024

Efficacy of Additional Vitamin D 1000 IU on Diabetic Neuropathy Peripheral for Sleep Quality, Moods, and Daily Activity

Tillandsia Filli Folia Primastuti[1], Rizaldy Taslim Pinzon*[1,2], Sugianto Adisaputro[1,2]
[1]Duta Wacana Christian University School of Medicine, Yogyakarta 55224, Yogyakarta, Indonesia
[2]Department of Neurology, Bethesda Hospital, Yogyakarta 55224, Yogyakarta, Indonesia

Keywords:
Brief pain inventory (BPI), diabetic neuropathy, vitamin D 1000 IU

A B S T R A C T

Diabetic neuropathy is one of the most common long-term microvascular complications in diabetes mellitus, in which diabetic neuropathic pain is the most frequent symptom. Diabetic neuropathic pain mostly gets worse at night leading to sleep disturbances. Prolonged pain that does not improve can be stressful and decrease quality of life, symptomatic therapy has not been able to reduce the pain completely. This study aims to investigate the efficacy of additional therapy with 1000 IU of vitamin D on sleep quality, mood, and daily activity in patients with diabetic neuropathy. This study was a randomized controlled trial comparing the experimental group which was given symptomatic therapy and 1000 IU of vitamin D supplementary therapy and the control group which was only given symptomatic therapy, both of them were given 3 months of therapy and the pain impact was checked with the Brief Pain Inventory (BPI). Sampling was conducted in February 2021 using consecutive sampling through a computerized block randomization technique. Data analysis was conducted univariately, and bivariate used Mann-Whitney. Based on the Mann-Whitney test, it was found that the administration of 1000 IU of vitamin D to the experimental group showed a significantly superior improvement in sleep quality (p = 0.004), mood (p = 0.002), and daily activities (p =0.003) in the experimental group compared to the control group after 3 months intervention. Additional therapy of 1000 IU of vitamin D improves sleep quality, mood, and daily activity abilities in patients with diabetic neuropathic pain.

1. Introduction

The global population of people with diabetes mellitus in 2030 is estimated to reach 366 million, double compared to 2000 (Khdour, 2020). Diabetic neuropathy is the most common microvascular complication, with approaching 50% of people with diabetes mellitus developing diabetic neuropathy. Diabetic neuropathy pain is characterized by burning, tingling, paresthesia, being stabbed, or an unusual sensation (Heidari et al., 2019). Generally, patients with diabetic neuropathy pain are limited in daily activity function, ability to sleep, anxiety as well depression might interfere with productivity (Alleman et al., 2015). So far, glucose index controlled and lifestyle management alone have not been able to overcome diabetic neuropathy pain on prediabetic mellitus or diabetic mellitus unless pharmacotherapy intervention such as tricyclic antidepressant agent (TCA), serotonin-norepinephrine reuptake inhibitor (SNRI) or gamma-aminobutyric acid analog (GABA) although only partially effective because unable to affect the underlying pathology of diabetic neuropathy (Heidari et al., 2019; Power, 2020).

Vitamin D deficiency, 25-hydroxyvitamin D level <20 ng/ml often occurs in diabetes mellitus patients and is related to the severity of sensory neuropathy, it can be argued that low vitamin D levels are a risk factor independent of the development of peripheral diabetic neuropathy (Ghadiri-Anari et al., 2019; Issa, 2017). Vitamin D is a potent inducer of neurotrophins and neurotransmitters. The addition of vitamin D has the potential to increase nerve growth factor, one of the proteins for the development and maintenance of neurons in the peripheral nervous system (Shehab et al., 2015). Vitamin D has been associated with neurotrophin regulation and Ca2+ homeostasis in neurons, both can protect neurons. Experimental studies in diabetic rats with nerve growth factor deficiency showed vitamin D increased nerve growth factor production and prevented neurotrophic deficits (Soderstrom et al., 2012). Previous studies by Shebab, et al (2015) show that 50,000 IU of vitamin D which is given orally once a week for 8 weeks able to correct vitamin D deficiency leading to improvement in symptoms of neuropathy pain, especially in neuropathic pain sensations, burning or hyperesthesia (Shehab et al., 2015) and vitamin D3 (cholecalciferol) 2000 IU daily for 3 months showing decreased in pain score as measured by the Visual Analogue Scale (VAS) as much as 50% (Alam et al., 2017).

Based on the above researchers will conduct research on the effect of chitosan bone powder squid against total cholesterol levels of rats (Rattus norvegicus). This research was conducted based on previous research which proved that squid bones contain chitosan, where chitosan can be used as an anticholesterolemic.

