



Determination of Visfatin Level in Patients with Diabetes and Peripheral Neuropathy as Early Predicted Factor

Haneen Ahmed Mohammed

Department of Chemistry, College of Science for Women, University of Baghdad, Baghdad – Iraq
hanin.ahmed1205a@cs.w.uobaghdad.edu.iq

Kadhim K. Ghudhaib

Department of Chemistry, College of Science for Women, University of Baghdad, Baghdad – Iraq
kadhemkg_chem@cs.w.uobaghdad.edu.iq

Firas Y. Mohsen

International Diabetes Center, University of Al-Mustansiriya, Baghdad-Iraq
Firasaldori@yahoo.com

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Abstract

Background: Peripheral neuropathy represents one of the common diabetic complications in patients with diabetes mellitus type 2 (DMT2). Peripheral neuropathy affects the feet, legs, hands, and arms. It was found that one-third to one-half of diabetics have peripheral neuropathy. Current study aimed to evaluate the level of visfatin in diabetic patient groups with or without peripheral neuropathy in comparison with healthy subjects to know whether visfatin can be applied as predictor factor for this type of disease complications.

Material and Methods: The study included 120 male and female ranging in age from 40 to 97 years old. (40 patients with type 2 diabetes, 40 patients with diabetic peripheral neuropathy, and 40 healthy people served as the control group.) All of the diabetes patients had a verified diagnosis (type 2). During the period from October-2021 to December 2021, the patients were assessed at the National Diabetes Center, Al-Mustansiriya University in Baghdad. Visfatin levels were tested using the ELISA technique, and HbA1c was assessed using Cobas C111.

Results: results showed

In patients, HbA1C levels are significantly higher ($p \leq 0.05$) than in controls. Males and females with DPN and DM have greater Visfatin mean values than the control group.

Conclusions: Visfatin levels are strong indications for early diagnosis of diabetic neuropathy in both males and females, according to the current study.

Keywords: Peripheral neuropathy (DPN), Visfatin, diabetes mellitus (DM).

1.Introduction

Diabetes complications such as periodontitis and nephropathy have recently been researched [1-6]. Previous studies on diabetic neuropathy and osteoporosis issues have also been conducted [7-9]. Diabetes type 2 starts when the pancreas doesn't produce enough insulin or when the body can't effectively use it. Insulin controls blood sugar. Hyperglycemia, or high blood glucose, is a typical complication of untreated diabetes that damages the neurons and blood vessels [10]. Type 1 diabetes, formerly termed insulin-dependent diabetic, is identified by insufficient insulin production and daily insulin delivery. Type 2 diabetes, formerly called non-insulin-dependent is caused by poor insulin use. Type 2 diabetes is most common. Gestational diabetes is "hyperglycemia with blood glucose levels above normal but below diabetes diagnostic levels" [11].

Diabetes causes peripheral neuronal damage, such as diabetic neuropathy, a major chronic consequence of diabetes with different clinical symptoms [10,11]. High blood glucose can harm nerve-supplying blood vessels over time. This blocks nerve nutrition. Nerve fibers might get injured or vanish [10,11,12].

Even with current care, DN prevalence is high [1]. DNs have been found in prediabetic individuals and, more recently, in type 1 and type 2 diabetic kids [11,12,13]. Diabetes' significant and long-term effects, neuropathy, are a burden on human health, with diabetic neuropathy being the most frequent kind. [14]. Peripheral neuropathy symptoms include slow onset numbness, prickling, or tingling in feet or hands, which can progress to legs and arms. Extreme sensitivity to touch, jabbing, throbbing, or scorching pain Pain during actions that shouldn't produce discomfort, such foot pain while weighted or beneath a blanket. Coordination issues, falling, Weakness, feeling like you're wearing gloves or socks, Motor nerve damage causes paralysis [15].

