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RESEARCH ARTICLE

Low Serum Nerve Growth Factor Levels Are Associated with Insulin Resistance, Beta Cell Dysfunction, and Neuropathy Screening Scores in Subjects with Type 2 Diabetes Mellitus

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Abstract

BACKGROUND: Diabetic peripheral neuropathy (DPN) is a common complication of type 2 diabetes mellitus (T2DM), associated with chronic hyperglycemia, insulin resistance, and neuroinflammation. Despite the widespread use of Michigan Neuropathy Screening Instrument (MNSI) for early identification in neuropathy screening, studies assessing its relationship between NGF, insulin resistance, and neuropathy in T2DM patients, particularly in Indonesia, remain limited. Therefore, this study was conducted to evaluate associations between serum NGF, insulin resistance, β-cell function, and MNSI scores in T2DM.

METHODS: Seventy-seven T2DM subjects were classified into DPN and non-DPN groups using MNSI. Subjects were excluded if they have comorbidities and conditions potentially affecting metabolic, immune, or organ function. Enzyme-linked immunosorbent assay (ELISA) was used for the measurement of serum NGF, enzymatic hexokinase method for fasting plasma glucose (FPG) and 2-hour postprandial glucose (2HPP), high-performance liquid chromatography (HPLC) for glycated hemoglobin (HbA1c), and chemiluminescent immunoassay for fasting insulin. Homeostatic model assessment of insulin resistance (HOMA-IR) and beta-cell function (HOMA-β) were then calculated.

RESULTS: Most of the study subjects had NGF level of <11 pg/mL. NGF concentrations showed inverse correlations with HOMA-IR (r=–0.263, p=0.021) and HOMA-β (r=–0.316, p=0.005). In the DPN subgroup, NGF demonstrated a stronger negative correlation with HOMA-β (r=–0.425, p=0.009), whereas no significant correlation was found in non-DPN. HbA1c was higher in DPN (p=0.014). No significant associations were observed between NGF and HbA1c, FPG, or 2HPP. NGF was significantly associated with MNSI Part B scores (p=0.032), reflecting objective neuropathic findings, but not with MNSI Part A or total scores.

CONCLUSION: Lower NGF levels were significantly associated with insulin resistance and β-cell dysfunction in T2DM. The association with MNSI part B suggests that physical examination findings may reflect NGF-related neuropathic alterations better than symptom-based assessments.

KEYWORDS: diabetic peripheral neuropathy, HOMA-IR, HOMA-β, Michigan Neuropathy Screening Instrument, nerve growth factor, T2DM

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Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent elevations in blood glucose levels, resulting from an inadequate insulin production, a reduced insulin sensitivity, or a combination of both. According to the International Diabetes Federation (IDF) Diabetes Atlas, 11th edition (2025), the global prevalence of diabetes has reached approximately 540 million people,

including 207 million in the Western Pacific region and 20 million in Indonesia.(1) Data from the 2023 Indonesian Health Survey (*Survey Kesehatan Indonesia*/SKI) indicate that 11.7% of individuals aged 15 years and older are living with diabetes, with clinically diagnosed cases accounting for 1.7% of the total population.(2) The rising prevalence of DM has increased the burden of both acute and chronic complications, one of the most common being diabetic peripheral neuropathy (DPN).

DPN is a progressive disorder characterized by damage to sensory, motor, and autonomic peripheral nerves. It results from a complex pathophysiological process involving chronic hyperglycemia, accumulation of advanced glycation end-products (AGEs), oxidative stress, and microvascular injury.(3,4) Insulin resistance significantly contributes by promoting mitochondrial dysfunction, systemic inflammation, and cellular stress responses. (5) Chronic hyperglycemia and insulin resistance in type 2 DM (T2DM) are frequently accompanied by immune dysregulation, including impaired regulatory T cell function, which may exacerbate neuroinflammation and contribute to nerve damage.(6) These mechanisms collectively lead to axonal degeneration and demyelination, the hallmarks of DPN. DPN typically develops after approximately 10–15 years of persistent hyperglycemia, although onset may occur earlier in individuals with poor glycemic control or additional metabolic risk factors. Chronic hyperglycemia plays a central role in this timeline by accelerating oxidative stress, promoting microvascular damage, and triggering inflammatory pathways that progressively impair peripheral nerve structure and function. Metabolic parameters such as the homeostatic model assessment of insulin resistance (HOMA-IR) and beta cell function (HOMA-β) have been proposed as useful indicators to assess insulin resistance and beta cell function, both of which are implicated in the development of diabetic neuropathy.(7)

