

## Effectiveness of Vitamin D and Vitamin B Supplementation Therapy in Diabetic Neuropathic Pain Standard Therapy

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### Abstract

The chronic complication from diabetes mellitus (DM) is painful diabetic neuropathy, and the treatment with standard therapy is inefficient. Furthermore, vitamin B combination is effective as a neuropathy treatment due to nerve repair acceleration by enhancing regeneration and restoring function, while individuals with type 2 DM are inseparable from vitamin D deficiency. This study aimed to measure diabetic neuropathy pain reduction in patients with type 2 DM by administration of additional vitamin D to standard therapy. This was a quasi-experimental study employing non-equivalent control group method on 77 patients selected using consecutive sampling at Bethesda Hospital Yogyakarta between December 2019 and February 2020. In addition, the subjects consisted of 48 men and 29 women, and were divided into 4 therapy groups executed within 1–3 months comprising (I) symptomatic therapy only; (II) symptomatic combination therapy with vitamin B; (III) symptomatic combination therapy with vitamin D; and (IV) symptomatic combination therapy with vitamin B-vitamin D. The pain assessment employed Visual Analogue Scale (VAS) prior and after administration, and demographic characteristics data between the 4 groups lacked noteworthy differences. The results indicated decreased pain intensity after therapy with the mean VAS in group I from  $53.36 \pm 14.65$  to  $42.27 \pm 17.16$ , group II from  $50.56 \pm 12.11$  to  $13.89 \pm 14.61$ , group III from  $50.77 \pm 15.98$  to  $19.23 \pm 18.09$ , and group IV from  $54.55 \pm 16.35$  to  $7.27 \pm 6.47$ . However, group administered with symptomatic combination therapy with vitamin D revealed higher significant improvement, while substantial pain intensity reduction was indicated from symptomatic therapy combined with vitamin B and vitamin D.

**Keywords:** Combination of vitamin D, pain intensity, painful diabetic neuropathy

## Efektivitas Pemberian Terapi Tambahan Vitamin D dan Vitamin B pada Terapi Standar Nyeri Neuropati Diabetik

### Abstrak

Neuropati diabetik merupakan salah satu komplikasi kronis yang sering terjadi dari penyakit diabetes melitus (DM). Pengobatan neuropati diabetik dengan terapi simptomatik hingga sekarang belum mencapai target. Vitamin B kombinasi efektif sebagai pengobatan neuropati karena mempercepat perbaikan saraf dengan meningkatkan regenerasi saraf dan memulihkan fungsi saraf. Pasien DM tipe 2 tak lepas dari keadaan defisiensi vitamin D. Penelitian ini bertujuan untuk mengukur penurunan nyeri neuropati diabetik pada pasien DM tipe 2 yang diberi terapi tambahan vitamin D terhadap terapi standar. Penelitian ini merupakan penelitian *quasi-experimental* dengan metode *non equivalent control group* kepada 77 pasien yang terpilih berdasarkan *consecutive sampling* di Rumah Sakit Bethesda Yogyakarta pada bulan Desember 2019–Februari 2020. Subjek dibagi menjadi 4 kelompok pemberian terapi yaitu kelompok yang diberi (1) terapi simptomatik saja, (2) terapi simptomatik kombinasi vitamin B, (3) terapi simptomatik kombinasi vitamin D, dan (4) terapi simptomatik kombinasi vitamin B-vitamin D. Pemberian terapi dilakukan dalam waktu 1–3 bulan. Penilaian nyeri menggunakan *Visual Analogue Scale* (VAS) sebelum diberikan terapi dan setelah pemberian terapi. Subjek terdiri dari 48 orang laki-laki dan 29 orang perempuan. Data karakteristik demografi di antara 4 kelompok tidak memiliki perbedaan yang bermakna. Hasil penelitian menunjukkan adanya penurunan intensitas nyeri dengan rata-rata VAS kelompok I sebelum terapi  $53,36 \pm 14,65$  menjadi  $42,27 \pm 17,16$  setelah terapi, kelompok II dari  $50,56 \pm 12,11$  menjadi  $13,89 \pm 14,61$ , kelompok III dari  $50,77 \pm 15,98$  menjadi  $19,23 \pm 18,09$ , dan kelompok IV dari  $54,55 \pm 16,35$  menjadi  $7,27 \pm 6,47$ . Kelompok dengan terapi tambahan vitamin D menunjukkan perbaikan nyeri yang lebih signifikan. Penurunan intensitas nyeri neuropati diabetik secara signifikan ditemukan pada pemberian terapi simptomatik yang dikombinasikan dengan vitamin B dan vitamin D.

