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## Research Article

## Evaluation of Neopterin as a Neuroinflammatory Marker for Peripheral Neuropathy in Type 2 Diabetic Patients

Israa Abdelmalik Salem<sup>1,2\*</sup> , Sura Ahmed Abdulsattar<sup>2</sup> , Haider Fadhil Alrubaye<sup>3</sup> 

<sup>1</sup>Al-Karama Teaching Hospital, Baghdad, Iraq; <sup>2</sup>Department of Chemistry and Biochemistry, College of Medicine, Mustansiriyah University, Baghdad, Iraq; <sup>3</sup>Department of Internal Medicine, College of Medicine, Mustansiriyah University, Baghdad, Iraq

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## Abstract

**Background:** Elevation of the marker neopterin is associated with the progression and consequences of diabetes. Although the clinical relationship between the high levels and peripheral neuropathies other than diabetic peripheral neuropathy is unknown, it has been linked to them. **Objective:** To evaluate the difference in serum neopterin levels between diabetic individuals who have peripheral neuropathy and those who do not. **Methods:** This seven-month cross-sectional study at the Diabetic Center began in December 2022 and included 126 patients with the second type of diabetes mellitus. Following verbal consent, the included patients were subjected to neurological and physical evaluations. Along with the blood pressure, the weight and height were noted. Glucose, TG, CH, HDL-c, fasting insulin, and neopterin were all analyzed using serum. Formulas were used to compute BMI, LDL-c, and VLDC. **Results:** When diabetic individuals with peripheral neuropathy were compared to those without, the serum levels of neopterin in the former group revealed a marginally higher level than in the latter, but this difference was not statistically significant. **Conclusion:** Neopterin levels were not altered in diabetic individuals with peripheral neuropathy, indicating that it is not a reliable indicator of the condition.

**Keywords:** Diabetes mellitus; Inflammation, Michigan Neuropathy Screening Instrument, Nerve conduction study, Neopterin, Peripheral neuropathy.

### تقييم النيوبترين كعلامة التهابية عصبية للاعتلال العصبي المحيطي في مرضى السكري من النوع الثاني

#### الخلاصة

**الخلفية:** يرتبط ارتفاع النيوبترين بتطور مرض السكري وعواقبه. على الرغم من أن العلاقة السريية بين المستويات العالية واعتلالات الأعصاب الطرفية بخلاف الاعتلال العصبي المحيطي السكري غير معروفة، فقد تم ربطها بها. **الهدف:** تقييم الفرق في مستويات النيوبترين في الدم بين الأفراد المصابين بالسكري الذين يعانون من الاعتلال العصبي المحيطي وأولئك الذين لا يعانون من ذلك. **الطريقة:** بدأت هذه الدراسة المقطعية التي استمرت سبعة أشهر في مركز السكري في ديسمبر 2022 وشملت 126 مريضاً يعانون من النوع الثاني من مرض السكري. بعد الموافقة الشفهية، خضع المرضى المشمولون لتقييمات عصبية وجسدية. جنباً إلى جنب مع تحديد ضغط الدم و الوزن والطول. تم تحليل الجلوكوز و TG و CH و HDL-C والأنسولين الصائم والنيوبترين باستخدام المصل. تم استخدام الصيغ الرياضية لحساب مؤشر كتلة الجسم و LDL-c و VLDC. **النتائج:** عندما تمت مقارنة الأفراد المصابين بالسكري الذين يعانون من الاعتلال العصبي المحيطي مع أولئك الذين ليس لديهم، كشفت مستويات مصل النيوبترين في المجموعة الأولى عن مستوى أعلى بشكل هامشي من المجموعة الأخيرة، لكن هذا الاختلاف لم يكن ذا دلالة إحصائية. **الاستنتاج:** لم تتغير مستويات النيوبترين لدى مرضى السكري المصابين بالاعتلال العصبي المحيطي، مما يشير إلى أنه ليس مؤشراً موثقاً لهذه الحالة.

