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Can Baseline Distal Symmetric Neuropathy (DISINI) Score Predict Treatment Outcomes in Painful Diabetic Neuropathy?

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Abstrak:
Pendahuluan: Suplementasi vitamin D berpotensi membantu memperbaiki gejala pada pasien neuropati perifer diabetik (NPD). Namun, saat ini masih minim studi yang menggunakan alat penilaian untuk memprediksi hasil terapi vitamin D. Penelitian ini bertujuan megevaluasi manfaat suplementasi vitamin D dan nilai prediktif skor *Distal Symmetric Neuropathy* (DISINI) pada NPD. **Metode**: Uji klinis teracak terbuka dua-lengan ini mengevaluasi nyeri (VAS, NRS, BPI) dan kadar vitamin D sebagai luaran utama. Kelompok perlakuan menerima pengobatan standar ditambah vitamin D oral 5000 IU, sedangkan kelompok kontrol hanya menerima pengobatan standar. Analisis regresi digunakan untuk menilai apakah skor DISINI awal dapat memprediksi perubahan nyeri dan kadar vitamin D setelah suplementasi. **Hasil**: Sebanyak 57 peserta diikutsertakan. Kelompok intervensi menunjukkan penurunan rerata skor VAS lebih besar (-3,22±1,54 vs -2,38±1,93), namun tidak signifikan (p = 0,076; d = -0,48), serta peningkatan median kadar vitamin D yang signifikan (27,45 [16,3–33,18] vs 2,8 [-0,1–4,7]; p < 0,001; r_{rb} = 0,941). Skor NRS sensasi terbakar menurun signifikan hanya pada kelompok intervensi (p = 0,008), sedangkan variabel lain (VAS, NRS rasa tersetrum, kesemutan, mati rasa, dan kadar vitamin D) berubah signifikan di kedua kelompok (p < 0,05). Skor DISINI awal tidak terbukti sebagai prediktor signifikan terhadap nyeri maupun kadar vitamin D pasca-terapi (p > 0,05). **Kesimpulan**: Suplementasi Vitamin D memperbaiki rasa nyeri dan meningkatkan kadar vitamin D secara signifikan pada pasien NPD, namun skor DISINI tidak memprediksi hasil terapi. Penelitian lebih lanjut diperlukan untuk mengevaluasi prediktor potensial lainnya dalam keberhasilan terapi.
Kata kunci: Neuropati perifer diabetik; Neuropati simetris distal; Tingkat keparahan nyeri; Vitamin D

Abstract:
Introduction: Vitamin D supplementation may help diabetic peripheral neuropathy (DPN) patients. Studies predicting vitamin D supplementation outcomes using assessment tools were still lacking. This study aimed to evaluate the benefit of vitamin D supplementations and the predictive value of the Distal Symmetric Neuropathy (DISINI) score in DPN. **Methods**: This is a two-armed, open-label, randomized clinical trial. The treatment group received standard treatment plus 5000 IU oral vitamin D, while the control group received standard treatment alone. The primary outcomes were Visual Analog Scale (VAS), Numerical Rating Scale (NRS), Brief Pain Inventory (BPI), and vitamin D levels. Regression analyses were performed to evaluate whether baseline DISINI scores could predict pain and vitamin D changes following supplementation. **Results**: We recruited 57 participants. The experimental group showed a greater decrease in mean VAS score (-3.22±1.54 vs -2.38±1.93), although not significant (p = 0.076; d = -0.48), while also having significant greater median vitamin D level change (27.45 (16.3, 33.18) vs 2.8 (-0.1, 4.7); p <0.001; r_{rb} = 0.941). Paired-sample tests revealed a significant difference in NRS burning scores only in the experimental group (p = 0.008), while other variables, including VAS, NRS electric shock, NRS tingling, NRS numbness, and vitamin D levels, significantly differed in both experimental and control groups (p < 0.05). However, regression analysis revealed that baseline DISINI scores were not significant predictors of post-treatment pain outcomes or serum vitamin D levels (p >0.05). **Conclusion**: Vitamin D supplementation significantly improved pain severity and vitamin D levels in DPN patients, but baseline DISINI scores did not predict treatment outcomes. Further studies are needed to explore other potential predictors of treatment efficacy.
Keywords: *Diabetic peripheral neuropathy; Distal symmetric neuropathy; Pain severity; Vitamin D*

1. Introduction

Diabetic neuropathy is a prevalent microvascular complication affecting 30–50% of patients with type 2 diabetes mellitus (T2DM), and it remains one of the most challenging aspects of diabetes care due to its impact on morbidity, mortality, and quality of life (1,2). Vitamin D deficiency is widespread in individuals with T2DM and has been consistently associated with both the presence and severity of DPN (2–5). Among the various subtypes, diabetic peripheral neuropathy (DPN) is the most common and frequently presents with painful symptoms, including burning, tingling, cramping, and electric-shock sensations that disrupt sleep, impair mobility, and reduce overall functioning (6,7). These symptoms often persist despite standard pharmacological treatment, underscoring the need for adjunctive therapies and improved strategies for symptom management.