The global prevalence of DPN is estimated at 26.7%, with regional variability depending on diagnostic methods and population characteristics.(8) In Indonesia, reported prevalence ranges from 28% to over 70%, with higher rates observed in rural and underserved areas.(9,10) Clinically, DPN presents with a spectrum of sensory disturbances, including burning pain, paresthesia, and numbness, which can progress to severe motor impairment and increase the risk of diabetic foot ulcers. Physical examination and screening tools are essential for early identification, and the Michigan Neuropathy Screening Instrument (MNSI), which includes a symptom-based questionnaire (Part A) and a physical examination component (Part B), is widely used due to its high sensitivity and specificity across multiple populations.(11,12) However, studies in diverse ethnic groups have shown variability in its diagnostic accuracy, highlighting the importance of local validation.(13,14)

In recent years, there has been growing interest in identifying molecular biomarkers to support the clinical diagnosis of DPN. One such marker was nerve growth factor (NGF), a neurotrophin essential for the survival, growth, and maintenance of peripheral neurons. Decreased levels of NGF have been implicated in the pathogenesis of DPN, contributing to axonal atrophy, loss of nerve fiber density and impaired neuro-regeneration.(15,16) Nonetheless, some studies have reported elevated NGF levels in subjects with neuropathy, possibly reflecting a compensatory mechanism in response to nerve injury.(17) This duality highlights the complexity of NGF dynamics in diabetic neuropathy and suggests that its clinical interpretation may depend on the stage and severity of nerve damage.

Despite the increasing burden of diabetic neuropathy, the widespread use of MNSI in clinical screening, and the potential role of NGF as a biomarker; however, studies evaluating NGF, MNSI, and insulin resistance indices in patients with T2DM, especially in Indonesia, are still limited. Therefore, this study was conducted to explore the relationships between serum NGF levels, neuropathy scores, and insulin resistance in individuals with T2DM, which may provide novel insights for identifying high-risk individuals and developing targeted prevention and management strategies. Unlike the MNSI, which primarily detects established neuropathy based on symptoms and physical findings, NGF has the potential to reflect early neurotrophic alterations before overt clinical signs emerge, thereby offering a complementary approach for earlier detection and risk stratification.

Methods

Study Design and Setting

A cross-sectional exploratory study was conducted at the Endocrinology Outpatient Clinic of H. Adam Malik General Hospital, Medan, Indonesia. The study was carried out over an 11-month period, from June 2024 to April 2025. Ethical approval for this study was obtained from the Health Research Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara (Approval No. 791/KEPK/USU/2024). All procedures complied with the ethical standards of the institutional committee and the principles outlined in the Declaration of Helsinki.

Subjects Recruitment

Subjects were recruited from subjects diagnosed with T2DM who attended the Endocrinology Outpatient Clinic of H. Adam Malik General Hospital Medan using a non-probability consecutive sampling method, whereby all eligible individuals who met the inclusion and exclusion criteria were enrolled sequentially until the target sample size was achieved. The inclusion criteria were adults aged 18 to 59 years diagnosed with T2DM, with or without DPN. Individuals with chronic kidney disease, liver cirrhosis, stroke, Alzheimer's disease, allergic disorders, rheumatoid arthritis, psoriatic arthritis, systemic lupus erythematosus, systemic sclerosis, other autoimmune conditions, leprosy, anemia or thrombocytosis, subjects receiving anti-tuberculosis drugs, cytostatic agents or steroids, as well as those consuming alcohol were also excluded were excluded from the study. In addition, subjects with diabetic foot ulcers classified as Wagner grade >2 or with a history of limb amputation were also not eligible to participate.

Calculation of sample size estimation was performed to ensure adequate statistical power. For group comparison (DPN non-DPN), assuming α=0.05. β=0.2, a standard deviation (SD) of 15 and a minimum detectable difference of 10, the required sample size was 28 per group. For correlation analysis with an expected correlation coefficient of 0.5, therefore a minimum of 24 subjects was required. After adjusting for a 15% anticipated dropout rate, the final minimum sample size was set at 64. A total of 77 subjects were successfully recruited for this study.

