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The relationship between vascular endothelial growth factor-A serum level and the severity of diabetic peripheral neuropathy

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Abstract

Background and aims: Diabetic peripheral neuropathy (DPN) is a common microvascular complication in type 2 diabetes mellitus (T2DM). The nerve fibers injury is caused by the interaction between metabolic and vascular factors. Vascular endothelial growth factor (VEGF) is an essential growth factor for vascular endothelial cells. We aimed to investigate the relation between VEGF-A serum level and the degree of DPN.

Results: This cross-sectional study was conducted on 81 patients with T2DM. Based on the combined clinical and electrophysiological assessment, 67 patients (82.7%) were diagnosed with peripheral neuropathy of which 32 patients (39.5%) had subclinical neuropathy, whereas 35 patients (43.2%) were confirmed cases of DPN. Patients with DPN had longer duration of DM and higher values of glycosylated hemoglobin (HbA1c). Although the mean serum VEGF-A level in diabetic patients without neuropathy was higher than that in diabetic patients with DPN, this difference did not reach statistical significance ($P = 0.07$). However, patients with subclinical DPN had significantly higher serum VEGF-A level compared to patients with confirmed DPN ($P < 0.001$).

Conclusion: DPN was found to be a common finding in the studied sample of T2DM patients. Longer duration of DM and poor glycemic control may be risk factors for development of severe DPN. Low VEGF-A serum levels may lead to more severe DPN in patients with T2DM.

Keywords: Type 2 diabetes, Diabetic peripheral neuropathy, Microvascular complications, Vascular endothelial growth factor-A

Background

Diabetes mellitus (DM) is characterized by chronic hyperglycemia that results from defects in insulin secretion, insulin action, or both and is associated with long-term damage, dysfunction, and failure of different organs, including the eyes, kidneys, nerves, heart, and blood vessels [1].

It was estimated that more than 400 million adults had DM in 2019 which is predicted to rise to 700 million by 2045 [2]. The International Diabetes Federation listed Egypt among one of the world highest 10 countries in the number of patients with diabetes with about 8.9 million patients [2].

Type 2 diabetes mellitus (T2DM) is a heterogeneous disease caused by an interaction between multiple factors [3]. These interactions increase the risk for insulin

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resistance, beta cell dysfunction, and obesity and ultimately lead to the development of DM [4, 5].

Chronic exposure to hyperglycemia creates several physiological and pathophysiological changes leading, over time, to dysfunction and failure of many of the body's organs [6].

Diabetic neuropathy (DN) is the most prevalent chronic complication of DM affecting different parts of the nervous system and presents with diverse clinical manifestations [7]. Various forms of neuropathy are categorized under the term of DN, and several types of nerve fibers may be affected including large-fiber sensory and small-fiber sensory, motor, and autonomic. Distal nerves, nerve roots, large nerve trunks, and cranial nerves can be involved in DN as well [8]. The loss of protective sensations as part of diabetic peripheral neuropathy (DPN) predisposes to the development of ulceration which may become aggravated by the continuous exposure of the affected site to repetitive pressure and shear forces caused by ambulation and weight bearing [9].

Factors leading to the development of DPN are not fully understood, and multiple hypotheses have been suggested. The most accepted theory regarding DPN is the multifactorial process that involves several metabolic pathways, triggered by hyperglycemia, which correlate with nerve dysfunction and injury [10, 11].

Vascular endothelial growth factor (VEGF) is a potent angiogenic factor that was first described as an essential growth factor for vascular endothelial cells. In addition to endothelial cells, various tissues can produce VEGF such as macrophages and activated T cells in addition to other cell types [12, 13]. The human VEGF family is composed of five glycoproteins: VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor [14].

VEGF-A is a pivotal regulator of endothelium physiology, which has been demonstrated to be the key growth factor specific for the endothelium. It shows the ability to activate vascular endothelial cell proliferation and enhance vascular permeability, and it aids in survival and migration of the endothelial cells [13].