Vitamin D's role in modulating neuroinflammation, supporting nerve repair, and regulating calcium channels has led researchers to explore its therapeutic potential in managing neuropathic pain. Although some interventional studies suggest that vitamin D supplementation may provide symptomatic relief in DPN, the response to treatment appears to vary between individuals (2,5,8–10). This variability highlights the clinical need to identify predictive markers that can help stratify patients and tailor treatment plans. Currently, limited research exists on clinical tools that can predict treatment outcomes following vitamin D supplementation in painful DPN. Most studies focus on group-level efficacy without incorporating individual-level symptom severity or functional status into treatment planning. Personalized treatment strategies remain difficult to implement in the absence of valid, accessible predictors of therapeutic response (12–14).

The Distal Symmetric Neuropathy (DISINI) score, a novel composite symptom-based tool developed by Maharani et al. (2024), offers a potential solution for this gap (11). Designed for ease of use in clinical settings, especially where comprehensive neurological testing may not be feasible, the DISINI score focuses on the core sensory symptoms of DPN. It has shown promising associations with neuropathy severity and may offer added clinical value in low-resource settings where time and equipment are limited (11). However, no study to date has assessed whether baseline DISINI scores can predict response to specific interventions such as vitamin D supplementation.

Given the variability in symptom profiles and treatment outcomes in painful DPN, it is essential to evaluate whether tools like the DISINI score can help anticipate which patients are likely to experience meaningful improvements. If effective as a predictive marker, the DISINI score could contribute significantly to individualized care approaches, enabling clinicians to identify likely responders, optimize resource allocation, and monitor treatment progress more effectively. The present study aims to evaluate the clinical efficacy of oral vitamin D supplementation and examine whether baseline DISINI scores can serve as predictors of treatment response in patients with painful DPN. Specifically, this two-armed randomized trial evaluates changes in pain severity and vitamin D levels and applies regression analyses to assess the predictive value of initial DISINI scores. By doing so, the study contributes to a growing body of evidence supporting more targeted and personalized approaches to managing diabetic neuropathic pain.

2. Materials and Methods

2.1 Study design

Our study was a two-armed, open-label, randomized clinical trial conducted at a tertiary hospital in Yogyakarta, Indonesia. We consecutively recruited participants from the pain clinic in our neurology department. A neurologist assessed all subjects by taking their history and performing a physical examination. Eligible participants were (1) all patients with T2DM, (2) aged >18 years old,(3) referred to the neurologist department due to diabetic peripheral neuropathy (DPN) symptoms (i.e., burning, tingling), and (4) willing to participate in our study. The exclusion criteria were (1) participants with significant renal and/or liver impairment, (2) subject to known hypersensitivity with vitamin D supplementation, (3) pregnant, and (4) lactating or breastfeeding. The intervention

group received standard treatment for diabetic neuropathy with an additional add-on oral vitamin D 5000 IU. The control group only received standard treatment for diabetic neuropathy without add-on vitamin D.

2.2. Ethical statement

The authors confirmed that all ongoing and related trials for this drug/intervention were registered. Ethical approval for the study was obtained from the Bethesda Hospital Ethics Committee with the number 120/KEPK-RSB/XII/20 and the study was registered in the Indonesian Clinical Trial Registry with the number INA-MEODDY6 and ClinicalTrials.gov with the number NCT04689958. All study participants gave signed informed consent to the Declaration of Helsinki.

2.3. Materials

We assessed all subjects using a monofilament test to confirm the presence of DPN (15). In addition to DISINI, we utilized Douleur Neuropathique 4 (DN4), Diabetic Neuropathy Examination (DNE), and Diabetic Neuropathy Symptoms (DNS) to assess DPN severity (16-18). All questionnaires were available in the Indonesian version(19,20).