2. Materials and Method

This study was conducted using the randomized controlled trial method by dividing the two groups into an experimental group given standard symptomatic therapy addition of vitamin D (cholecalciferol) 1000 IU (25mcg) tablet once a day for 3 months and a control group given standard symptomatic therapy in the form of gabapentin 100 mg once daily, pregabalin 75 mg once daily and amitriptyline 10 mg once

Received 27-03-2023; Received in revised form 27 Maret 2022;
Accepted 21-12-2023; Available online 07-08-2024
E-mail address: drpinzon17@gmail.com

daily. The data obtained were secondary data from randomized clinical trials.

The inclusion criteria in this study were men and women who were willing to be a respondent, aged >18 years old and suffering from type 2 diabetes mellitus, which has been diagnosed with neuropathy who have been diagnosed with diabetic neuropathy pain with Diabetic Neuropathy Symptoms (DNS) and Diabetic Neuropathy Examination (DNE) at the neurology polyclinic of Bethesda Yogyakarta Hospital. Meanwhile, the exclusion criteria are patients who have hypersensitivity to vitamin D 1000 IU, are pregnant and breastfeeding, have severe renal and hepatic dysfunction, have a probability of loss of follow-up because they lived out of town, and were currently taking part in other clinical trials.

Sampling was conducted using a computerized block randomization technique and obtained a total research sample of 50 subjects in each group of 25 subjects. Data analysis of the research uses statistical analysis including univariate and bivariate analysis. The bivariate analysis used Mann-Whitney because the normality test with Shapiro-Wilk showed abnormal data distribution so it used a non-parametric test. This study has obtained ethical clearance from the Ethics Committee for Health Research of Bethesda Hospital Yogyakarta in letter number 17/KEPK-RSB/II/21.

3. Result and Discussion

As many as 50 subjects fill in the inclusion and exclusion criteria, and each group contains 25 subjects. Base sample characteristics including age, gender, comorbid, and comedication were not significantly associated between the control group and experimental group (p>0,05) (**Table 1**).

The bivariate analysis (**Table 2**) found sleep quality (p=0.004), mood (p=0.002), and daily activities (p=0.003) had significant differences between the control group and the experimental group after 3 months of intervention (p<0.05). Brief Pain Inventory (BPI) tests are only carried out after intervention for 3 months in each group. The average Brief Pain Inventory (BPI) of each variable can be seen in **Table 2.** A score of 0 indicates worse pain impact and 100 indicates excellent pain impact.

Serum 25-hydroxyvitamin D (25-OH-D) as the main form of vitamin D circulating in the body is a steroid hormone, the addition of vitamin D can potentiate nerve growth factor (NGF) which is a protein for the development and maintenance of neurons, especially in the peripheral nervous system. In animal studies, it was also found that vitamin D was able to potentiate the repair of neurotrophic deficits and there were reports that vitamin D was effective for inducing nerve growth factor (NGF) in human cells, wherein the skin epidermal keratinocytes are the main source of nerve growth factor (NGF) (Esteghamati et al., 2016; Shehab et al., 2015).

Sleep disturbance is one of the common symptoms of type 2 diabetes mellitus (Meng et al., 2016). Patients with type 2 diabetes mellitus with peripheral neuropathy have a higher risk of experiencing sleep disorders, especially obstructive sleep apnea (OSA), decreased sleep efficiency, and sleep fragmentation, and often experience nocturnal hypoxia which can interfere with the patient's activities which causes daytime sleepiness, decreased productivity, impaired cognition, mood disorders, increased insulin resistance and poor glycemic control (Bahnasy et al., 2018).

In this study, there was a significant difference in terms of sleep quality between the control group and the experimental group after the intervention was given which was in line with research by Majid, et al (2018) which proved that vitamin D supplementation could improve sleep quality, reduce sleep latency, increase sleep duration and improve sleep quality subjectively in people aged 20-50 years with sleep disturbances (Majid et al., 2018). It was also recently discovered that vitamin D plays an important role in the regulation of serotonin and melatonin which suggests a link between vitamin D and mental health, especially in the regulation of mood and sleep (Huiberts and Smolders, 2021).

Decreased function in daily life can occur in patients with diabetes mellitus, especially with complications such as diabetic neuropathy which can cause a decreased sensation, and weakness, especially in the feet and hands with or without diabetic neuropathy pain in patients who experience diabetic neuropathy pain can also experience difficulty sleeping, the impaired balance of walking and interference at work (Brod et al., 2015; Win et al., 2019).