Hyperglycemia acts as a stimulus to the endothelial cells via increasing oxidative stress and enhancing the production of vasoconstrictor compounds, which lead to hypoxia, which is a potent stimulus of VEGF-A secretion [15]. The secretion of VEGF-A in turn leads to vasculogenesis and angiogenesis, which is also known as vascular permeability factor. The impacts of VEGF on neuronal tissue are not completely determined; it is thought to provide the mechanistic link between hyperglycemia and DM structural and hemodynamic alterations [16].

Little information is available regarding the role of VEGF in the development of diabetic neuropathy. We aimed in this study to investigate the relationship between VEGF-A serum level and the degree of DPN.

Subjects and methods

This cross-sectional study was conducted on 81 patients with T2DM who fulfilled the diagnostic criteria of American Diabetes Association for T2DM [17]. The cases were recruited from the diabetes outpatient clinic. The study was conducted between March 2020 and November 2020.

Exclusion criteria

Patients with history of cancer, chemotherapy, acute stroke or myocardial infarction, peripheral vascular disease, thyroid disease, personal or family history of neuropathy other than DN, history of autoimmune disease, pregnant, and lactating females were excluded from the study [18].

Ethical considerations

All the participants enrolled in the study were informed about the nature of the study, and their written consent for participating was obtained. The study was approved by the local ethical committee, serial number 0106446.

Study procedures

After giving their consent, all study participants were subjected to full demographic and medical history assessment including age, duration of diabetes, type of treatment, symptoms of DPN, and any associated medical conditions in addition to surgical history.

Complete physical examination was done including pulse, blood pressure measurement, complete cardiac examination, complete chest examination, body mass index (BMI) estimation which was calculated as weight/height^2 in kg/m^2, examination of peripheral pulses, and calculation of ankle brachial index was performed to rule out peripheral arterial disease.

Neurological examination

Full neurological evaluation was performed. The Toronto clinical neuropathy score (TCNS) was used to assess the clinical severity of neuropathy [19]. In the TCNS, clinical severity of DPN was recorded by a numerical value ranging from 0 to 19 points, which was calculated by adding symptom score points (the presence or absence of foot pain, numbness, tingling, weakness, ataxia, and upper limb symptoms), reflex score points (bilateral knee and ankle reflexes, each graded as absent, reduced, or normal), and physical examination score points (the presence or absence of pinprick, temperature, light touch, vibration and position sense).

Classifying the severity of DPN was as follows:

- Zero to 5 points indicated no neuropathy.
- Six to 8 points indicated mild neuropathy.
- Nine to 11 points indicated moderate neuropathy.
- Twelve to 19 points indicated severe neuropathy [19].

Vibration perception threshold (VPT) was assessed by biothesiometry. Normal VPT was indicated if it was less than 25 V and altered VPT indicated if it was more than 25 V [20].

Nerve conduction studies

A total of 10 sensory and motor nerves were assessed in 3 limbs, which included bilateral sural and superficial peroneal sensory nerves, bilateral deep peroneal and posterior tibial motor nerves, and left ulnar sensory and motor nerves. The peak sensory latency, nerve conduction velocity and sensory nerve action potential amplitude of the sensory nerves and the distal latency, nerve conduction velocity and compound muscle amplitude of the distal segment of the motor nerves were compared to those of age- and sex-matched healthy controls as reference values to normality in our lab.

The quantification of the severity of the neuropathic findings was done using the electrophysiological assessed severity score (EPHAS) which was adopted and validated by Hidasi et al. [21] where each nerve was given a score of 0 (normal nerve compared to control values) to 7 (unobtainable response). The EPHAS of DPN was determined by a value ranging from 0 to 70 points, which was calculated by summing up the sensory and motor nerve scores of the 10 nerves in each patient. An EPHAS of 0 point was awarded when the parameters in all the studied nerves were normal, whereas a maximum of 70 points was awarded if there was no response in all of the studied nerves.

The EPHAS was considered mild if the score was less than 25 points, moderate if between 25 and 40, and severe if more than 40. A score of 0 reflected no neuropathy detected by electrophysiological methods.