Data and Blood Sample Collection

Following the obtained informed consent, demographic and clinical data of subjects, including age, sex, ethnicity, lifestyle factors, duration of diabetes, comorbidities, body mass index (BMI) and neuropathy status assessed using the MNSI, were collected through structured interviews and physical examinations. Subjects were classified into groups with or without DPN based on MNSI results.

Blood sampling procedures were conducted at the outpatient clinics in collaboration with the Prodia Clinical Laboratory, Medan. Five mL of venous blood samples were collected from each subject after an overnight fast to measure serum NGF, HbA1c, glucose, and insulin levels, from which HOMA-IR and HOMA-β indices were subsequently calculated.

NGF Measurement

Blood samples for NGF analysis were processed immediately or stored at 2–8°C for no longer than 24 hours for long-term storage samples were frozen at –20°C or –80°C while avoiding repeated freeze-thaw cycles. Serum was obtained by collecting blood in serum tubes, allowing clot formation for 30–60 minutes, followed by centrifugation. The serum samples were then aliquoted and stored at –20°C or –80°C until analysis, while avoiding repeated freeze–thaw cycles. Standard reagents were prepared by dilution to generate a standard curve. and detection reagents were freshly diluted according to the protocol. The Enzyme-linked immunosorbent assay (ELISA) procedure involved adding standards and samples to wells. incubating at 37°C for 90 minutes, followed by the addition of detection reagents with multiple wash steps. The enzymatic reaction was developed using TMB substrate and stopped with stop solution. and absorbance was measured at 450 nm, NGF concentrations were determined based on the standard curve and adjusted for dilution factors. Serum NGF levels were measured using a commercial Human NGF ELISA kit (Cat. No. abx050171; Abbexa, Cambridge, UK; 2024) with a sensitivity of 9.38 pg/mL and a detection range of 15.6–1000 pg/mL. This ELISA assay was performed in duplicate, and absorbance was measured using a standard microplate reader (18), and performed at Prodia Clinical Laboratories, Jakarta.

Glucose, HbA1c and Insulin Levels Measurements

Fasting plasma glucose (FPG) and 2-hour postprandial plasma glucose (2HPP) were determined using the enzymatic hexokinase method. For FPG, venous blood samples were collected after an overnight fast of 8–12 hours, while 2HPP samples were obtained 2 hours after the start of a standard meal. Blood was collected and plasma was separated within 60 minutes to ensure sample stability prior to analysis. HbA1c levels were measured with high-performance liquid chromatography (HPLC). The whole blood samples collected in ethylenediaminetetraacetic acid (EDTA) tubes were used for analysis without prior plasma separation.

Meanwhile, the fasting insulin concentrations were assessed using chemiluminescent immunoassay (CLIA) which was performed on an automated immunoassay analyzer. Serum samples for insulin measurement were obtained from blood collected in plain or serum-separator tubes and centrifuged within 60 minutes. This method employs monoclonal antibodies specific to human insulin in a sandwich immunoassay format, with detection achieved through a chemiluminescent substrate that generates light intensity proportional to insulin concentration. These assays were performed in duplicate and analyzed at Prodia Clinical Laboratories, Medan.

HOMA-IR and HOMA-β Calculation

After FPG and insulin levels were measured, HOMA-IR and HOMA-β were calculated. The homeostatic model assessment indices were then calculated using standard formulas, with HOMA-IR defined as [fasting glucose (mmol/L)×fasting insulin (μIU/mL)]/22.5 and HOMA-β as [20×fasting insulin (μIU/mL)]/[fasting glucose (mmol/L)–3.5].

MNSI Screening

Peripheral neuropathy screening using the MNSI score comprised two components: a questionnaire and a physical examination. The questionnaire included 15 yes/no items assessing symptoms such as foot pain, numbness, and temperature changes with a maximum score of 13 based on symptom relevance. Subjects completed the questionnaire independently after receiving instructions.