\* **Corresponding author:** Israa A. Salem, Al-Karama Teaching Hospital, Baghdad, Iraq; Email: [esraaha2000@gmail.com](mailto:esraaha2000@gmail.com)

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## INTRODUCTION

Neuropathy is present in half of the individuals with long-duration diabetes mellitus and affects roughly about 10% of diabetic patients with type 2 in the early course of their diagnosis [1]. The elevated blood glucose level seen in diabetic patients disrupts the capacity of the neurons to connect, in which case the blood capillary that supplies the neuron with oxygen and nutrients will become weak in addition to insulin resistance and dyslipidemia, causing the loss of axonal vitality along with nerve dysfunction and finally cell death [2]. This in turn indicates the association between the inflammatory process and the development of DPN [3]. Additionally, it has been found that many inflammatory changes are associated with the development of diabetic peripheral neuropathy (DPN) [3]. Neopterin (NP) is an immune system activation biomarker whose concentration is elevated in many inflammatory states due to its production by activated macrophages and monocytes [4,5]. It is created from guanosine triphosphate (GTP) when interferon-gamma (INF- $\gamma$ ) is secreted from T lymphocytes upon identification of the pathogen and injured tissue, which in turn activates GTP cyclohydrolase I (GTPCH I), producing 7,8-dihydroneopterin that, under oxidative stress, yields neopterin, a small molecule also known as the “pteridine molecule” [6-8]. NP is a product of the oxidation of 7,8-dihydroneopterin, and its level reflects the level of oxidative stress during inflammation. It acts as a mediator and modulator of inflammation by inducing antioxidant and anti-inflammatory conditions in addition to the extracellular marker of activated immune cells [9,10]. It provides a potential tool for evaluating the development of different inflammatory disorders [11]. It has been found that the serum concentration of NP is strongly associated with the parameters of glucose metabolism and is closely related to glucose intolerance [12]. Despite the description of NP as a marker of diabetic progression and its complications, along with the marked elevation of their level in peripheral neuropathies other than diabetic peripheral neuropathy (DPN), little is known about its clinical association with DPN [13]. Neural damages that arise due to DM result in the overproduction of several pro-inflammatory molecules by activating local immune cells, altering capillary permeability, and infiltrating peripheral leukocytes [14,15]. Neopterin can be employed as a biomarker for the detection and monitoring of neuroinflammatory disorders [16]. It has been found that elevated NP levels are correlated to the pain that accompanies diabetic neuropathy, attributed to sensory neuron damage and the inflammatory process [17]. This study aimed to find out if the level of NP is affected in patients with T2DM when they get DPN by comparing NP levels among patients using different methods for recognizing DPN presence.

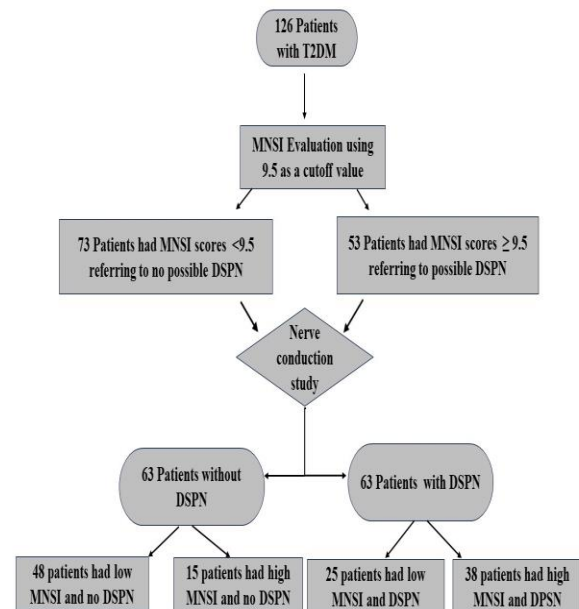
## METHODS

### Study design

This study was intended to be cross-sectional. The studied patients were chosen at random from those who visited the diabetic institute between December 2022 and June 2023. The 126 diabetic patients with type 2 who completed the informed permission first underwent an initial examination in order to investigate whether the diabetic patients had peripheral neuropathy through the use of the Michigan Inspection Instrument for Neuropathy (MNSI) to identify which patients could possibly have DPN. After that, the whole group of patients also underwent an evaluation of their nerve conductivity to verify the presence of DPN at Al-Yarmouk Teaching Hospital in Baghdad, as shown in Figure 1. Patients were comparable in age, BMI, and disease duration.

### Sample collection

A gel separator tube was used for blood collection of about 2 ml; serum was obtained after allowing the blood to coagulate and pass through a centrifuge. Then serum was used for the analysis of sugar in fasting, TG, CH, HDL, and insulin on the same day as blood was drawn. Neopterin was assessed by throwing a frozen serum that was kept for a few months at  $-20^{\circ}\text{C}$  using the ELISA method according to the instructions of the kit-produced company. VLDL-c, LDL-c, and BMI were calculated mathematically. were classified into main groups and subgroups based on the MNSI outcomes beside the nerve investigation results, as shown in Figure 1.