Combined neuropathy grade [22]

The electrophysiological assessed severity score together with the Toronto clinical neuropathy score was used to determine the combined neuropathy grade [22]. It was determined as follows:

i. Patients were considered to have no neuropathy if they had normal TCNS and normal EPHAS.
ii. Patients were considered to have subclinical neuropathy if they had normal TCNS with abnormal EPHAS.
iii. Patients were considered to have confirmed neuropathy if they had abnormal TCNS with abnormal EPHAS.

Laboratory investigations

Blood sampling was done in the morning (8.00–10.00 am) after an overnight fast of 10 h for assessment of the following: glycosylated hemoglobin (HbA1c), total cholesterol (TC), and serum creatinine. VEGF-A levels were measured using a commercial enzyme-linked immunosorbent assay kit.

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. The Kolmogorov-Smirnov test was used to verify the normality of distribution. Number and percent were used to describe qualitative data. Mean, standard deviation, and range (minimum and maximum) were used to describe quantitative data. Significance of the obtained results (P) was judged at the 5% level.

For normally distributed quantitative variables, Student *t*-test (t) was used to compare between two studied groups, while ANOVA test (F) was used to compare between more than two groups and post hoc test (Tukey) for pairwise comparisons. For abnormally distributed quantitative variables, Kruskal-Wallis test (H) was used to compare between more than two studied groups and post hoc (Dunn's multiple comparisons test) for pairwise comparisons.

For correlation between two abnormally distributed quantitative variables, Spearman coefficient (r_s) was used.

Results

Demographic characteristics and general examination results of the studied patients

This study was conducted on 81 patients with T2DM. The age of studied patients ranged from 32 to 70 years with a mean of 47.28 years. The distribution of females in the sample was 66.7%, while males were 33.3%.

Patients on insulin therapy comprised 55.6% of the studied group, while 44.4% of them were on oral hypoglycemic agents. A total of 43.25% of the patients in the study were hypertensive. Nonsmokers accounted for 86.4% compared to 13.6% smokers. The main characteristics of the studied population are described in Table 1.

Neurological examination, nerve conduction studies, and combined neuropathy grade results

As shown in Table 2, the number of patients diagnosed with DPN by the TCNS was 35 (42.8%) and by the VPT was 21 (25.9). On the contrary, 67 patients were

Table 1 Characteristics of the studied patients ($n = 81$)

	No.	%
Age (years)		
Mean ± SD	47.28 ± 12.9	
Min.–max.	18–70	
Gender		
Male	27	33.3
Female	54	66.7
Duration of diabetes (years)		
Mean ± SD	9.15 ± 7.31	
Min.–max.	0.08–40	
Treatment		
Insulin	45	55.6
Oral	36	44.4
Hypertension		
No	46	56.8
Yes	35	43.2
Smoking		
Nonsmoker	70	86.4
Smoker	11	13.6
BMI (kg/m^2)		
Underweight (< 18)	1	1.2
Normal (18–< 25)	13	16.0
Overweight (25–< 30)	26	32.1
Obese (≥ 30)	41	50.6
Mean ± SD	30.06 ± 5.65	

No. Number, *%* Percentage, *SD* Standard deviation, *min* Minimum, *max* Maximum, *BMI* Body mass index

Table 2 Distribution of the studied patients according to neuropathy assessment ($n = 81$)

	No.	%
VPT		
< 25 (no neuropathy)	60	74.1
≥ 25 (with neuropathy)	21	25.9
Mean ± SD	19.83 ± 17.18	
Toronto score		
No neuropathy (0–5)	46	56.8
Abnormal (6–19)	35	43.2
Mild (6–8)	17	21.0
Moderate (9–11)	12	14.8
Severe (12–19)	6	7.4
Mean ± SD	4.94 ± 4.05	
Electrophysiological score (EPHAS)		
No neuropathy	14	17.3
With neuropathy	67	82.7
Mild	24	29.6
Moderate	33	40.7
Severe	10	12.3
Mean ± SD	23.26 ± 16.68	
Combined neuropathy score		
No neuropathy	14	17.3
With neuropathy	67	82.7
Subclinical	32	39.5
Confirmed	35	43.2

No. Number, *%* Percentage, *SD* Standard deviation, *VPT* Vibration perception threshold, *EPHAS* Electrophysiological assessed severity score

diagnosed with DPN by EPHAS (comprising 82.7% of the studied subjects), while 14 patients (17.3%) had no neuropathy, which was higher in comparison with the clinical neuropathy diagnosis and the VPT test results.