The primary outcomes were the change from the baseline of pain-related scores, which are (a) the Visual Analog Scale (VAS), (b) the Numerical Rating Scale (NRS), and (c) the Brief Pain Inventory (BPI). Specifically for BPI, we measured the subjects' BPI scores before and after the trial and grouped them into Subjective Global Assessment (SGA) categories, which are vastly 'improved' (>50% improvement), 'improved' (30-50% improvement), 'slightly improved' (10-30% improvement) and 'no improvement' (<10% improvement).

The secondary outcomes were the change in vitamin D levels and the predictive power of baseline DISINI score to predict symptom changes. Serum 25(OH)D was measured using an enzyme-linked immunoassay (ELISA) method. We also measured the safety profile by monitoring any adverse events.

2.4. Procedures

Following written informed consent, participants who fulfilled the criteria for the treatment phase of the study were allocated to 1 of 2 groups. Randomization was done using block randomization with a 1:1 ratio and assigned to the intervention (n = 28) or control (n = 29) trial group. A statistician not involved with the study generated a randomization list using blocks of 5 stratifications. Complete blinding was considered difficult and not possible. Participants were informed of key elements of the respective intervention and follow-up they were randomized to, but not on information about the treatment and follow-up alternatives in the other group or the study's hypotheses.

2.5. Statistical analysis

We assessed all continuous variables for normality using the Shapiro–Wilk test. The Shapiro-Wilk test would then determine whether the continuous variables would be presented as mean and standard deviation (SD) or median and interquartile range (IQR). As for categorical variables, frequency and percentage were employed.

Pearson's chi-square test or Fisher's exact test was utilized when comparing categorical variables across intervention groups, with the addition of absolute adjusted standardized residuals (|ASR|) to identify cells contributing most to significant associations. To evaluate ordinal variables' trends across groups, the Cochran-Armitage trend test was selected. We compared continuous variables across intervention groups using an independent-sample t-test or Mann–Whitney U test. To evaluate changes from baseline to week 8 within each group, we used a dependent t-test, Wilcoxon signed-rank test, or paired-sample sign test. Effect size measures, such as Phi' coefficient (ϕ), Cohen's d, and rank-biserial correlation (r_{rb}), were applied according to the appropriate tests.

We performed linear regression models and ordinal logistic regression, using the baseline DISINI score as the independent variable. If key assumptions were violated, Spearman's rank correlation and Kruskal–Wallis tests were used as non-parametric alternatives.

Analyses were conducted on an intention-to-treat basis. Missing data were imputed. Statistical significance was set at $\alpha = 0.05$, and all analyses were performed in SPSS version 29.

3. Results

We recruited 68 subjects who fulfilled the inclusion criteria and did not meet the exclusion criteria. All subjects were randomly assigned to experimental and control groups, with 34 subjects in each group. Eleven subjects were excluded from our study due to incomplete vitamin D level data (six from the intervention group and five from the control group), resulting in 57 included samples. The Shapiro-Wilk test revealed that only three variables had normal distribution: age, BMI, and VAS score changes.

3.1 Baseline characteristics

Table 1 presents baseline characteristics. Participants were predominantly female (56.1%), elderly (68.4%), and had T2DM for ≥5 years (56.1%), with a mean age of 64.21 ± 8.39 years and BMI of 25.83 ± 3.62 kg/m². Most had controlled glycemia (93%) and hypertension (56.1%) as the most common comorbidities. Alpentin was the most prescribed analgesic (80.7%), while anti-hypertensives (57.9%) and vitamin B (54.4%) were frequently used non-analgesics. All had DPN (monofilament test). Median baseline scores: DISINI 4 (3,6), DN4 5 (4,5), DNE 4 (3,4), DNS 2 (1,2.5). Significant group differences were found in vitamin B use ($p = 0.045$; $\phi = 0.27$; |ASR| = 2), monofilament test ($p = 0.016$; $r_{rb} = 0.35$), DN4 ($p = 0.022$; $r_{rb} = 0.34$), and DNS ($p = 0.048$; rrb = 0.28).