The physical examination involved inspection of the feet for abnormalities such as dry skin, calluses, ulcers or deformities. Vibration sensation was tested using a 128 Hz tuning fork applied bilaterally to the great toes. Ankle reflexes were assessed with a reflex hammer, and pressure sensation was evaluated using the Semmes–Weinstein 10-gram monofilament applied to the dorsal surface of the great toe. Examination findings were systematically recorded and subjects requiring further management were referred accordingly. The MNSI instrument had been validated for use in the Indonesian population.(14)

Statistical Analysis

Data normality was assessed using the Kolmogorov–Smirnov test. Continuous variables were expressed as mean±SD for normally distributed data or as median (minimum–maximum) for skewed data. To evaluate the relationships between serum NGF levels, MNSI scores, HOMA-IR and HOMA-β. Pearson or Spearman correlation tests were applied according to data distribution. All statistical analyses were performed using SPSS Statistics version 25.0 (IBM Corporation, Armonk, NY, USA) with a significance level set at $p<0.05$.

Results

No Significant Differences in NGF and Metabolic Parameters between DPN and non-DPN Groups

A total of 77 subjects with T2DM were enrolled from the Endocrinology Outpatient Clinic at RSUP H. Adam Malik, Medan. Based on the MNSI, subjects were categorized into two groups, which were 37 subjects with DPN and 40 subjects without neuropathy. The full master dataset (n=77), containing raw values of NGF, MNSI scores, HbA1c, HOMA indices, and relevant clinical variables used in the analysis are presented in the Supplementary 1. No statistically significant differences in demographic or clinical characteristics were observed between groups, including age distribution, BMI, duration of diabetes and type of diabetes treatment (all $p>0.05$). For instance, 43.2% of DPN subjects and 40.0% of non-DPN subjects were in the 55–59-year age group. Class I obesity, which was defined as BMI 30.0–34.9 kg/m², was observed in 43.2% of the DPN group and 35.0% of the non-DPN group, with no significant difference between groups ($p=0.478$). Insulin therapy was used by 55.6% of the DPN group and 37.5% of the non-DPN group ($p=0.116$) (Table 1).

Table 1. Demographic characteristics of study subjects based on MNSI results in T2DM subjects.

Demographic Characteristics	Neuropathy		*p*-value
	Yes (n=37)	No (n=40)	
Sex, n (%)			0.220[a]
Male	13 (35.1%)	9 (22.5%)	
Female	24 (64.9%)	31 (77.5%)	
Age Group, n (%)			0.918[b]
<40 years	1 (2.7%)	2 (5.0%)	
40–44 years	4 (10.8%)	3 (7.5%)	
45–49 years	6 (16.2%)	9 (22.5%)	
50–54 years	10 (27.0%)	10 (25.0%)	
55–59 years	16 (43.2%)	16 (40.0%)	
BMI Category, n (%)			0.754[b]
Underweight	0	1 (2.5%)	
Normal	5 (13.5%)	4 (10.0%)	
Overweight	7 (18.9%)	8 (20.0%)	
Obesity I	16 (43.2%)	14 (35.0%)	
Obesity II	9 (24.3%)	13 (32.5%)	
Duration of DM, n (%)			0.437[b]
<6 years	21 (58.3%)	30 (75.0%)	
6–10 years	9 (25.0%)	6 (15.0%)	
11–15 years	5 (13.9%)	3 (7.5%)	
16–20 years	1 (2.8%)	0	
>20 years	0	1 (2.5%)	
DM Therapy, n (%)			0.171[b]
Oral agents	15 (41.7%)	25 (62.5%)	
Insulin	20 (55.6%)	15 (37.5%)	
Combination	1 (2.8%)	0	

[a]Tested with Chi-Square test; [b]Tested with Kruskal-Wallis test.

HbA1c was Significantly Higher in DPN, while Other Metabolic Parameters Showed No Differences

The biochemical and metabolic profiles of both groups, including FPG, 2HPP, HbA1c, HOMA-β and HOMA-IR were summarized in Table 2. There were no statistically significant differences in FPG, PPG, HOMA-β or HOMA-IR values between the DPN and non-DPN groups (p>0.05). However, a significant difference was observed in HbA1c levels, which were higher in the DPN group (mean: 9.53%) compared to the non-DPN group (median: 7.85%), with a p=0.014. Although median FPG and PPG levels were elevated in both groups, the differences were not significant.