Using the combined (clinical and electrophysiological) method of neuropathy assessment, 67 patients were diagnosed with peripheral neuropathy of which 32 patients had subclinical neuropathy, whereas 35 patients were confirmed cases of neuropathy. Fourteen patients had no DPN.

Laboratory investigations results

The mean HbA1c level of studied patients was 8.74 ± 1.83%, the mean serum creatinine was 1.10 ± 0.55 mg⁄dL, and the mean TC level was 203.59 ± 31.51 mg⁄dL. The mean serum levels of VEGF-A for the studied patients were 224.35 ± 53.63 ng/L.

Comparative results between the 3 subgroups according to the combined neuropathy grade

Patients with confirmed DPN had longer duration of DM and higher values of HbA1c and TC compared with patients without neuropathy, while no difference was observed between the patients regarding BMI. Also, patients with confirmed DPN had higher HbA1c compared to those with subclinical neuropathy, but no difference was found regarding duration of DM, BMI, and TC as shown in Table 3.

Although the mean serum VEGF-A level in diabetic patients without neuropathy (247.94 ± 60.47 ng/L) was higher than that in diabetic patients with DPN "both subclinical and clinical" (219.42 ± 51.22 ng/L), this difference did not reach statistical significance ($t = 1.836$, $P = 0.07$). However, the mean serum VEGF-A levels in patients with subclinical neuropathy (249.76 ± 47.71 ng/L) were significantly higher than in patients with confirmed DPN (198.47 ± 45.26 ng/L) ($F = 10.443$, $P < 0.001$), Table 4.

Correlation studies between VEGF-A levels and the different studied parameters in patients with DPN

Moreover, among patients with DPN, there was a significant negative correlation between the VEGF-A serum levels and EPHAS ($r_s = -0.514$, $P < 0.001$). Furthermore, a significant negative correlation was also found between serum VEGF-A levels and the Toronto score and VPT

Table 3 Relation between combined neuropathy score with different parameters ($n = 81$)

	Combined categories						Test of sig.	*P*
	No neuropathy		Subclinical neuropathy		Confirmed neuropathy			
	No.	%	No.	%	No.	%		
Duration of DM (years)								
Median	2.0		7.50		10.0		***H*= 16.537***	**< 0.001***
Min.–max.	0.08–20.0		1.0–25.0		1.0–40.0			
Mean ± SD	3.84 ± 5.47		8.27 ± 6.03		11.66 ± 7.76			
Sig. between categories	P_1**= 0.010***,P_2**< 0.001***,$P_3 = 0.073$							
BMI (kg/m^2)								
Median	28.70		28.95		31.95		$F = 0.425$	0.655
Min.–max.	18.30–36.0		20.30–47.60		17.40–40.30			
Mean ± SD	28.75 ± 4.74		30.15 ± 5.89		30.43 ± 5.81			
HbA1c								
Median	7.50		8.0		9.55		***F*= 15.507***	**< 0.001***
Min.–max	6.90–7.90		6.30–11.40		5.40–13.90			
Mean ± SD	7.43 ± 0.34		8.03 ± 1.24		9.75 ± 1.98			
Sig. between categories	$P_1 = 0.489$, P_2**< 0.001***,P_3**< 0.001***							
Total cholesterol								
Median	185.0		206.50		220.0		***F*= 4.210***	**0.018***
Min.–max.	141.0–224.0		130.0–252.0		132.0–272.0			
Mean ± SD.	185.54 ± 23.80		199.97 ± 27.09		212.63 ± 34.33			
Sig. between categories	$P_1 = 0.329$, P_2**= 0.018***,$P_3 = 0.208$							

F F for ANOVA test, pairwise comparison bet. Each 2 groups was done using post hoc test (Tukey). *H* H for Kruskal-Wallis test, pairwise comparison bet. Each 2 groups was done using post hoc test (Dunn's multiple comparisons test. *P p*-value for comparing between the different categories. P_1*p*-value for comparing between patients without DPN and patients with subclinical DPN. P_2*p*-value for comparing between patients without DPN and patients with confirmed DPN. P_3*p*-value for comparing between patients with subclinical DPN and patients with confirmed DPN