Table 1. Baseline characteristics of the study's subjects

Variable	Total (n = 57)	Treatment (n = 28)	Control (n = 29)	|ASR|	*p*	Effect size
Gender						
Male (n (%))	25 (43.9)	11 (39.3)	14 (48.3)	0.7	0.49[a]	-0.09[f]
Female (n (%))	32 (56.1)	17 (60.7)	15 (51.7)			
Age, years (mean (SD))	64.21 (8.39)	64.36 (8.55)	64.07 (8.38)	-	0.9[b]	0.03[g]
≥60 (n (%))	39 (68.4)	20 (71.4)	19 (65.5)	0.5	0.63[a]	0.06[f]
<60 (n (%))	18 (31.6)	8 (28.6)	10 (34.5)			
BMI, kg/m² (mean (SD))	25.83 (3.62)	25.51 (4.05)	26.14 (3.2)	-	0.52[b]	-0.69[g]
Disease duration, years (median (IQR))	7 (3, 15.5)	4 (3, 13.25)	10 (3.5, 20)	-	0.14[c]	0.23[h]
≥5 (n (%))	32 (56.1)	13 (46.4)	19 (65.5)	1.5	0.15[a]	-0.19[f]
<5 (n (%))	25 (43.9)	15 (53.6)	10 34.5)			
Glycemic control						
uncontrolled (n (%))	4 (7)	3 (10.7)	1 (3.4)	1.1	0.35[d]	0.14[f]
controlled (n (%))	53 (93)	25 (89.3)	28 (96.6)			
Comorbidities						
HT (n (%))	32 (56.1)	15 (53.6)	17 (58.6)	0.4	0.7[a]	-0.05[f]
CV (n (%))	31 (54.4)	12 (42.9)	19 (65.5)	1.7	0.09[a]	-0.23[f]
GI (n (%))	7 (12.3)	2 (7.1)	5 (17.2)	1.2	0.42[d]	-0.15[f]
Neuropathic pain analgetic						
alpentin (n (%))	46 (80.7)	24 (85.7)	22 (75.9)	1.1	0.33[d]	0.14[f]
gabapentin (n (%))	8 (14)	3 (10.7)	5 (17.2)	1.6	0.14[d]	0.21[f]
pregabalin (n (%))	3 (5.3)	1 (3.6)	2 (6.9)	0.6	1.0[d]	-0.74[f]
Other medications						
anti-HT (n (%))	33 (57.9)	16 (57.1)	17 (58.6)	0.1	0.91[a]	-0.02[f]
vitamin B (n (%))	31 (54.4)	19 (67.9)	12 (41.4)	2.0[#]	0.045[a*]	0.27[f]
anti-platelets (n (%))	27 (47.4)	10 (35.7)	17 (58.6)	1.7	0.08[a]	-0.23[f]
statins (n (%))	12 (21.1)	5 (17.9)	7 (24.1)	0.6	0.56[a]	-0.8[f]
Monofilament (median (IQR))	1 (1, 2.5)	2 (1, 3)	1 (1, 2)	-	0.016[c]	0.35[h]
Baseline neuropathic pain assessment						
DISINI (median (IQR))	4 (3, 6)	4 (2.25, 6)	4 (3.5, 6)	-	0.927[c]	0.01[h]
DN4 (median (IQR))	5 (4, 5)	4 (3, 5)	5 (4, 6)	-	0.022[c]	0.34[h]
DNE (median (IQR))	4 (3, 4)	4 (3, 4)	4 (3, 4)	-	0.115[c]	0.22[h]
DNS (median (IQR))	2 (1, 2.5)	2 (1, 2)	2 (2, 3)	-	0.048[c]	0.28[h]

Notes: ASR: Adjusted Standardized Residuals; BMI: Body Mass Index; CV: cardiovascular; DISINI: Distal Symmetric Neuropathy; DN4: Douleur Neuropathique 4; DNE: Diabetic Neuropathy Examination; DNS: Diabetic Neuropathy Symptom; GI: gastrointestinal; HT: hypertension; IQR: Inter-quartile range; SD: Standard deviation, a = Pearson' chi-square; b = Student' t-test; c = Mann-Whitney U test; d = Fisher' exact test; e = Cochrane-Armitage test, f = Phi coefficient; g = Cohen' d; h = rank-biserial correlation; * = p <0.05; # = >1.96

3.2 Pain & vitamin D assessment

3.2.1 Pain outcomes

Within groups, all pain assessments showed statistically significant improvements in the experimental group following vitamin D supplementation. In contrast, the control group demonstrated no significant change in NRS burning score (p = 0.146), although improvements in other pain parameters were observed.

3.2.2 Vitamin D levels

The experimental group experienced significantly higher median endpoint vitamin D levels (39.5 (31.68, 52.48) vs 19.9 (16.15, 22.35); p <0.001, r_{rb} = 0.93) and a greater increase in median vitamin D levels (27.45 (16.3, 33.18) vs 2.8 (-0.1, 4.7); p <0.001, r_{rb} = 0.941) compared to control group [**Table 2**].