**Figure 1:** The Scheme of the study strategy and progression.

### Exclusion criteria

Type 2 diabetic patients with complications other than peripheral neuropathy were excluded in addition to the other

possible causes of peripheral neuropathy due to other causes other than DM, such as tumors, autoimmune diseases, patients taking neurotoxic medication, smokers and any thyroid gland abnormality. Additionally, patients with other types of diabetes mellitus were excluded.

**Ethical consideration**

According to the document with the number 432 dated December 21, 2022, the local scientific committee at Al-Karkh Directorate of Health in Baghdad province authorized the study protocol. The goals of the research were conveyed to each patient in order to acquire their consent to participate in it. They were made aware of their right to leave the study at any time.

**Statistical Analysis**

For the statistical analysis of this study, Graph Pad Prism (version 9) was used for data analysis and visualization of the data using student's *t*-test and ANOVA methods for data analysis (comparing between two groups and more than two groups, respectively), in addition to the use of Pearson's correlation coefficient to show the associations between the studied parameters [18].

**RESULTS**

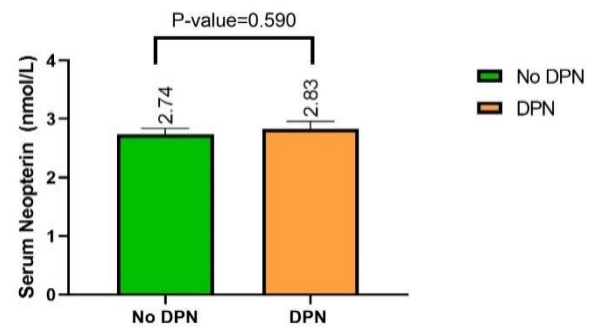
As shown in Table 1, no significant statistical changes were noticed between the two groups regarding patients' clinical features (age, the index of body mass (BMI), and disease duration in addition to the means of serum insulin and lipid profile. However, there was a statistical difference between the two groups regarding fasting blood glucose (FBG) levels.

**Table 1:** The comparison of the clinical features, glycemic and lipid profiles among Type 2 diabetic patients with and without peripheral neuropathy

Parameters	non-DPN (n=63)	DPN (n=63)	p-value
Age (Year)	56.3±1.38	57.9±1.26	0.383
BMI (kg/m <sup>2</sup> )	30.65±0.55	31.42±0.77	0.414
Disease duration (Year)	9.10±0.77	10.78±0.90	0.160
FBG (mg/dL)	165.16±7.68	197.34±9.98	0.012
Insulin (mIU/mL)	9.82±0.91	11.48±1.31	0.302
HOMA-IR	4.13±0.50	5.70±0.75	0.085
TG (mg/dL)	153.02±9.10	163.86±11.20	0.454
Cholesterol (mg/dL)	177.04±4.68	175.23±6.15	0.815
HDL-c (mg/dL)	40.75±1.17	41.15±1.23	0.816
LDL-c (mg/dL)	103.85±4.13	99.46±5.24	0.512
VLDL-c (mg/dL)	31.56±1.96	33.12±2.33	0.614

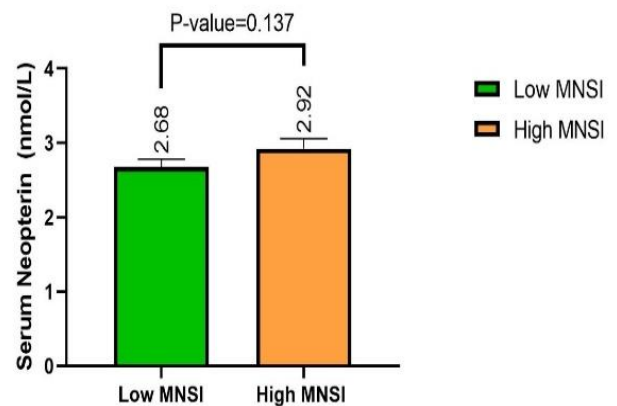
Values are presented as mean±SE. non-DPN: diabetes only; DPN: diabetic peripheral neuropathy.

In this study, no notable changes in the mean of neopterin were noted after comparing diabetic patients who did not have DPN (2.74±0.10) and those who did have DPN (2.83±0.31) (*p*=0.590) as shown in Figure 2.



**Figure 2:** Comparison of the means of serum neopterin levels between patients based on nerve conductivity study.

Additionally, the mean of neopterin in diabetic patients with high marks of MNSI showed a slight elevation (2.93±0.13) compared to those with low marks (2.68±0.10), but it was not statistically notable (*p*=0.137) as shown in Figure 3.