**Kata kunci:** Intensitas nyeri, kombinasi vitamin D, nyeri neuropati diabetik

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## Introduction

Indonesia ranks for the sixth for the number of diabetic mellitus (DM) patients in the world with a total of 10.3 million people in 2017.<sup>1</sup> Complications that often arise in patients with DM is diabetic neuropathy (DN) or diabetic neuropathy.<sup>2</sup> It is estimated that around 25–30% of patients with DM experience painful diabetic neuropathy (PDN).<sup>2</sup> About 80% of DM patients with PDN complain of severe pain.<sup>2</sup>

Vitamin B are commonly added as a treatment for neuropathy. Vitamin B combination is effective as a neuropathy treatment because it accelerates nerve repair by increasing nerve regeneration and restoring nerve function.<sup>3</sup> Vitamin B combination is effective as a neuropathy treatment because it accelerates nerve repair by increasing nerve regeneration and restoring nerve function.<sup>4,5</sup>

DM is associated with a state of vitamin D deficiency.<sup>6</sup> Study by Indra et al. explains that 49% or almost half of diabetes mellitus patients have vitamin D deficiency.<sup>7</sup> Vitamin D deficiency can cause a deficiency of neurotropic factors, which can cause neurological damage or dysfunction that triggers neuropathy.<sup>8</sup> Antiepileptic drugs that block calcium channels, SNRIs, and tricyclic antidepressants as first line drugs in treatment of neuropathic pain.<sup>9</sup> First-line treatment for diabetic neuropathy pain has limited benefits and low level of effectiveness.<sup>9</sup> There is no satisfactory treatment in a number of guidelines.<sup>10</sup> Only a few symptomatic treatments for neuropathic pain have been proven effective.<sup>10</sup>

Vitamin D is an essential neurosteroid that plays a major role in the physiology of the central and peripheral nervous system.<sup>11,12</sup> Vitamin D supplementation can help reduce pain intensity.<sup>13</sup> Vitamin D has neurotropic effects, anti-inflammatory effects and immunoregulatory effects that play a role in pain management.<sup>14,15</sup>

The nervous system in patients with diabetes mellitus undergo a pro-inflammatory process which will cause neuropathy symptoms.<sup>16,17</sup> The anti-inflammatory effect of vitamin D can suppress the release of pro-inflammatory cytokines and T cell responses.<sup>15</sup> Vitamin D can reduce nerve threshold by inhibiting COX-2 expression and stimulating 15-prostaglandin dehydrogenase (15-PGDH) which will reduce prostaglandin.<sup>18</sup> It is hoped that further research can make a combination of effective treatments for diabetic neuropathy pain and this study adding vitamin D as a treatment for diabetic neuropathic pain.<sup>9,10,19</sup>

## Methods

This research is a quasi experimental research with non equivalent control group method and used prospective data taken from the patient's medical records. Subjects examined were patients with DM especially type 2 with DN pain at Bethesda Hospital Yogyakarta from December 2019 until February 2020. Subjects numbered 77 people which were divided into 4 groups and each was given therapy namely (1) symptomatic therapy (Gabapentin 100–300 mg or amitriptylin 10–25 mg or pregabalin 50–75 mg or combination) group, (2) symptomatic combination therapy with vitamin B, (3) symptomatic combination therapy with vitamin D, and (4) symptomatic combination therapy with vitamin B-vitamin D. Additional vitamin D therapy is given at a dose of 400 IU taken two times daily for groups 3 and 4. The vitamin B is vitamin B combination of 100 mg B1, 100 mg B6, and 5000 mcg B12 taken once daily for groups 2 and 4. Provision of therapy is carried out for 1–3 months. Each group was assessed for pain scale before and after administering therapy using Visual Analogue Scales (VAS). Data obtained from research subjects were analyzed using Kruskal-Wallis analysis and displayed in tabular form.

**Table 1 Comparison of Basic Characteristics between the Four Treatment Groups**

Characteristics	n(%)				p
	Group I	Group II	Group III	Group IV	
<b>Age (Mean±SD)</b>	61.73±9.95	58.61±9.03	61.58±8.60	68.55±10.57	0.767
<b>Gender</b>					0.524
Male	10(45.5)	11(61.1)	21(80.8)	6(54.5)	
Female	12(54.5)	7(38.9)	5(19.2)	5(45.5)	
<b>Comorbid</b>					0.84
<b>Hypertension</b>					
Yes	11(50)	9(50)	19(73.1)	4(35.4)	
No	11(50)	9(50)	7(26.9)	7(63.6)	
<b>Cardiovascular Disease</b>					0.143
Yes	12(54.5)	16(88.9)	17(65.4)	9(81.8)	
No	10(45.5)	2(11.1)	9(34.6)	2(18.2)	
<b>Commedication</b>					
<b>Anti Hypertensive Agent</b>					0.143
Yes	11(50)	8(44.4)	18(69.2)	4(36.4)	
No	11(50)	10(55.6)	8(30.8)	7(63.6)	
<b>Anti Platelet Agent</b>					0.475
Yes	16(72.7)	16(88.9)	24(92.3)	8(72.7)	
No	6(27.3)	2(11.1)	2(7.7)	3(27.3)	
<b>Statin</b>					0.113
Yes	7(31.8)	7(38.9)	8(30.8)	0 (0)	
No	15(68.2)	11(61.1)	18(69.2)	11(100)	