Table 2. Overview of pain and Vitamin D level outcomes

Variable	Total (n = 57)	Treatment (n = 28)	Control (n = 29)	*p*	Effect size
VAS - baseline (median (IQR))	5.4 (4.4, 7)	5.45 (4.1, 6.9)	5.4 (4, 7.2)	0.962[c]	0.07[h]
VAS - endpoint (median (IQR))	2 (1, 4.9)	1.55 (0.825, 3.425)	2.8 (1, 5.3)	0.204[c]	0.2[h]
ΔVAS (mean (SD))	-2.79 (1.78)	-3.22 (1.54)	-2.38 (1.93)	0.076[b]	-0.48[g]
p[1]	< 0.001*	< 0.001*	< 0.001*		
NRS burning - baseline (median (IQR))	0 (0, 20)	0 (0, 20)	0 (0, 40)	0.498[c]	0.09[h]
NRS burning - endpoint (median (IQR))	0 (0, 0)	0 (0, 0)	0 (0, 0)	0.161[c]	0.13[h]
ΔNRS burning (median (IQR))	0 (-20, 0)	0 (-20, 0)	0 (-25, 0)	0.94[c]	0.01[h]
p[2]	0.003*	0.008*	0.146		
NRS electric shock - baseline (median (IQR))	0 (0, 30)	0 (0, 7.5)	0 (0, 50)	0.057[c]	0.25[h]
NRS electric shock - endpoint (median (IQR))	0 (0, 0)	0 (0, 0)	0 (0, 0)	0.772[c]	0.03[h]
ΔNRS electric shock (median (IQR))	0 (-20, 0)	0 (-7.5, 0)	0 (-30, 0)	0.048[c*]	0.26[h]
p[2]	0.001*	0.016*	< 0.001*		
NRS tingling - baseline (median (IQR))	30 (5, 60)	30 (0, 60)	50 (20, 65)	0.312[c]	0.15[h]
NRS tingling - endpoint (median (IQR))	10 (0, 25)	0 (0, 10)	10 (0, 40)	0.041[c*]	0.3[h]
ΔNRS tingling	-20 (-35, 0)	-20 (-40, 0)	-20 (-25, 0)	0.336[c]	0.15[h]
p[2]	< 0.001*	< 0.001*	< 0.001*		
NRS numbness - baseline (median (IQR))	40 (20, 60)	50 (5, 67.5)	40 (20, 50)	0.765[c]	0.05[h]
NRS numbness - endpoint (median (IQR))	10 (0, 30)	10 (0, 30)	20 (0, 35)	0.436[c]	0.12[h]
ΔNRS numbness (median (IQR))	-20 (-30, 0)	-20 (-30, 0)	-20 (-30, 0)	0.702[c]	0.06[h]
p[2]	< 0.001*	< 0.001*	< 0.001*		
Baseline vitamin D level, ng/mL (median (IQR))	17.1 (11.7, 21.1)	16.95 (11.08, 21.8)	17.1 (11.9, 20.7)	0.968[c]	0.006[h]
deficiency	39 (68.4)	15 (53.6)	24 (82.8)		
insufficiency	14 (24.6)	10 (35.7)	4 (13.8)	0.025[e*]	0.31[f]
normal	4 (7)	3 (10.7)	1 (3.4)		
Endpoint vitamin D level, ng/mL (median (IQR))	26.6 (19.55, 39.5)	39.5 (31.68, 52.48)	19.9 (16.15, 22.35)	<0.001 [e*]	0.93[h]
deficiency	15 (26.3)	5 (17.9)	10 (34.5)		
insufficiency	15 (26.3)	8 (28.6)	7 (24.1)	0.191[e]	0.19[f]
normal	27 (47.4)	15 (53.6)	12 (41.4)		
p[2]	< 0.001*	< 0.001*	0.014*		
ΔVitamin D level, ng/mL (median (IQR))	6.2 (2.65, 27.45)	27.45 (16.3, 33.18)	2.8 (-0.1, 4.7)	<0.001 [e*]	.941[h]

Notes : VAS: Visual Analog Scale; NRS: Numerical Rating Scale, a = Pearson' chi-square; b = Student' t-test; c = Mann-Whitney U test; d = Fisher' exact test; e = Cochrane-Armitage test, f = Phi coefficient; g = Cohen' d; h = rank-biserial correlation; * = p <0.05; [1] = Wilcoxon signed-rank; [2] = paired-sample sign test