No. Number, *%* Percentage, *DM* Diabetes mellitus, *BMI* Body mass index, *HbA1c* Glycosylated hemoglobin, *SD* Standard deviation, *sig*. Significance, *min* Minimum, *max* Maximum

*Statistically significant at $P \leq 0.05$

Table 4 Comparing between VEGF-A levels in the 3 subgroups according to the combined neuropathy grade ($n = 81$)

	Combined categories			Test of sig.	*P*
	No neuropathy	Subclinical neuropathy	Confirmed neuropathy		
VEGF-A levels					
Median	245.3	246.25	210.2	***F*= 10.443***	**< 0.001***
Min.–max.	104.2–326.6	166.1–336.1	107.2–288.7		
Mean ± SD	241.38a ± 57.52	249.76a ± 47.71	198.47b ± 45.26		

F F for ANOVA test, pairwise comparison bet. Each 2 groups was done using post hoc test (Tukey)

VEGF Vascular endothelial growth factor, *min* Minimum, *max* Maximum, *SD* Standard deviation, *sig*. Significance

*Statistically significant at $P \leq 0.05$

($r_s = -0.456$, $P < 0.001$, $r_s = -0.375$, $P = 0.001$, respectively) among them.

Discussion

Diabetic neuropathy is the most common microvascular complication in DM [7, 22]. DN is a leading cause for morbidity and disability due to foot ulceration, gait disturbance, amputation, and fall-related injury which lowers the quality of life and increases diabetes associated health costs [22–26].

From the 81 patients studied with T2DM, 43.2% had clinical DPN, and 39.5% of them had subclinical neuropathy, with a total of 82% indicating very high prevalence of DPN among patients with T2DM. These results are much higher than those of various previous studies [27–29]. In the Action to Control Cardiovascular Risk in Diabetes

trial, DPN was present in 42% of adults with T2DM at baseline [27]. Also, the Bypass Angioplasty Revascularization Investigation 2 Diabetes trial showed that 51% of adults with T2DM had history of DPN at baseline [28]. A recent meta-analysis including twenty-nine studies reported that the estimated prevalence of DPN was 46.5% [29].

Despite its high prevalence, our understanding of the pathophysiology of DPN is incomplete, and the specific mechanisms causing the condition are unknown. Furthermore, no effective disease-modifying pharmacotherapies have been approved for the treatment of DPN. Moreover, until this date, the mainstay of DPN management is controlling its risk factors and managing its complications [7, 30–32].

Among numerous growth factors that are involved in the development of DM microvascular complications, VEGF has gained growing attentions as it was found to have a role in development of diabetic retinopathy (DR) and diabetic kidney disease, where VEGF has been implicated in initiating and worsening both DR and diabetic nephropathy [32–34]. However, there is limited clinical evidence available regarding the link between VEGF and DN as well as the potential role VEGF plays in DPN.

Despite the fact that the results of the current study showed that there was no difference regarding VEGF-A serum levels in patients with neuropathy compared to those without neuropathy, patients with subclinical neuropathy had significantly higher VEGF-A serum levels compared to patients with confirmed DPN. This may suggest that low VEGF-A levels may lead to more severe DPN in patients with T2DM.

Similarly, Deguchi et al. [18] found that levels of VEGF in patients with DM first rise in patients complaining of neuropathic symptoms and then falls in those with disabling DPN. This similarity may be due to the fact that they utilized the same classification system for DPN by Dyck et al. [22] but with some modification. They suggested that VEGF production increases in the early stages of DPN due to nerve regeneration and decreases in established DPN due to the decrease in nerve fiber number with associated degeneration [18].

The findings from our study and those from Deguchi et al. [18] are supported by the loss of intraepidermal nerve fibers with reduction in VEGF expression in patients with DM with increasing neuropathic severity reported by Quattrini et al. [35].