This study showed that there were significant differences in terms of the ability to carry out daily activities between the control group and the experimental group after 3 months of intervention, in contrast to research belonging to Alam, et al (2017) which showed that vitamin D was only able to improve emotional distress but there was no improvement in symptoms of pain and paresthesia, loss of touch and temperature sensation, imbalance, limitations of daily activities and interpersonal problems(Alam et al., 2017). This difference is possible due to the difference in the dose of vitamin D given where a study belonging to Alam, et al (2017) used a single dose of vitamin D 600,000 IU intramuscularly while this study used vitamin D 1000 IU orally which was given once a day for 3 months.

The presence of uncontrolled blood sugar is associated with higher anxiety and generalized anxiety disorder (GAD) in people with diabetes mellitus. Tumor necrosis factor-α (TNF-α) and C-reactive protein (CRP) are increased in anxiety conditions due to inflammation from the psychoneuroimmunological pathway. Previous research has determined that rates of depression and/or anxiety are high in patients with diabetes mellitus and higher if they have diabetic neuropathy pain (Naranjo et al., 2020).

In this study, it was found that there were significant differences in terms of mood between the control group and the experimental group after intervention provision, supported by research belonging to Fazelian, et al (2019) which showed that vitamin D can increase anti-inflammatory biomarkers, reduce cardiovascular risk factors and reduce anxiety in women with type 2 diabetes mellitus with vitamin D deficiency (Siavash Fazelian, Reza Amani, Zamzam Paknahad, Soleiman Kheiri, 2019). Vitamin D as a neurohormone plays a role in maintaining calcium homeostasis and bone health for the growth and development of neuron cells, nerve function, synthesis, release, and regulation of neurotransmitters, and affects mood (Kaviani et al., 2020).

Table 1. Baseline characteristics

Sample characteristic	Experimental group (n=25)	%	Control group (n=25)	%	p-value
Aged	64,04±9,449		59,56 ± 6,272		0,540
Gender					
Male	15	60	15	60	1,000
Female	10	40	10	40	
Comorbid: Hypertension					
Yes	12	48	13	52	1,000
No	13	52	12	48	
Comorbid: Cardiovascular disease					
Yes	16	64	17	68	1,000
No	9	36	8	32	
Comedication: Anti-hypertension					
Yes	11	44	13	52	0,777
No	14	46	12	48	
Comedication: Anti-platelet					
Yes	23	92	22	88	1,000
No	2	8	3	12	
Comedication: Statin					
Yes	8	32	11	44	0,560
No	17	68	14	56	

Experimental group received symptomatic therapy + Vit D 1000 IU, control group received symptomatic therapy

Table 2. A score of 0 indicates worse pain impact and 100 indicates excellent pain impact

Variable	Experimental group	Control group	p-value
Sleep quality after intervention	57,60 ± 10,116	64,80 ± 10,456	0,004
Mood after intervention	53,20 ± 11,446	62,00 ± 11,180	0,002
Daily activities after intervention	54,40 ± 10,440	62,40 ± 8,307	0,003

Experimental group received symptomatic therapy + Vit D 1000 IU, control group received symptomatic therapy

The limitations of this study were not measuring the Brief Pain Inventory (BPI) prior to therapy to be precise at week 0 so that the differences between each group could not be seen, and in the data collection process, the duration of the subject suffering from diabetes mellitus and the diabetes therapy used was not taken so that the basic characteristics of the subject were incomplete.

4. Conclusion

Administration of additional vitamin D 1000 IU therapy to standard symptomatic therapy in diabetic neuropathy patients can reduce the impact of diabetic neuropathy pain in the form of improving sleep quality, mood, and ability to daily activities. Suggestions for clinicians, namely giving additional vitamin D therapy can be used consideration as adjuvant therapy in reducing the impact of pain in diabetic neuropathy pain patients. Meanwhile, future researchers are expected to be able to include data regarding the duration of the patient suffering from diabetes mellitus and the type of anti-diabetic therapy used as well as measuring daily activity level, sleep quality, and mood before giving therapy so that it can be used as a comparison in pain impact assessment of both groups.

Acknowledge

The author declares no conflict of interest for this paper.

5. References

Alam U, Fawwad A, Shaheen F, Tahir B, Basit A, Malik RA, 2017. Improvement in neuropathy-specific quality of life in patients with diabetes after vitamin D supplementation. *Journal of Diabetes Research*, 2017, 7928083.