Visfatin, also known as nicotinamide phosphoribosyltransferase (NAMPT) or pre-B cell colony-enhancing factor (PBEF), regulates a number of physiological and pathological processes [15]. Visfatin levels have been linked to inflammation and endothelial dysfunction in metabolic disorders. Visfatin has also been linked to cardiovascular disease. Visfatin plasma levels may induce vascular inflammation and plaque instability [16,17]. Patients with type 2 diabetes or metabolic syndrome had higher blood Visfatin levels and carotid atherosclerosis [18,19]. Visfatin levels in type 2 diabetic atherosclerotic plaque development or connection with damaged vascular area are unknown. Visfatin is nicotinamide phosphoribosyl transferase (NAMPT). In mammals, intracellular NAMPT catalyses the rate-limiting step in the salvage route leading to NAD⁺ production [19]. NAMPT condenses nicotinamide and 5-pyrophosphoribosyl-1-pyrophosphate to make NMN and inorganic pyrophosphate (PRPP). NMN is converted to NAD [19]. Obesity and type 2 diabetes are separate atherothrombotic disease risk factors. Visfatin may be a biomarker of metabolic-related cardiovascular problems [19].

1.1. Diabetes Mellitus (DM):

Diabetes is characterized by elevated blood glucose levels and changes in lipid, carbohydrate, and protein metabolism due to aberrant insulin synthesis, insulin function, or both. [20] Type 1, type 2, MODY, gestational diabetes, neonatal diabetes, and secondary causes induced by endocrinopathies, steroid use, and other variables are all kinds of diabetes. Type 1 and Type 2 diabetes are caused by inadequate insulin synthesis and/or action (T2DM). T1DM affects children and adolescents, whereas T2DM affects middle-aged and older persons with persistent

hyperglycemia from poor lifestyle and nutritional choices. T1DM and T2DM have different pathophysiologies, etiologies, symptoms, and treatments. [21]

Diabetes mellitus is one of four non-communicable diseases that demand prompt attention from all major stakeholders, and hyperglycemia is the third biggest cause of early mortality globally [22].

1.2. Diabetes Peripheral Neuropathy (DPN)

Peripheral diabetic neuropathy is sometimes called distal polyneuropathy. We'll call it Peripheral Neuropathy in this Patient Guide. Diabetic peripheral neuropathy is most common. It affects feet, legs, hands, and arms. After branching off the spinal cord in the low back, the nerves to your feet travel down your legs and into your feet. Because nerves to your feet are so long, they are more susceptible to be damaged. Diabetes-related foot abnormalities, infections, ulcers, and amputations can develop from nerve loss. [21]

2. Materials and Methods

The research included 120 men and women ranging in age from 40 to 97 years old. (40 individuals with type 2 diabetes, 40 patients with diabetic peripheral neuropathy, and 40 healthy people served as the control group.) All of the diabetes patients had a verified diagnosis (type 2). During the period from to, the patients were assessed at the National Diabetes Center, AL-University in Baghdad (october-2021 to December 2021).

2.1. Groups of analysis included:

Group 1 (DPN): (40 patients with type 2 diabetes mellitus Peripheral Neuropathy)

Group 2 (DM Type 2): (40 patients with type 2 diabetes mellitus)

Group 3 (Control group): Consisting of 40 healthy people with no history of diabetes and no systemic illness.

2.2. Inclusion criteria:

1. Patients ranging in age from 40 to 97 years.
- 2.Type 2 diabetes medical history.
- 3.HbA1c-based diagnostic criteria for type 2 diabetes
- 4.A control group of volunteers was formed using the following criteria:
 - a. Clinically healthy
 - b. Negative for clinical indicators of systemic illnesses
 - c. Negative for diabetes

2.3. Exclusion criteria

The following patients/individuals were removed from the research;

1. physiological conditions such as pregnancy and breastfeeding
2. behaviors such as smoking, drinking, and chewing tobacco
3. Subjects under the age of 40.
4. Those who have had radiation treatment and chemotherapy.