Neuropathy Assessment by MNSI Showed No Significant NGF Differences between Groups

Neuropathy assessment using the MNSI demonstrated a median score of 5 (range: 0–11) for MNSI part A and 1 (range: 0–7) for MNSI part B. The prevalence of neuropathy was 14.3% based on MNSI part A, 13.0% based on part B, and 20.8% when both parts were combined (Table 3). Serum NGF concentrations were lower in the DPN group, with a median value of 3.68 pg/mL, compared to 4.01 pg/mL in the non-DPN group. However, this difference was not statistically significant (Table 4).

Although the results of ELISA analysis showed a detection range of 15.6–1000 pg/mL, the manufacturer also indicated a sensitivity of 9.38 pg/mL. The measured NGF values in current study subjects were within the sensitivity threshold but below the linear detection range, which indicates very low serum NGF levels. These findings were consistent with previous reports in T2DM patients, suggesting widespread subclinical neurotrophic impairment. Therefore, the NGF data in this study should be interpreted as relative comparisons rather than absolute quantifications.

NGF Level Has Significant Negative Correlations with HOMA-IR, HOMA-β, and MNSI Part B Scores

Spearman correlation analysis revealed no significant associations between serum NGF levels and HbA1c, fasting plasma glucose, or postprandial glucose, either in the overall population or within the DPN subgroups. However, NGF level was shown to had significant inverse correlations with both HOMA-IR (r=–0.263, p=0.021) and HOMA-β (r=–0.316, p=0.005). The negative correlation between NGF and HOMA-β indicates that individuals with higher NGF levels tended to have lower estimated β-cell activity. This finding did not imply β-cell dysfunction; rather, it may reflect a compensatory downregulation of insulin secretion or complex neuro–metabolic interactions in the context of chronic hyperglycemia and neuropathic changes. These findings were summarized in Table 5 and visualized in Figure 1.

Additionally, NGF levels were significantly correlated with MNSI Part B scores (p=0.032), suggesting a potential link between physical examination findings of neuropathy

Table 2. Glycemic profile characteristics in type 2 diabetes mellitus subjects based on neuropathy status.

Laboratory Parameters	Neuropathy		p-value
	Yes (n=37)	No (n=40)	
FBG, n (%)			0.378[a]
Normal	13 (35.1%)	18 (45.0%)	
High	24 (64.9%)	22 (55.0%)	
PPG, n (%)			0.539[a]
Normal	15 (40.5%)	19 (47.5%)	
High	22 (59.5%)	21 (52.5%)	
HbA1c, n (%)			0.153[a]
Controlled	6 (16.2%)	12 (30.0%)	
Uncontrolled	31 (83.8%)	28 (70.0%)	
HOMA-β, n (%)			0.528[b]
<70%	15 (40.5%)	21 (52.5%)	
70–150%	9 (24.3%)	9 (22.5%)	
>150%	13 (35.1%)	10 (25.0%)	
HOMA-IR, n (%)			0.699[a]
<2.6	7 (18.9%)	9 (22.5%)	
≥2.6	30 (81.1%)	31 (77.5%)	

[a]Tested with Chi-Square test; [b]Tested with Kruskal-Wallis test.

Table 3. MNSI examination results.

MNSI Score Category	Median (Min–Max)	n (%)	Group
MNSI A >7	8 (7.0–10.0)	11 (14.3%)	Neuropathy
MNSI B ≥2	3.25 (3.0–4.0)	10 (13.0%)	Neuropathy
MNSI A & B Positive	—	16 (20.8%)	Neuropathy
MNSI A ≤7	2 (0.0–6.0)	—	Non-Neuropathy
MNSI B <2	0 (0.0–2.0)	40 (51.9%)	Non-Neuropathy

MNSI A = questionnaire component; MNSI B = physical examination component; Neuropathy = MNSI A >7 and/or MNSI B ≥2.

Table 4. Differences in glycemic and NGF profiles based on MNSI results.