Across groups, the reduction in mean VAS score was greater in the experimental group (–3.22 ± 1.54) than in the control group (–2.38 ± 1.93), but this difference did not reach statistical significance (p = 0.076; Cohen's d = –0.48). No significant between-group difference was observed in NRS burning scores. For NRS electric shock, both groups had a median change of 0, with the experimental group exhibiting a narrower interquartile range (–7.5 to 0) compared to the control group (–30 to 0), indicating a more consistent improvement. This difference in distribution

was statistically significant (p = 0.048). The NRS tingling score at endpoint was significantly lower in the experimental group, with a median of 0 (0–10), compared to a median of 10 (0–40) in the control group (p = 0.041), suggesting more favorable symptom relief. However, the median change from baseline was identical in both groups (–20), and the difference in change scores was not statistically significant (p = 0.336). For NRS numbness, the experimental group had a lower endpoint median (10 (0–30)) than the control group (20 (0–35)), though the median score change was the same (–20 in both groups), and these differences were not statistically significant [**Table 2**].

3.3 Sleep quality, general activity, and mood

Table 3 shows BPI-based outcomes [**Table 3**]. There was no significant association between the degree of sleep quality (p = 0.239; ϕ = 0.17), general activity (p = 1.0; ϕ = 0.34), and mood (p = 0.239; ϕ = 0.17) across groups.

Table 3. Pain impact on sleep, general activity, and mood, based on BPI

Variable	Total (n = 57)	Experimental group (n = 28)	Control group (n = 29)	*p*	Effect size
SGA - Pain severity					
Vastly improved (n (%))	14 (24.6)	6 (21.4)	8 (27.6)		
Improved (n (%))	25 (43.9)	11 (39.3)	14 (48.3)	0.239[e]	.17[f]
Slightly improved (n (%))	12 (21.1)	7 (25)	5 (17.2)		
No improvement (n (%))	6 (10.5)	4 (14.3)	2 (6.9)		
SGA - Sleep Quality					
Vastly improved (n (%))	22 (38.6)	13 (46.4)	9 (31)		
Improved (n (%))	23 (40.4)	12 (42.9)	11 (37.9)	0.192[e]	.37[f]
Slightly improved (n (%))	7 (12.3)	3 (10.7)	7 (24.1)		
No improvement (n (%))	5 (8.8)	0 (0)	2 (6.9)		
SGA - General activity					
Vastly improved (n (%))	17 (29.8)	10 (35.7)	7 (24.1)		
Improved (n (%))	30 (52.6)	11 (39.3)	19 (65.5)	1.0[e]	.34[f]
Slightly improved (n (%))	9 (15.8)	7 (25)	2 (6.9)		
No improvement (n (%))	1 (1.8)	0 (0)	1 (3.4)		
SGA - Mood					
Vastly improved (n (%))	17 (29.8)	7 (25)	10 (34.5)		
Improved (n (%))	31 (54.4)	15 (53.6)	16 (55.2)	0.239[e]	.17[f]
Slightly improved (n (%))	6 (10.5)	4 (14.3)	2 (6.9)		
No improvement (n (%))	3 (5.3)	2 (7.1)	1 (3.4)		

Notes: SGA: Subjective Global Assessment, a = Pearson' chi-square; b = Student' t-test; c = Mann-Whitney U test; d = Fisher' exact test; e = Cochrane-Armitage test, f = Phi coefficient; g = Cohen' d; h = rank-biserial correlation; * = p <0.05

3.4 Regression analyses

Table 4-5 displays the regression analysis results [**Table 4; Table 5**]. Regression analyses were conducted to evaluate whether baseline DISINI scores could predict post-treatment vitamin D levels or patient-reported outcomes measured by the BPI. However, the assumptions required for linear and ordinal regression models were not fully met, limiting the interpretability of the analyses.

In linear regression models, baseline DISINI scores were not significant predictors of post-treatment vitamin D levels ($F(1, 55) = 0.051$, $p = 0.822$, $R^2 = 0.001$) or of changes in vitamin D levels ($F(1, 55) = 0.574$, $p = 0.452$, $R^2 = 0.102$). Corresponding regression coefficients also failed to reach statistical significance for post-treatment vitamin D levels ($B = -0.31$, $SE = 1.37$, $\beta = -0.03$, $t(55) = -0.23$, $p = 0.822$) and for vitamin D changes ($B = 0.95$, $SE = 1.25$, $\beta = 0.10$, $t(55) = -0.76$, $p = 0.452$).