This research was registered at National Institute of Health Research and Development and obtained ethical clearance from the Faculty of Medicine Duta Wacana Christian University, Yogyakarta, Indonesia as the institutional ethics clearance committee (ethical approval no. 1125/C.16/FK/2019).

## Results

In this study, the data were obtained from 77 subjects. The data of this study were divided into 4 treatment groups, (1) symptomatic therapy only, (2) symptomatic combination therapy with vitamin B, (3) symptomatic combination therapy with vitamin D, and

(4) symptomatic combination therapy with vitamin B-vitamin D. As shown in Table 1, the age of the subjects of this study were in group I 61.73±9.95, group II 58.61±9.03, group III 61.58±8.60, and group IV 68.55±10.57. The characteristics of the subjects in this study did not have a significant relationship to the decrease in pain severity ( $p>0.05$ ) (Table 1). The results of the average Diabetic Neuropathy Examination (DNE) and Diabetic Neuropathy Symptoms (DNS) assessments with comparable Diabetic Neuropathy Examination (DNE) and Diabetic Neuropathy Symptoms (DNS) results between subjects in each group (Table 2).

As shown in Table 3, assessment of pain

**Table 2 Comparison of Diabetic Neuropathy Examination (DNE) and Diabetic Neuropathy Symptoms (DNS) Values between the 4 Groups**

	Mean±SD				p
	Group I	Group II	Group III	Group IV	
DNE	2.73±0.985	2.78±1.00	2.92±1.13	2.73±1.01	0.967
DNS	2.27±0.63	2.33±0.84	2.31±0.68	3.45±2.25	0.973

**Table 3 Comparison of Decrease Pain Scale between 4 Groups**

Visual Analogue Scales Score	$\Delta\text{Mean} \pm \Delta\text{SD}$				p
	Group I	Group II	Group III	Group IV	
Before therapy	56.36 $\pm$ 14.65	50.56 $\pm$ 12.11	50.77 $\pm$ 15.98	54.55 $\pm$ 16.35	0.458
After therapy	42.27 $\pm$ 17.16	13.89 $\pm$ 14.61	19.23 $\pm$ 18.09	7.27 $\pm$ 6.47	0.000
Difference before and after	14.09 $\pm$ 5.90	36.67 $\pm$ 7.67	31.54 $\pm$ 15.92	42.27 $\pm$ 16.18	0.000

**Table 4 Description of Categorical Pain Levels**

Pain Improvement	n(%)				p
	Group I	Group II	Group III	Group IV	
Pain is greatly reduced (>50%)	0(0)	7(38.9)	7(26.9)	8(72.7)	0.000
Pain is reduced (30%–50%)	4(18.2)	9(50)	13(50)	2(18.2)	
Pain is slightly (10%–30%)	17(77.3)	2(11.1)	6(23.1)	1(9.1)	
Pain does not decrease	1(4.5)	0(0)	0(0)	0(0)	
Pain worsens	0(0)	0(0)	0(0)	0(0)	

intensity prior to the administration of therapy for group I obtained a mean of 56.36 $\pm$ 14.65, group II 50.56 $\pm$ 12.11, group III 50.77 $\pm$ 15.98 and group IV 54.55 $\pm$ 16.35 ( $p=0.458$ ). After administering the therapy, it was found that the mean decrease in group I was 42.27 $\pm$ 17.16, group II 13.89 $\pm$ 14.61, group III 19.23 $\pm$ 18.09, and group IV 7.27 $\pm$ 6.47 ( $p=0.000$ ). The difference in average pain scale of the 4 groups that experienced the greatest reduction in group IV was 42.27 $\pm$ 16.18 ( $p=0.000$ ).

Pain scale assessment also uses categories.

As shown in Table 4, the category of pain that decreased >50% was most experienced in group IV (group with additional therapy of vitamin D and vitamin B) was 72.7% ( $p=0.000$ ). Comparison of pain assessment in Table 5 with reduced pain >30% was most experienced by the group receiving additional therapy as much as 83.6% ( $p=0.000$ ). The comparison of pain relief in Table 6 with reduced pain > 30% was more experienced by the group with additional therapy of vitamin D and vitamin B ( $p=0.312$ ).