**Figure 3:** Comparison of the means of serum neopterin levels among diabetic patients based on the marks of MNSI.

Regarding the comparison of serum neopterin among patients based on the results of the nerve study and scoring system of MNSI, this study showed no statistically significant differences between the four groups (*p*=0.534), however, in the groups of patients with high scores (had or did not have DPN), the mean was slightly raised, as shown in Table 2.

**Table 2:** The comparison of NP means between different studied subgroups

DPN		non-DPN		<i>p</i>
1 <sup>st</sup> subgroup (n=25)	2 <sup>nd</sup> subgroup (n=38)	3 <sup>rd</sup> subgroup (n=48)	4 <sup>th</sup> subgroup (n=15)	
2.69±0.22	2.92±0.16	2.67±0.11	2.94±0.23	0.534

Values are expressed as mean±SE.

Regarding neopterin associations, this study exhibited a very weak positive association with the physical examination of MNSI in overall diabetic patients, with no associations with the other studied parameters, as shown in Figure 4.

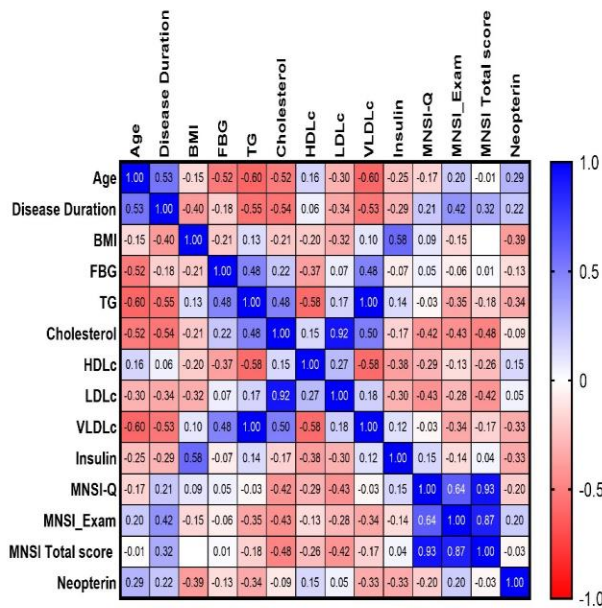


Figure 4: Correlation of neopterin serum levels with the studied parameters showing the regression value.

Additionally, the only association shown in subgroups was the association of serum neopterin with serum HDL-c, which was positive and moderate, as shown in Figure 5.

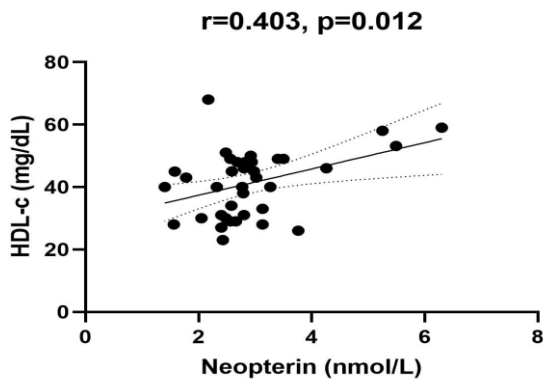


Figure 5: The correlation between serum levels of neopterin (nmol/L) and HDL-c (mg/dL).

DISCUSSION

Damage to the peripheral nervous system's structure has been linked to DPN. This includes microangiopathy of the endoneurium, axonal damage, demyelination, and Schwann cells that don't work right [19]. In DPN, neuroinflammation results from neural damage caused by hyperglycemia and a decrease in oxygen supply that leads to oxidative stress and the production of reactive oxygen species [20]. Normally, immune cells have the ability to produce neurotropic factors that contribute to nerve recovery and remyelination; however, if the cause of neuroinflammation persists, this could result in further damage [21]. Neopterin serum level increased nonspecifically in inflammatory conditions

