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Early prediction and diagnosis of peripheral neuropathy in type 2 diabetes using biochemical parameters

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Early Prediction and Diagnosis of Peripheral Neuropathy in Type 2 Diabetes Using Biochemical Parameters

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Abstract

Background: **Type II diabetes mellitus is commonly related to diabetic peripheral neuropathy (DPNP), which manifests as a gradual progression of damage to the peripheral nerves after excluding other causes. As initial alterations may lie hidden, focus has moved to easy crude markers. Neuron-specific Enolase (NSE) was chosen since it increases early after axonal injury, Whereas, Nerve Growth Factor (NGF) reflects neurotrophic activity.**

Material and methods: **A case control study was done on 45 cases of DPNP after diagnosing through a nerve conduction study (NCS), 48 diabetics without neuropathy DWNP and 45 healthy individuals. Ages ranged from 35 to 60. Neuropathy subjects were divided according to their DPNP severity into two groups. Sandwich and competitive ELISA determined serum NSE and NGF.**

Results: **A significant increase in NSE levels was observed with DPNP patients compared to controls ($p = 0.037$, OR = 1.587). Patients with DPNP showed significant NGF disappearance ($p = 0.599$, OR = 1.005). Additionally, DPNP patients had higher NSE levels ($p = 0.008$, OR = 1.529) and lower NGF levels ($P = 0.022$, OR = 0.982) compared to DWNP patients. Multiple logistic regression analysis revealed a correlation between study parameters and neuropathy ($p = 0.013$, OR = 1.612) for NSE. DPNP and DWNP groups had AUC values of 0.723, 0.525 for NSE and NGF, respectively, on the ROC curve.**

Conclusion: **Neuron-specific enolase (NSE) biomarker was useful for diagnosis and prediction. Other biochemical criteria for early prediction.**

Aims: **This study explored whether changes in serum NSE and NGF could provide early clues for predicting or diagnosing diabetic peripheral neuropathy.**

Keywords: Diabetic Peripheral neuropathy, NSE biomarker, NGF, Type II diabetes mellitus

Introduction

Diabetic peripheral neuropathy (DPNP) is defined as the onset of damage or dysfunction of the peripheral nerves in individuals with diabetes, after exclusion of other potential causes of neuropathy. Diabetic peripheral neuropathy (DPN) is usually diagnosed using clinical tools such as monofilament testing, vibration perception threshold, and nerve conduction studies. Although these methods are widely used in practice, they are not ideal for detecting early stages of neuropathy. Clinical bedside tests often miss subtle or subclinical nerve damage, and nerve conduction studies require specialized equipment and trained personnel, making them less accessible. More importantly, these diagnostic approaches tend to identify neuropathy only after structural nerve injury has already occurred. Given these impediments, there is a rising interest in developing biochemical markers that may help identify early nerve dysfunction before irreversible damage occurs (Tesfaye *et al.*, 2010). The most common form of DPN is distal symmetrical polyneuropathy (DSPN), which affects both sides of the body in a symmetrical pattern. The risk of developing this complication increases 10 with the duration of diabetes, from