Laboratory Parameters	Neuropathy		*p*-value
	Yes (n=37)	No (n=40)	
FBG (mmol/L)	8.94 (4.39-20.11)	7.35 (4.72-20.61)	0.251
PPG (mmol/L)	14.24 ± 6.23	11.63 (5.27-25.96)	0.185
Fasting Insulin (pmol/L)	93.75 (14.58-1605.35)	87.92 (20.83-1527.56)	0.578
HOMA-IR	5.6 (0.8–115.9)	4.8 (0.7–170.9)	0.389
HOMA-β	103.3 (5.3–2981)	69.4 (6.4–1330.6)	0.610
HbA1c (%)	9.53 ± 2.52	7.85 (5.8–11.7)	0.014*
NGF (ng/L)	3.68 (3.01–47.72)	4.01 (3.1–40.89)	0.162

*$p<0.05$ considered statistically significant. Statistical comparison was performed using the Mann–Whitney U test.

and NGF levels. No significant associations were found between NGF and MNSI Part A or the combined MNSI total scores (Table 6).

Discussion

In this study, no significant differences were found in demographic factors such as age, sex, or BMI between subjects with and without DPN (Table 1), minimizing the risk of confounding. This is consistent with previous studies where neuropathy was independent of age and sex distribution in well-controlled cohorts.(19–21) Likewise, diabetes duration did not differ significantly between groups, suggesting that factors beyond disease duration, such as poor glycemic control, may influence neuropathy onset.(22,23)

Regarding metabolic parameters, no differences were observed in FPG, 2HPP, HOMA-IR, or HOMA-β between groups, which may reflect heterogeneity in therapy or glycemic variability. In contrast, HbA1c was significantly higher in the DPN group, reinforcing the established role of chronic hyperglycemia in neuropathy via oxidative stress and advanced glycation end-products (AGEs).(24,25)

Although serum NGF levels tended to be lower in DPN, the difference was not significant (Table 4). However, the finding that all participants had NGF levels below the reference cut-off (<11 pg/mL) suggests widespread subclinical neurotrophic impairment. This supports the idea that NGF measurement may complement MNSI in detecting early neuropathic changes, even in patients with low MNSI scores.(17,26)

Importantly, NGF showed significant inverse correlations with HOMA-IR and HOMA-β (Table 5), indicating that neurotrophic alterations are associated with broader metabolic dysregulation beyond hyperglycemia. This is in line with mechanistic studies demonstrating that chronic inflammation, oxidative stress, and impaired insulin signaling can reduce NGF support in diabetes.(26–29) The observed correlations strengthen the concept that insulin resistance and β-cell dysfunction contribute to impaired neuronal repair capacity.

Previous research also supports this interpretation. Reduced NGF expression in skin biopsies was linked to small fiber neuropathy and insulin resistance in T2DM patients (30), while other study found lower circulating NGF levels in diabetic subjects compared to controls (31). However,

Table 5. Correlation between NGF levels and metabolic parameters in T2DM subjects.

Group	Parameter	*p*-value*	Correlation (r)
All Subjects (n=77)	HbA1c	0.767	-0.034
	FBG	0.899	0.015
	PPG	0.761	-0.035
	HOMA-IR	0.021	-0.263
	HOMA-β	0.005	-0.316
NDP (n=37)	HbA1c	0.414	0.139
	FBG	0.155	0.238
	PPG	0.490	0.117
	HOMA-IR	0.110	-0.276
	HOMA-β	0.009	-0.425
Non-NDP (n=40)	HbA1c	0.757	-0.051
	FBG	0.507	-0.108
	PPG	0.580	-0.090
	HOMA-IR	0.310	-0.165
	HOMA-β	0.369	-0.146

*Tested with Spearman correlation test.