involving the activation of macrophages and monocytes, such as T2DM; additionally, it can predict the level of oxidative stress [22]. In this study, serum fasting blood glucose levels were statistically elevated in those with DPN, which implicated the effect of hyperglycemia on DPN occurrence [23]. Additionally, this study showed that the prevalence of DPN is more common in male patients, and this finding agreed with the findings of a previous study by Dhillon et al. (2023) [24]. A previous study done in southern Iraq enrolled 4926 type 2 diabetic patients by Mansour et al. (2009) [25], who found that DPN was seen in 13.8% of type 2 diabetic patients, with female patients more likely than male patients. It's noteworthy that no previous study was made on estimating serum neopterin in type 2 diabetic patients with peripheral neuropathy; thus, one of the findings of this study was that it showed no significant statistical changes in the mean of serum NP between the diabetic patients with and without DPN ( $p=0.590$ ) as shown in Figure 2. However, a previous study that measured urinary neopterin concentration found no significant change between diabetic patients with and without DNP [26]. The only previous study involving the assessment of serum NP in DPN involving type 1 diabetic patients (who were between six and seventeen years old with less than five years of disease duration) showed serum neopterin levels were significantly elevated in type 1 diabetic patients with DPN [13]. As it is known, DPN is one of the problems that influence diabetic patients with type 1 and type 2, but in a different way due to the differences in the causal mechanisms of DM, in which type 1 results from immune dysfunction while IR and relative insulin deficiency are responsible for the occurrence of T2DM [27]. This leads to differences in the type of nerve damage and probably the underlying inflammatory process [27,28]. This could explain the differences in the findings of the current study and the previous study with T1DM. Another finding of this study (since no previous studies to our knowledge compared serum NP based on the Michigan method for scoring alone and with nerve conductivity) was that when the Michigan scoring method was used alone to classify patients, no substantial changes were found in the mean serum NP level ( $p=0.137$ ) when comparing the patients according to their scores. Additionally, by comparing the mean serum NP levels between the participants' subgroups, there were no significant differences ( $p=0.534$ ) between the studied subgroups; however, it was slightly elevated in those subgroups with scores ( $\geq 9.5$ ) whether they had or did not have DPN, as shown in Table 1. It is worthy to mention that no previous study compared serum neopterin based on the Michigan scoring method with nerve conductivity. This study also showed that among all participants, NP exhibited a substantial but very weak positive association with Michigan physical examination ( $r=0.185$ ,  $p=0.038$ ). This could probably indicate that the NP could be related to those signs of DPN in diabetic patients since the physical

examination part of the scoring system used to evaluate any abnormalities could affect the lower limbs (feet) and related to the manifestation of DPN, including dry skin, wounds, infections, decreased reflexes, and tremors [29]. Since no previous study was found to compare the findings with, Moreover, among the four subgroups of this study, NP showed no association with any of the studied parameters regarding the 1<sup>st</sup>, 3<sup>rd</sup>, and 4<sup>th</sup> subgroups, while in the 2<sup>nd</sup> subgroup, which included patients who had both DPN and high grades of the scoring system, NP exhibited a moderate positive association with HDL-c ( $r=0.403$ ,  $p=0.012$ ) as shown in Figure 5. To our knowledge, no previous studies were available to compare this result with. However, the association could indicate the presence of additional phenomena related to unidentified pathophysiological defects. Since previous studies showed that in T2DM and as a result of inflammation associated with it, HDL-c suffers from structure and function changes that could be involved in the occurrence of diabetic-related complications [30,31]. However, those changes can also be observed in individuals with high HDL-c levels, according to the finding of Sasso et al., (2019) [32], which indicated HDL-c may be a possible independent indicator of risk in type 2 diabetic patients for diabetic retinopathy; moreover, the same study suggested a complex role could be played by HDL-c in the development of diabetic complications; however, further research was suggested. The patients' hypoglycemic medications may have an impact on the serum level of NP. Based on a study done by Gürcü et al. (2020) [7] the type of medication received by diabetic patients affects the inflammatory process in which type 2 diabetic patients using oral antihyperglycemic medication (as a single therapy or combination therapy) showed the higher levels of NP than those patients with type 1 whom receiving insulin as a therapy, the study attributed this difference to the immunomodulatory effect of the hypoglycemic agent through changes in immune cell activity in which orally recovering medication can cause inflammation and thus led to elevation in serum neopterin level compared to anti-inflammatory effect of insulin, however, no significant differences was recorded between both patients.

### Study limitations

Small number of patients involved in this study leads to small numbers of patients in the subgroups; thus, the finding of this study cannot be generalized to a larger population.

### Conclusion

This study found that serum neopterin did not predict the onset and progression of diabetic peripheral neuropathy. More research (ideally on the genetic level) involving more newly diagnosed DM patients with more biomarkers, as well as the use of study designs other than cross-sectional type, are required.

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### Conflict of interests

No conflict of interest was declared by the authors.

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The authors did not receive any source of fund.

### Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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