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approximately 10–15 % at the time of diagnosis to more than 50 % after ten years of disease (Zhu et al., 2023). There are approximately one hundred known causes of polyneuropathy; however, the most common are systemic disorders such as autoimmune diseases and hepatic or renal conditions, drug-related causes including certain chemotherapeutic agents, and metabolic disorders such as diabetes mellitus and vitamin deficiencies (McKinley & Perkins, 2019). The methods for diagnosing diabetic neuropathies are still inadequate despite the significant personal and financial burden (Bönhof et al., 2022). Pain, paresthesia, and numbness are common neuropathic symptoms, especially in the calves and feet. Neuropathic symptoms and indicators (deficits) are the basis for the clinical diagnosis of DSPN (Ziegler et al., 2022). Distal symmetrical diabetic polyneuropathy (DSPN) is often underdiagnosed or inadequately treated. Three principal therapeutic approaches are recommended: (i) lifestyle modification, including healthy nutrition, regular physical activity, near-normoglycemic control, and reduction of cardiovascular risk factors such as hypertension; (ii) causal (disease-modifying) treatment using appropriate pharmacological agents; and (iii) alleviation of neuropathic pain symptoms (Ziegler et al., 2021). However, despite available medications, treatment of DSPN continues to be challenging, and many patients do not have access to proper medications; therefore, it is very important to establish better pharmacotherapy as well as new clinical guidelines for its management (Khdour, 2020). Treatment pharmacotherapy should be individualized based on patients, comorbidities, cost, potential drug–drug interactions, and risk of side effects. Opioids are discouraged as they carry high risk for abuse, misuse and harm. Capsaicin and a variety of non-pharmacological approaches are available, with combination therapy possibly required (Pop-Busui et al., 2022). Given these therapeutic limitations, the recognition of consistent biochemical biomarkers is essential for early diagnosis and effective treatment of diabetic peripheral neuropathy. Of all these biomarkers, nerve growth factor (NGF) is of special interest, since it is a crucial protein for the growth and survival of sensory and sympathetic neurons, as well as a modulator of pain in adults. As such, novel analgesics are being designed that directly modulate this protein (Barker et al., 2020a, 2020b). Rat NSE, an enzyme involved in glycolysis, can not only damage and inflame peripheral nerves but also exhibit multitropism and multiprotection for nerve cells (Xie et al., 2024). Despite being mainly present in the cytoplasm, enolase is a multifunctional enzyme. Enolase can translocate to the cell surface induced by certain stimuli and play a role in various pathological pathways such as injury, autoimmune disease, infection, inflammation and cancer upon triggering signals (Isgrò et al., 2015a, 20215b). This study investigates the possibility of using NSE and NGF to predict and diagnose diabetic peripheral neuropathy. The study also investigated whether there is any relationship between the levels of these parameters and the severity of neuropathy.

Methods

Study design

This study was a case-control study comprising 93 male diabetic patients. Once the test of nerve conduction study (NCS) was conducted, the volunteers were divided into two groups: 45 in the first group. Diabetic peripheral neuropathy patients (DPNP), the second group had 48 diabetes without neuropathy patients (DWNP) between September 2024 and January 2025, and the third group included 45 healthy participants as controls. Participants were aged between 35 and 60 years. BMI was calculated for all participants using their body weight (in kilograms) divided by the square of height (in meters) (kg/m^{-2}). This approach is based on the classification outline published by the World Health Organization (World Health Organization, 2000). Persons with the following diseases were excluded from our research: type 1 diabetes, participants under eighteen years of age, cancer, neuropathy due to nerve compression, neuropathy disease and hypertension.

Tests performed in the study

All individuals received a number of evaluations:

- Assessment of glycemic control by measurement of HbA1c.
- Measurement of serum NSE and NGF levels with an ELISA.
- Nerve conduction study (NCS) for classification of neuropathy.
- Weight, height and BMI measurements.

Specimen collection:

Venous blood 5 mL was obtained from both diabetic patients and non-diabetic volunteers.

Samples were kept at room temperature in gel tubes until clotting, and then centrifuged.

Filtration, followed by centrifugation at 3000 × *g* for 10 min. The serum separated and transferred into an Eppendorf tube was stored at −80 °C for future application.

Evaluation of biochemical biomarkers

Serum NSE and NGF levels were determined by ELISA kits provided by BT LAB (Bioassay Technology Laboratory, China). The following commercial kits were used: Human Neuron-Specific Enolase for NSE (Cat. E0937Hu, Lot 202411019; available in 48-well and 96-well formats). NGF concentrations were assessed using the Human Nerve Growth Factor kit (Cat. No. E2102Hu, Lot 202411019; also provided in 48-well and 96-well formats).

All kits were stored at 2–8 °C, and the assays were performed strictly according to the manufacturer's instructions to ensure consistency and reliability of the measurements.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) was utilized to analyze the data. Moreover, many statistical tools are used to perform the comparison and normalize the data. Finally, A p-value of 0.05 or less was deemed statistically significant in all conducted statistical.

Results

Baseline demographic and clinical characteristics

Questionnaire: Table 1 was designed to obtain patient information. The demographic questions included name, age, duration of diabetes, weight, height, HbA1C, blood pressure measurement, smoking status, family history of the disease, and neuropathy symptoms (muscle weakness, paresthesia, numbness, burning sensation, or pain).

Distribution of samples

The results exhibited a non-normal distribution ($p < 0.05$), depending on the distribution tests (Kolmogorov–Smirnov and Shapiro–Wilk tests). Figs. 1 and 2.

The results indicated a significant increase in NSE levels ($p = 0.037$), whereas no considerable differences in NGF ($p = 0.59$) were observed between DPNP patients and healthy control participants (Table 2).