Similarly, ordinal regression models examining the association between baseline DISINI and SGA also yielded non-significant results. Model fitting statistics indicated no significant predictive value for pain (p = 0.824), sleep (p = 0.459), general activity (p = 0.054), and mood (p = 0.402). Pseudo R-squared values ranged from 0.001 to 0.064, suggesting minimal variance explained. At the level of individual predictors, baseline DISINI scores were not significantly associated with pain (b = 0.036, p = 0.818), sleep (b = –0.12, p = 0.455), or mood (b = –0.14, p = 0.399). A marginal association was observed for the general activity domain (b = –0.323, p = 0.061), suggesting a trend toward

higher DISINI scores being associated with better-perceived activity improvement, though this did not reach statistical significance.

Table 4. Linear regression analysis results

Independent variable (predictor)	Dependent variable	F(1, df)	*p-value*	R^2	B	SE	*t*	95%CI for B	β	VIF	Durbin-Watson
Pre-treatment DISINI	Post-treatment vitamin D level	0.051	0.822	0.001	-0.311	1.372	-0.226	[-3.06, 2.439]	-0.031	1.000	1.555
	Changes in vitamin D level	0.574	0.452	0.102	0.95	1.254	0.758	[-1.563, 3.464]	0.102	1.000	1.543

B: Unstandardized beta; β: Standardized beta; df: degree of freedom; DISINI: Distal Symmetric Neuropathy; F: F-statistic; NRS: Numerical Rating Scale; R2: R-squared; SE: Standard error; SGA: Subjective Global Assessment; t: Test statistic; VAS: Visual Analog Scale; VIF: Variance Inflation Factor

Table 5. Ordinal regression analysis results

Independent variable (predictor)	Dependent variable	Pseudo R^2	B	SE	Wald	*p-value*			
						Model fitting	Goodness of fit	Parameter estimates [95%CI]	Parallel lines
Pre-treatment DISINI	SGA pain domain	0.001	0.036	0.158	0.053	0.824	0.028	0.818 [-.274, .347]	0.186
	SGA sleep domain	0.01	-0.12	0.16	0.558	0.459	0.311	0.455 [-.433, .194]	<0.001
	SGA general activity domain	0.064	-0.323	0.173	3.499	0.054	0.82	0.061 [-.661, .015]	0.009
	SGA mood domain	0.012	-0.14	0.166	0.71	0.402	0.917	0.399 [-.466, .186]	0.764

B: Unstandardized beta; β: Standardized beta; df: degree of freedom; DISINI: Distal Symmetric Neuropathy; F: F-statistic; NRS: Numerical Rating Scale; R2: R-squared; SE: Standard error; SGA: Subjective Global Assessment; t: Test statistic; VAS: Visual Analog Scale; VIF: Variance Inflation Factor

3.5 Exploratory non-parametric analyses

Tables 6-8 displayed additional analyses of baseline DISINI scores.

Table 6. Spearman multi-correlation analysis

	DISINI	DN4	DNE	DNS
DISINI	1.0			
DN4	0.354**	1.0		
DNE	0.351**	0.019	1.0	
DNS	0.267*	0.461**	-0.006	1.0

Table 7. Multi-correlation matrix analysis

	DISINI	ΔVAS	ΔNRS burning	ΔNRS electric shock	ΔNRS tingling	ΔNRS numbness	ΔVitamin D level
DISINI	1.0						
ΔVAS	-0.148	1.0					
ΔNRS burning	-0.085	0.408**	1.0				
ΔNRS electric shock	-0.18	0.086	0.496**	1.0			
ΔNRS tingling	-0.143	0.408**	0.284**	0.203	1.0		
ΔNRS numbness	-0.19	0.547**	0.047	0.043	0.32*	1.0	
ΔVitamin D level	0.125	-0.305*	-0.137	0.12	-0.207	-0.142	1.0

DISINI: Distal Symmetric Neuropathy; DN4: Douleur Neuropathique 4; DNE: Diabetic Neuropathy Examination; DNS: Diabetic Neuropathy Symptom; VAS: Visual Analog Scale; * = p <0.05; ** = p <0.01

Table 8. Kruskal-Wallis's analysis

	DISINI
Pain severity	.234
Sleep Quality	.038*
General activity	.211
Mood	.782

DISINI: Distal Symmetric Neuropathy; VAS: Visual Analog Scale; NRS: Numerical Rating Scale; * = p <0.05

The baseline DISINI score showed statistically significant positive correlations with DN4 (r = 0.354, p <0.01), DNE (r = 0.351, p <0.01), and DNS (r = 0.267, p <0.05). In contrast, it was not significantly correlated with any pain scores or vitamin D levels (all p >0.05). Furthermore, a Kruskal–Wallis test revealed a significant association between baseline DISINI score and sleep quality outcomes (p = 0.038).