**Table 5 Comparison of Pain Reduction between Groups that Receive Additional Therapy and Without Additional Therapy**

Category	Group Symptomatic		Group Symptomatic+ Add On		p
	n=22	%	n=55	%	
Pain reduced <30%	18	81.8	9	16.4	0.000
Pain reduced > 30%	16	88.9	20	76.9	

**Table 6 Comparison of Pain Reduction between Groups Getting Vitamin D Supplementary Therapy and Vitamin B Supplementary Therapy**

Category	Group Symptomatic + Vitamin D		Group Symptomatic + Vitamin B		p
	n=22	%	n=55	%	
Pain reduced <30%	2	11.1	6	23.1	0.312
Pain reduced > 30%	16	88.9	20	76.9	

## Discussion

This study aims to measure the reduction in DN pain in patients with type 2 DM who are given additional vitamin D therapy to standard therapy. After administration of therapy, the smallest average pain scale value obtained by group IV was  $7.27 \pm 6.47$ . The greatest decrease in pain scale was also experienced by group IV was  $42.27 \pm 16.18$ . Based on the assessment of the pain scale categories, pain reduction  $>50\%$  is most experienced by group IV as much as 72.7%. Comparison of pain reduction with a limit of 30% shows that pain reduction  $>30\%$  occurred in the group given symptomatic and additional therapy. The overall results of the smallest mean pain scale after administration of therapy the largest significant reduction in pain scale, the reduction in pain categorically more than 50% significantly obtained by group IV or combination therapy group vitamin B and vitamin D. With a limit of 30%, the group given additional therapy experienced greater pain reduction.

Ghadiri et al. concluded that hypovitaminosis D being one of the factors can improve the symptoms and signs of peripheral neuropathy and recommend the provision of vitamin D therapy in patients with type 2 DM with low vitamin D levels.<sup>20</sup> There are several possible mechanisms of vitamin D participating in the development of diabetic neuropathy.<sup>14</sup> Vitamin D has neurotrophic effects that play a role in nerve function and nerve growth factor (NGF).<sup>14</sup> Vitamin D may also improve the nociceptors by increasing the pain threshold value where there is a contribution from the effects of anti-inflammatory and immunoregulatory effects.<sup>14</sup>

In the inflammatory process, vitamin D will play a role by increasing the regulation of TGF- $\beta$ 1 in astrocytes and microglia thereby suppressing cytokine activity.<sup>18</sup> Other study also showed that vitamin D can reduce levels of inflammatory cytokines such as Prostaglandin

E2 (PGE2), TNF  $\alpha$  and Leukotriene B4 (LTB4).<sup>15</sup>

Vitamin D plays a role in the pathogenesis of inflammation, which has a correlation with inflammatory cytokines (IL-13 and IL-17) in the body that influence the development of the emergence of painful DM.<sup>16,17</sup> The appearance of inflammatory cytokines reflects the presence of low-level inflammation in patients with DM.<sup>17</sup> The role of vitamin D in its anti-inflammatory effect also by reducing prostaglandin E2 (PGE2) which plays an important role as an inflammatory factor<sup>(15)</sup>. Vitamin D can reduce nerve threshold by inhibiting COX-2 expression and stimulating 15-prostaglandin dehydrogenase (15-PGDH) which will reduce prostaglandin.<sup>18</sup> Increased neurotrophin synthesis by vitamin D is useful for the development and maintenance of neurons.<sup>18</sup>

Study by Basit et al. (2016) showed treatment with a single dose of 600,000 IU of vitamin D could be a safe and effective treatment for patients with DN for 20 weeks.<sup>21</sup> Study by Ghadiri et al. (2019) showed that oral administration of vitamin D3 at a dose of 50,000 IU once a week for 12 weeks can increase serum vitamin D levels and significantly reduce the symptoms and signs of DN.<sup>20</sup>

In general, vitamin B is also given as a treatment for neuropathy.<sup>4,5</sup> Vitamin B which is also a neurotropic vitamin has a role to play in maintaining optimal nerve function and assisting in treatment by relieving neuropathy symptom.<sup>3</sup> Vitamin B has a role as an active coenzyme in metabolic pathways including neurotransmitter synthesis and neuronal membrane synthesis. Therefore, vitamin D and vitamin B are safe to use as a combination therapy for peripheral neuropathy to maintain nervous system function and reduce pain.

This study has some implications in daily clinical practice. The use of vitamin B and D should be considered as add on therapy for



patients with painful diabetic neuropathy. Further studies and review are warranted like measure duration of diabetes in each subject to know whether the diabetes is controlled or not. This study did not measure HbA1c so it did not know the average blood glucose level in the last 2–3 months.

### Conclusion

Additional vitamin D therapy in standard therapy for diabetic neuropathy pain gives greater pain reduction compared with standard symptomatic therapy alone.

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### Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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