Table 2 shows the median serum levels and ranges of NSE and NGF in the DPNP and control

Table 1. Clinical characteristic feature.

Variable		DPNP Patients	DWNP Patients	Control
Age (Mean ± SD) Year		54.04 ± 8.345	47.44 ± 6.364	44.51 ± 6.291
Duration of DM (years)		13.07 ± 5.594	3.04 ± 2.518	–
HbA1c (Mean ± SD) mmol/mol		9.29 ± 1.93	7.69 ± 1.58	–
Smoking	Yes	12 (26.7 %)	10 (20.8 %)	24 (53.3 %)
	No	33 (73.3 %)	38 (79.2 %)	21 (46.7 %)
Pain sensation	Yes	7 (15.6 %)	–	–
	No	38 (84.8 %)	48 (100 %)	45 (100 %)
Weakness	Yes	9 (20 %)	–	–
	No	36 (80 %)	48 (100 %)	45 (100 %)
Numbness	Yes	40 (88.9 %)	–	–
	No	5 (11.1 %)	48 (100 %)	45 (100 %)
Burning sensation	Yes	25 (55.6 %)	–	–
	No	20 (44.4 %)	48 (100 %)	45 (100 %)
Family history	Yes	31 (68.9 %)	23 (47.9 %)	–
	No	14 (31.1 %)	25 (52.1 %)	45 (100 %)
Education	Primary	27 (60 %)	18 (37.5 %)	12 (26.7 %)
	Secondary	15 (33.1 %)	22 (45.8 %)	19 (42.3 %)
	Bachelor	3 (6.9 %)	8 (16.7 %)	14 (31 %)
Severity of neuropathy	Mild	17 (37.7 %)	–	–
	Sever	28 (62.3 %)	–	–
Body mass index	Normal	11.1 %	8.3 %	17.8 %
	Overweight	40 %	52.1 %	48.9 %
	Obese class I	44.4 %	25 %	28.9 %
	Obese class II	4.5 %	14.6 %	4.4 %

DPNP refers to diabetic patients who developed peripheral neuropathy, while DWNP refers to diabetic patients without neuropathy; the control group includes healthy individuals. Continuous measurements are expressed as mean ± standard deviation (SD), whereas categorical variables are presented as counts with their corresponding percentages. HbA1c values are reported in mmol/mol.

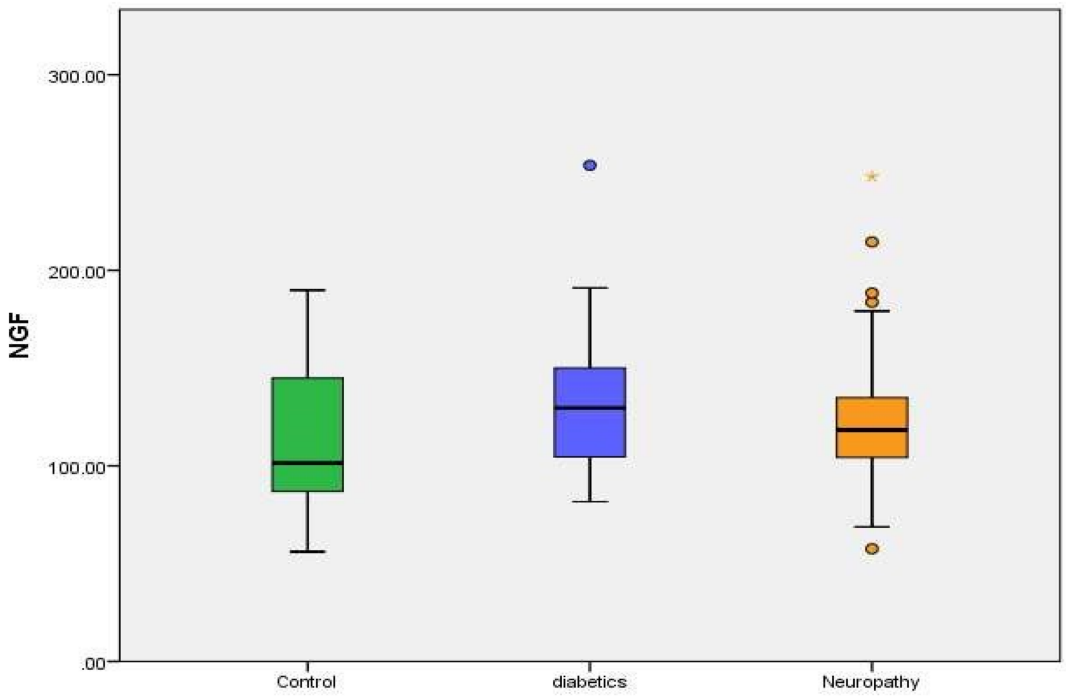

Fig. 1. Box-whisker plots of serum nerve growth factor (NGF) level in neuropathy, diabetes patients, and a healthy group.