4. Discussion

Our findings indicate that baseline DISINI scores lack sufficient prognostic value for guiding vitamin D supplementation in DPN. Although DISINI correlated moderately with established neuropathy measures (DN4, DNE, DNS), it did not translate into meaningful prediction of either biochemical or symptomatic outcomes in this study. This suggests that while DISINI is a valid contemporary indicator of neuropathy severity, it may not capture the dynamic factors that determine treatment responsiveness.

Previous studies have established associations between low vitamin D status and neuropathic pain, while some studies have even reported symptom relief following supplementation (2,6,8,21,22). Some studies also reported that vitamin D deficiency is a significant independent predictor of DPN (23-25). Few studies have utilized control groups, but this remains scarce, especially in Indonesia (12,14). Our trial's incorporation of a comparator arm and explicit focus on DISINI as a predictive marker addresses this gap and suggests that initial symptom burden alone may be insufficient for tailoring vitamin D therapy. Prior studies had already utilized regression analyses, but none tailored a specific diabetic neuropathy scoring to predict pain outcomes nor vitamin D levels (26). Vitamin D may exert neuroprotective and anti-inflammatory effects irrespective of baseline neuropathy severity, suggesting a relatively uniform physiological response across patients (27). Additionally, genetic variation in vitamin D metabolism or receptor sensitivity, unmeasured in our study, could moderate treatment effects more strongly than clinical severity scores (28). Indeed, our exploratory finding linking DISINI to post-treatment sleep quality hints at domain-specific nuances that warrant further investigation, though this should be interpreted cautiously given the preliminary nature of the data.

In our study, we conducted a rigorous evaluation of the DISINI score's utility as a predictive marker for vitamin D supplementation outcomes in DPN, addressing a gap in existing research. Although the DISINI score did not predict treatment outcomes, our findings contribute valuable insights into the complexities of DPN management. Additionally, by incorporating a comparator arm, we enhanced the validity of our findings, allowing for a clearer assessment of vitamin D's effects on DPN symptoms. The study's limitations include a short follow-up period and a limited sample size, which may not fully capture the long-term effects of vitamin D supplementation on diabetic peripheral neuropathy. Additionally, the absence of genetic and biochemical assessments, such as vitamin D receptor polymorphisms and inflammatory markers, limits the understanding of individual variability in treatment response. Looking ahead, longer follow-up periods will be important to capture the full trajectory of nerve regeneration and functional recovery that may unfold beyond eight weeks. Integrating multimodal predictors, including baseline 25(OH)D levels, vitamin D receptor genotypes, and inflammatory biomarkers, alongside clinical scales like DISINI, could improve prognostic accuracy. Systematic dose-response studies would help establish optimal supplementation regimens, while double-blind, placebo-controlled designs can minimize bias and strengthen causal inference. Furthermore, examining adjunctive therapies, such as combining vitamin D with anti-inflammatory agents, and incorporating targeted patient-reported outcome measures for pain, sleep, mood,

and activity domains may uncover subgroups that derive the greatest benefit. Clinically, these findings underscore that relying solely on baseline neuropathy severity to guide vitamin D supplementation is insufficient. Instead, a personalized approach may ultimately optimize treatment strategies and improve outcomes for patients with painful diabetic neuropathy.

5. Conclusions

Baseline DISINI scores, while correlated with established neuropathy assessments, were not found to predict pain-related or biochemical outcomes following vitamin D supplementation in patients with diabetic peripheral neuropathy. This study highlights the limited utility of using neuropathy severity alone to guide treatment decisions. A more personalized approach, incorporating genetic, biochemical, and clinical factors, is needed to better identify patients who may benefit from vitamin D therapy. Future research should focus on longer follow-up durations, multimodal predictive models, and domain-specific outcomes to refine patient stratification and optimize therapeutic strategies.

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List of Abbreviations

DISINI	Distal Symmetric Neuropathy
DN4	Douleur Neuropathique 4
DNE	Diabetic Neuropathy Examination
DNS	Diabetic Neuropathy Symptom
VAS	Visual Analog Scale
NRS	Numeric Rating Scale
BPI	Brief Pain Inventory
SGA	Subjective Global Assessment

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