On the contrary, Mahdy et al. [36] found significant serum VEGF elevations in diabetic patients with microvascular complications compared to uncomplicated diabetic patients. In this study, they used clinical and electrophysiological assessment to diagnose DPN, but they grouped all microvascular complications (both DPN and DR) as present or absent. This grouping of microvascular complications dilutes and complicates the results as the role of VEGF in DR and diabetic nephropathy is thought to be harmful [32–34], contrary to its suggested role in DN which is thought to be protective [18, 35].

These discrepancies in the results may be due to the fact that diabetic patients with no neuropathy and subclinical DPN are grouped together, or those with any microvascular complication are grouped together. This faulty classification leads to faulty results or dilution of results as each complication as well as each stage of DPN has distinct pathogenesis. Furthermore the level of VEGF seems to impact the degree of DPN rather than its mere presence or absence.

Additionally, our study was the only one that utilized clinical evaluation combined with nerve conduction studies in the diagnosing of neuropathy, the most reliable and objective method of diagnosing of neuropathy.

To the best of our knowledge, few studies [18, 35] that attempted to examine the relationship between VEGF and degree of DPN were in agreement with our results. Furthermore, Schratzberger et al. [37, 38] reported that axonal loss and myelin degeneration were prevented or reversed, and neural blood flow was preserved at normal levels in VEGF-treated animals. VEGF was also shown to stimulate the migration and prevent hypoxia-induced apoptosis of Schwann cells in vitro, indicating that VEGF could have direct effects on neuronal integrity as well [37, 38].

The exact mechanisms that explain the possible role of VEGF-A in prevention of DPN progression are not fully understood. This may be explained by the fact that ischemia and reduced oxygen tension in the nerves of diabetic patients are thought to be the pathogenetic mechanisms of DN. VEGF-A by inducing neovascularization which enhances blood and oxygen supply to the diabetic nerves may counteract the effects of ischemia induced by hyperglycemia and advanced glycated end products preventing progression of DPN [35, 39].

Limitations of the study

Our study has some limitations; one limitation is the small number of the cases. However, this is due to the fact that we used clinical evaluation combined with electrophysiological studies in diagnosing neuropathy which is more objective and accurate method of diagnosing neuropathy. Also, the cross-sectional design of the study does not confirm the protective role of VEGF-A in DPN progression, and further longitudinal studies will be needed to confirm this finding. Finally, the study population was limited to patients attending diabetes outpatient clinic, which may differ from patients seen by general

practitioners or patients who are not seeking medical care at all.

Conclusion

Diabetic peripheral neuropathy was found to be a common finding in the studied sample of T2DM patients. Longer duration of DM and poor glycemic control may be risk factors for development of severe DPN. Low VEGF-A serum levels may lead to more severe DPN in patients with T2DM.

Abbreviations

BMI: Body mass index; DM: Diabetes mellitus; DN: Diabetic neuropathy; DPN: Diabetic peripheral neuropathy; DR: Diabetic retinopathy; EPHAS: Electrophysiological assessed severity score; F: ANOVA test; H: Kruskal-Wallis test; HbA1c: Glycosylated hemoglobin; r_s: Spearman coefficient; t: Student *t*-test; T2DM: Type 2 diabetes mellitus; TC: Total cholesterol; TCNS: Toronto clinical neuropathy score; VEGF: Vascular endothelial growth factor; VPT: Vibration perception threshold.

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Authors' contributions

All authors have read and approved the manuscript, and all authors have contributed significantly and are in agreement with the content of the manuscript. MB contributed to the idea and collection and analyzed and interpreted the patient data regarding the DPN. TA contributed to the idea, study design, and editing of manuscript. SI handled all laboratory investigation work carried out, interpretation, and data editing. YA contributed to the idea and handled all electrophysiological tests carried out and its interpretation and analysis. WS contributed to the idea, data collection, and clinical assessment of the patients and was a major contributor in writing the manuscript. AE was a major contributor in writing the manuscript and editing. The authors read and approved the final manuscript.

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Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

All participants were informed about the nature of the study, and a written informed consent was taken from all of them. The ethical committee Faculty of Medicine, Alexandria University, approved the study, serial number 0106446. The research was conducted in accordance with the Declaration of the World Medical Association of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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