groups, along with the p-values, odds ratios (OR), and 95 % confidence intervals (CI) to make the comparison between the groups clear, N = number of samples.

Patients were classified into subgroups: patients with diabetic peripheral neuropathy (DPNP) and patients with diabetes without neuropathy (DWNP). The parameters under study showed a

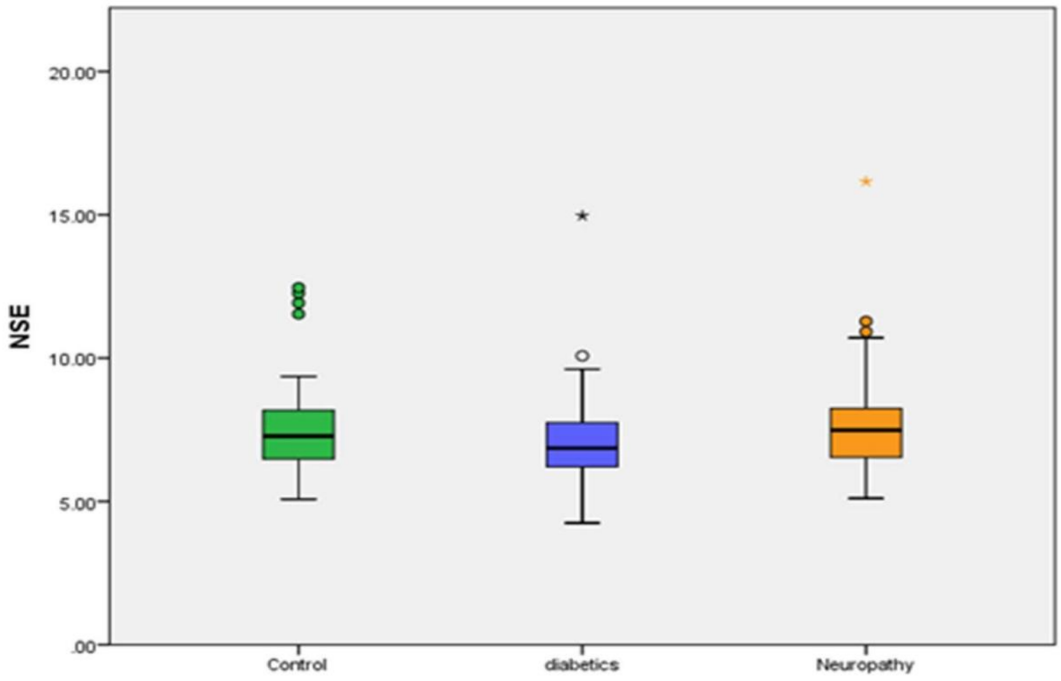

Fig. 2. Box-whisker plots of serum neuron-specific enolase (NSE) level in neuropathy, diabetes patients, and a healthy group.

Table 2. The concentration of NSE and NGF in patients with the DPNP and control groups.

Parameters	Patients with DPNP	Control	P value	OR	95 % Confidence Interval	
	Median (Range) N = 45	Median (Range) N = 45			Lower Bound	Upper Bound
NSE ng/mL	7.48 (7.38)	7.27 (11.5)	0.037	1.587	1.228	2.451
NGF pg/mL	118.36 (190.41)	101.48 (133.67)	0.599	1.005	0.987	1.023

significantly increased value within the levels of NSE ($p = 0.008$) and a decrease in the level of NGF ($p = 0.022$) in patients with DPNP compared with those of DWNP (Table 3).

Table 3 summarizes the median serum concentrations of NSE and NGF in the DPNP and DWNP groups and presents the corresponding odds ratios (OR) with their 95 % confidence intervals (CI). These values help clarify the strength and direction of the association between each biomarker and neuropathy. The OR and CI provide additional context for interpreting the comparison.