Alleman CJM, Westerhout KY, Hensen M, Chambers C, Stoker M, Long S, van Nooten FE, 2015. Humanistic and economic burden of painful diabetic peripheral neuropathy in Europe: A review of the literature. *Diabetes Research and Clinical Practice*, 109(2), 215-225.

Bahnasy WS, El-Heneedy YAE, El-Seidy EAS, Labib NAA, Ibrahim ISE, 2018. Sleep disturbances in diabetic peripheral neuropathy patients: A clinical and polysomnographic study. *Egyptian Journal of Neurology, Psychiatry and Neurosurgery,* 54(1), 23.

Brod M, Pohlman B, Blum SI, Ramasamy A, Carson R. 2015. The burden of illness of diabetic peripheral neuropathic pain: A qualitative study. *Patient* 8, 339–348.

Esteghamati A, Fotouhi A, Faghihi-Kashani S, Hafezi-Nejad N, Heidari B, Sheikhbahaei S, Zandieh A, Nakhjavani M. 2016. Non-linear contribution of serum vitamin D to symptomatic diabetic neuropathy: A case-control study. *Diabetes Research and Clinical Practice*, 111, 44–50.

Fazelian S, Amani R, Paknahad Z, Kheiri SLK. 2019. Effect of vitamin D supplement on mood status and inflammation in vitamin D deficient type 2 diabetic women with anxiety: A randomized clinical trial. *International Journal of Preventive Medicine*, 10, 1–9.

Ghadiri-Anari A, Mozafari Z, Gholami S, Khodaei SA, Aboutorabi-zarchi M, Sepehri F, Nadjarzade A, Rahmanian M, Namiranian N. 2019. Dose vitamin D supplementations improve peripheral diabetic neuropathy? A before-after clinical trial. *Diabetes and Metabolic Syndrome: Clinical Research and Reviews,* 13, 890–893.

Heidari N, Sajed, F, Mohammadi Y, Mirjalili M, Mehrpooya M. 2019. Ameliorative effects of n-acetylcysteine as adjunct therapy on symptoms of painful diabetic neuropathy. *Journal of Pain Research*, 12, 3147–3159.

Huiberts LM, Smolders KCHJ.,2021. Effects of vitamin D on mood and sleep in the healthy population: Interpretations from the serotonergic pathway. *Sleep Medicine Reviews*, 55, 101379.

Issa CM. 2017. Vitamin D and type 2 diabetes mellitus. *Advances in Experimental Medicine and Biology*, 996, 193–205.

Kaviani M, Nikooyeh B, Zand H, Yaghmaei P, Neyestani TR. 2020. Effects of vitamin D supplementation on depression and some involved neurotransmitters. *Journal of Affective Disorders*, 269, 28–35.

Khdour MR. 2020. Treatment of diabetic peripheral neuropathy: A review. *Journal of Pharmacy and Pharmacology*, 72(7), 863-872.

Majid MS, Ahmad HS, Bizhan H, Hosein HZM, Mohammad A. 2018. The effect of vitamin D supplement on the score and quality of sleep in 20–50-year-old people with sleep disorders compared with control group. *Nutritional Neuroscience*, 21, 511–519.

Meng LL, Liu Y, Geng RN, Tang YZ, Li DQ. 2016. Association of diabetic vascular complications with poor sleep complaints. *Diabetology & Metabolic Syndrome*, 8, 1–7.

Naranjo C, Ortega-Jiménez P, del Reguero L, Moratalla G, Failde I. 2020. Relationship between diabetic neuropathic pain and comorbidity. Their impact on pain intensity, diabetes complications and quality of life in patients with type-2 diabetes mellitus. *Diabetes Research and Clinical Practice*, 165, 108236.

Power D. 2020. Standards of medical care in diabetes: Response to position statement of the American Diabetes Association, *Diabetes Care*, 29(2), 476.

Shehab D, Al-Jarallah K, Abdella N, Mojiminiyi OA, Al Mohamedy H.,2015. Prospective evaluation of the effect of short-term oral vitamin D supplementation on peripheral neuropathy in type 2 diabetes mellitus. *Medical Principles and Practice*, 24, 250–256.

Soderstrom LH, Johnson SP, Diaz VA, Mainous AG. 2012. Association between vitamin D and diabetic neuropathy in a nationally representative sample: Results from 2001-2004 NHANES. *Diabetic Medicine* 29, 50–55.

Win MMTM, Fukai K, Nyunt HH, Hyodo Y, Linn KZ. 2019. Prevalence of peripheral neuropathy and its impact on activities of daily living in people with type 2 diabetes mellitus. *Nursing and Health Sciences*, 21, 445–453.