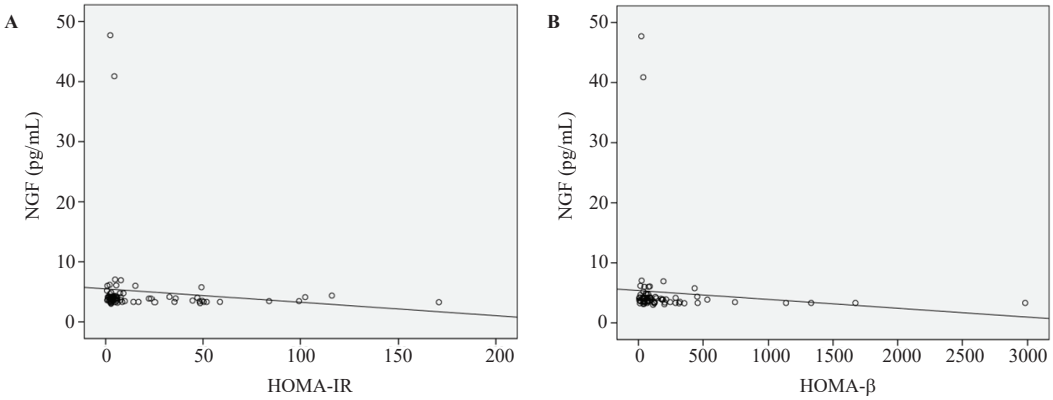

Figure 1. Correlation between HOMA-IR/HOMA-β and NGF levels in T2DM subjects.

conflicting findings have also been reported, suggesting that genetic factors or comorbid inflammatory conditions may modulate NGF regulation.(30,31) This variability highlights the need for longitudinal studies to clarify whether NGF reduction precedes or follows metabolic deterioration.

Furthermore, our finding that NGF was associated with MNSI Part B but not Part A underscores the importance of objective physical examination in neuropathy detection, as subjective symptoms may be nonspecific. This strengthens the argument for combining NGF measurement with validated clinical tools for early neuropathy detection in T2DM. Taken together, NGF levels were not independently predictive of neuropathy status but appear to represent early neuro-metabolic disturbances. From a clinical perspective, measuring NGF alongside MNSI Part B may help detect subclinical neuropathic changes and enable earlier preventive interventions. This study has strengths, including its comparative design and simultaneous analysis of NGF, HOMA indices, and MNSI scores in an underrepresented Indonesian cohort. Limitations include its cross-sectional design, possible influence of insulin therapy on HOMA-β, unmeasured confounders such as vitamin B12 or lipid profiles, and lack of electrophysiological confirmation.

The current findings are in line with prior evidence linking oxidative stress, advanced glycation end-products, and disrupted neurotrophic signaling in diabetic neuropathy (32–35), as well as emerging metabolic therapies involving probiotics and phytochemical antioxidants targeting insulin resistance and inflammation (35–37). Therefore, future longitudinal studies are needed to evaluate whether baseline NGF predicts the progression from subclinical to clinically overt neuropathy in patients with T2DM and to explore the impact of different therapies on NGF. Broader biomarker panels and more sensitive diagnostic modalities, such as nerve conduction studies or corneal confocal microscopy, are recommended to provide a comprehensive understanding of diabetic neuropathy pathogenesis.

Conclusion

This study demonstrated a significant association between serum NGF levels and markers of insulin resistance and β-cell function (HOMA-IR and HOMA-β) in subjects with T2DM, with the strongest correlation observed between NGF and HOMA-β among those with DPN. NGF levels

Table 6. Association between NGF levels and the categorical data of MNSI scores.

Category	n	NGF (pg/mL)	*p*-value
MNSI A >7 (Neuropathy)	11	4.01 (3.5–47.72)	0.180
MNSI A ≤7 (Non-Neuropathy)	66	3.82 (3.01–40.89)	
MNSI B ≥2 (Neuropathy)	10	3.56 ± 0.38	0.032
MNSI B <2 (Non-Neuropathy)	67	3.91 (3.01–47.72)	
MNSI A >7 and B ≥2	16	3.64 (3.01–7.04)	0.269
MNSI A ≤7 or B <2	61	3.91 (3.1–47.72)	

MNSI A = questionnaire component; MNSI B = physical examination component; *Tested with Mann–Whitney test.

also showed a significant association with the MNSI scores, particularly the physical examination component (MNSI-B), highlighting NGF's potential as an early biomarker for DPN. This suggests that serum NGF may serve as a complementary biomarker alongside clinical tools such as the MNSI for early detection of subclinical neuropathic changes in T2DM. Integrating NGF measurement with routine neuropathy screening could help identify high-risk patients earlier, allowing timely preventive interventions.

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Authors Contribution

DS, DL, and SS were involved in concepting and planning the research. DS performed the data acquisition/collection and drafted the manuscript. DL and SS aided in interpreting the results. All authors took parts in giving critical revision of the manuscript and have agreed to the final version of the manuscript.

Conflict of Interest

The authors declare no conflicts of interest.

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