The results showed no significant differences ($p = 0.18$, $p = 0.16$) between the two groups of patients when diabetic neuropathy patients were divided into the severe and the mild groups (Table 4).

Multiple logistic regression was used to find the association between the parameters under study and the neuropathy (Table 5).

Binary logistic regression was used to find the association between variables (age, duration, BMI) and disease in Table 6.

The finding from the ROC curve is that NSE has good sensitivity for patients with DPNP compared with those of DWNP (Table 7 and Fig. 3).

Spearman's correlation coefficient (rho) was used to determine if there is any correlation between the parameters under study. The results revealed a moderate positive correlation between NSE and NGF in patients with DPNP (Table 8).

Discussion

Diabetic peripheral neuropathy (DPNP) represents one of the most frequent and disabling complications of type 2 diabetes mellitus. Its clinical impact is considerable, as it can lead to foot 7 ulcers, neuropathic pain, and other sequelae that significantly diminish quality of life. Accordingly, early diagnosis is regarded as the key point for enhancing therapeutic effect. The present study aimed to investigate values of NSE and NGF in the early diagnosis of DPNP. Numbness is the most typical and earliest symptomatic clinical presentation of DPN, or sensory nerve damage, which leads to an elevated risk of foot injury impairment and ulcerations (Hicks and Selvin, 2019; McDermott et al., 2023; Zhu et al., 2024)., neuron-specific Enolase is one of the three enolase isoenzymes found in mammals; it results in the catalysis of 2-phospho-D-glycerate to phosphoenolpyruvate. There are three genetically distinct enolase isozymes in vertebrates: α-enolase,8 found as a ubiquitous form in most tissues; β-isoform, which is exclusive to muscle cells and γ-enolase, specific to neurons. NSE primarily contains γ-subunits and as such represents a highly specific neuronal marker. It is a worthy

Table 3. The concentration of NSE and NGF in the patients with DPNP and DWNP groups.

Parameters	Patients with DPNP	Patients with DWNP	*P* value	OR	95 % Confidence Interval	
	Median (Range) N = 45	Median (Range) N = 48			Lower Bound	Upper Bound
NSE ng/mL	7.48 (12.05)	6.85 (10.72)	0.008	1.529	1.118	2.092
NGF pg/mL	118.36 (190.41)	129.59 (172.04)	0.022	0.982	0.966	0.997

Table 4. The concentration of parameters under study between subgroups of DPNP.

Parameters	Neuropathic patients		P value
	Mild (N = 17)	severe (N = 28)	
	Median (Range)	Median (Range)	
NSE ng/mL	7.41 (3.42)	8.08 (11.05)	0.180
NGF pg/mL	107.95 (126.12)	123.67 (162.65)	0.16

N= Number of Samples, Mild DPNP refers to the early stage nerve impairment, Severe DPNP indicates more advanced stages of the nerve damage.

Table 5. Associations between parameters under study and neuropathy.

Parameters	β	*P* value	OR	95 % Confidence Interval	
				Lower Bound	Upper Bound
NSE ng/mL	0.384	0.013	1.612	1.216	1.901
NGF pg/mL	-0.019	0.343	0.991	0.973	1.010

β: Regression Coefficient, β follows the unit of the corresponding biomarker.

Table 6. Association between (age, duration, BMI) and diabetic neuropathy.

Variables	β	P-value	OR	95 % Confidence Interval	
				Lower	Upper
Age	0.129	<0.001	1.137	1.061	1.219
Duration	0.589	<0.001	1.802	1.430	2.270
BMI	−0.041	0.432	0.960	0.867	1.063

Table 7. Coordinates of ROC curve for serum NSE, NGF.

Parameters	NSE ng/mL	NGF pg/mL
The area under the curve	0.723	0.525
Cutoff value	6.4712	112.44
Sensitivity	77.8 %	64.4 %
Specificity	64.6 %	62.5 %
CI 95 %	0.509–0.738	0.40–0.543
PPV%	67.32 %	61.69 %
NPV%	75.63	65.19 %
Accuracy	70.99 %	63.42 %

marker of neuronal maturation, being generally expressed at late stages of neuronal differentiation in the form of γγ and αγ dimers (Isgrò et al., 2015a, 20215b). After stimulation of immune and supportive glial cells in the context of inflammation, enolase translocates to the cell surface where it assumes a double function: first as an initiator of proinflammatory signaling that recruits further immune effector cells; second, as a degrading enzyme for extracellular matrix with suspected contributions to tissue injury. This emphasizes its importance not only for the metabolic pathways, e.g., glycolysis, but also as a direct participant in inflammatory reactions and tissue damage (Haque et al., 2016a). The present study demonstrated that the NSE level in patients with neuropathy is significantly higher than that of the control group and the diabetic group. Furthermore, the ROC curve was observed to have a high sensitivity with the neuropathy group. These results indicate that NSE could be a potential biomarker for early diagnosis of peripheral neuropathy. This result is consistent with other research in rats on NSE of rat glia cells, suggesting that NSE be used prudently as a neuron-specific marker for studies relating to normal and pathological brain development (Sensenbrenner et al., 1997). Other studies

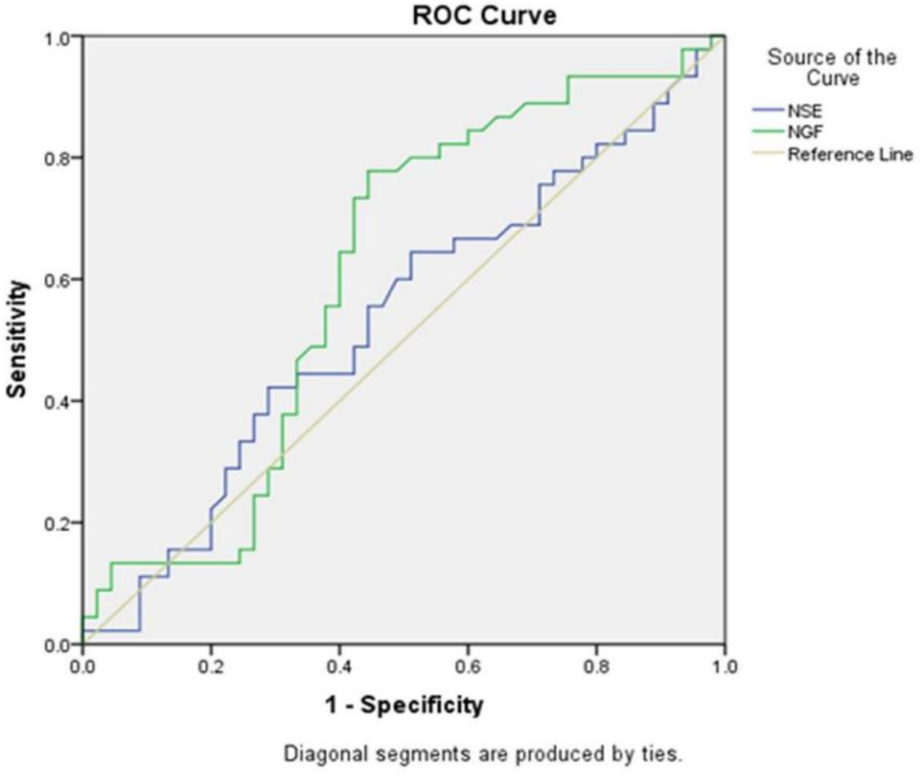

Fig. 3. ROC analyses for NSE, NGF.

Table 8. Correlation between NSE and NGF.

Correlations between NSE and NGF			
		NSE	NGF
NSE	**Spearman's rho**	**1**	**0.596**[a]
	Sig. (2-tailed)		<0.001

Spearman's test shows a clear correlation between NSE and NGF.

The bold font indicates that the value is statistically significant.

[a] Indicating a highly significant result.

hypothesizes that NSE levels in the blood could be a sign of diabetic peripheral neuropathy (DPNP), which may indicate neuronal damage and axonal degeneration, as NSE is primarily localized in neurons and is released into the circulation when neuronal cell membranes are damaged or disrupted (Li et al., 2013; M et al., 2020; Polcyn et al., 2017; Xie et al., 2024). In an interesting study on rats and monkeys, they looked for any changes in NSE in cranial motor neurons after separation of their cell bodies from their axon terminals. Surprisingly, the NSE immunostaining diminished in the damaged neurons from two to ten days post-axonal injury. Significant alteration observed on the tenth day. Twenty days post-nerve crush. The follow-up for NSE staining showed recovery on the operated side and had normalized by the 45th day. The NSE alterations in the monkey mirrored those observed in the rat. In rats, following the severance of the nerve and the relocation of the proximal stump to a regularly innervated muscle to prevent the re-establishment of synaptic connections, the NSE remained diminished for 60 days post-nerve injury. As NSE levels declined during degeneration. The findings indicate that NSE levels in neurons act as a molecular indicator of axonal damage, regeneration, and target reinnervation (Kirino et al., 1983; Haque et al., 2016b; Polcyn et al., 2017; Rossor & Reilly, 2022). The nerve growth factor (NGF) level showed no significant difference when comparing the neuropathic group with the control; it may reflect a limited sensitivity of NGF as a diagnostic biomarker or may be due to other factors, such as the sample size and individual variability. This result disagrees with several studies that observed a decrease in the availability of NGF with neuropathy, which was assumed to possibly result from metabolic abnormalities or being independent of glycemic regulation (Hellweg & Hartung, 1990; Apfel, 1999; Pittenger & Vinik, 2003; Fundaun et al., 2022). A significant decrease in the level 9 of NGF in patients with neuropathy when comparing the neuropathic with the diabetic group; these results may mean that NGF has a role in distinguishing diabetic patients who develop peripheral neuropathy. It is consistent with a prior clinical research which reported the decrease of NGF in patients with peripheral neuropathy and concluded that the deficiency of NGF contributes to the impaired nerve repair (Sun et al., 2018). Nerve growth factor (NGF) acts mainly through 2 different receptors. The high-affinity TrkA channels survival signals favoring neuronal maintenance and survival, while the low-affinity p75 neurotrophic receptor can mediate apoptotic signaling to programmed cell death. Interestingly, NGF can activate both receptor systems by integrating and counteract pro-survival/pro-apoptotic signaling as a function of the cellular context and physiological substrate. The binding of NGF molecules to their receptor(s) takes place at the aC-terminus of TrkA: a region important in transducing downstream signals, which are necessary for the survival of neurons. Any mutation or any deviation in the crystal structure of the aC-terminus region can preclude binding of NGF to its receptors, thus disrupting survival pathways and allowing apoptotic pathways to prevail with possible damage on neurons (Apfel, 1999; Wiesmann & de Vos, 2001). Consistent with the NGF alterations, a recent study revealed that NGF plays a role in healing of injured nerves in diabetic peripheral neuropathy (Li et al., 2020). A great deal of studies in animals and humans demonstrates that NGF is extremely important for altering how we experience pain as adults (Barker et al., 2020a, 2020b). This analysis demonstrates that age and duration of diabetes are associated with the extent of DPN. These results also support that being old is a major risk factor for developing and aggravating of diabetic peripheral neuropathy among persons living with diabetes (Abdissa, 2020; Nagarathna et al., 2020; Wang et al., 2023; Salih et al., 2024). In the oldie, nerve regeneration is an inefficient process and neuronal plasticity significantly reduced. Moreover, longer diabetes duration 6 results in persistent and accumulative nerve damage over time and decreases the repair capacity of nerves (Liu et al., 2019; Lu et al., 2020). The Weak values of serum NGF could be counted with the sensitivity and specificity, thus suggestive that negative result may not use it for diagnosing peripheral neuropathy (Hamoud & Al-Saadi, 2024, 2025).

Conclusion

The research's result demonstrated that NSE can be used as a biomarker for the early detection of 2 peripheral neuropathy. The increased concentration levels of NSE in the serum of patients with

DPNP, can be considered a marker of the disease. Moreover, age and duration are critical risk factors for uncontrolled diabetes, as the regression coefficient values corroborate. More research is necessary to explore the use of biomarkers in diagnosis and treatment. Future research should focus on enhancing neuroprotection in other neurodegenerative disorders.

Ethics

The experimental protocols were approved by the Ethics Committee of University of Karbala, College of Science. All the experiments were performed as per the committee guidelines. All participants were informed about the protocol of the study, and written consent was taken before any blood samples were obtained. The sampling was carried out in Imam Al-Hassan Center for Diabetes and Endocrinology, Karbala. The reference number [007CSE] was allocated to and approved by the study.

Author contribution

Conceptualization: Dr. Narjis, Supervision: Dr. Narjis, Validation: Dr. Narjis, Writing – review & editing: Dr. Narjis, Proofreading: Dr. Narjis; Methodology: Eman, Investigation: Eman, Formal analysis: Eman, Visualization: Eman, Writing – original draft: Eman.

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Conflict of interest

The authors state that the release of this manuscript causes no conflict of interest.

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