2.4. Blood collection

For individuals with an unknown HbA1c level, five milliliters of venous blood were obtained from the antecubital vein and divided into two halves. Part (1) in gel tube (3ml) samples were allowed to coagulate at room temperature for 30 minutes. . After 10 minutes of centrifugation, the serum was separated and kept in Eppendorf tubes. The first component was utilized to rapidly identify (Cho, TG, uric acid, HDL,LDL, and VLDL) in serum using an Auto Spectrophotometer;

a clinical chemistry analyzer performs diagnostic tests. The second half was maintained at -20°C to assess Visfatin and Progranulin, which were evaluated using an ELISA kit manufactured by My Biosource, USA . Part (2) test tube containing anticoagulant for HbA1c measurement by Cobas C111 a device (2 ml). BMI was determined for both the patient and control groups.

Statistical analysis

Data uploading was a daily process from the participant’s case sheets into the software of Microsoft Office Excel 2013., analysis of data was done by using Statistical Package for Social Science version 9.1th (SPSS), (Cary. N.C. USA.). Chi-square, Least Significant Difference (LSD) test was employed to compare the means.

3. Results

The age of all patients with Diabetic Peripheral Neuropathy, Diabetic Mellitus and healthy control groups ranged from (40-97) years and the mean ±SD age was 57.43±10.13 years. Fifty-eight 58(48%) were female and sixty-two 62 (52%) of males, as illustrated in **Table 1, Figure 1**, respectively.

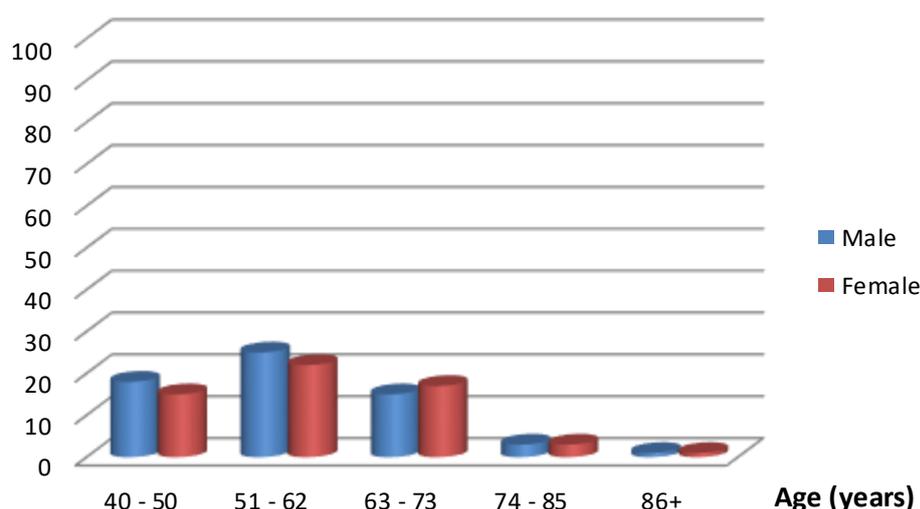


Figure 1. Age and sex of all DPN, DM2 and healthy

Table 1. Demographic data of Diabetic Peripheral Neuropathy, Diabetic Mellitus and Healthy Control

Gender		Study groups			Total	P. value
		Diabetic Peripheral Neuropathy No. (%)	Diabetic Mellitus No. (%)	Healthy Control No. (%)		
Female		18 (31.0%)	20 (34.5%)	20 (34.5%)	58 (48%)	0.875 ^{NS}
Male		22 (35.5%)	20 (32.3%)	20 (32.3%)		
Total		40 (100.0%)	40 (100.0%)	40 (100.0%)	120 (100.0%)	
Age	Mean ±SD Rang	60.50±11.22 (41-97)	57.60 ±7.49 (42-87)	54.20 ±11.69 (40-82)	57.43±10.13 (40-97)	0.154 ^{NS}
Chi-Square= 0.267 * (P≤0.05), ** (P≤0.01).						

Table (2) shows the mean values of both age and BMI for males and females in the studied groups in the present study. The results revealed no considerable differences in age of diabetic peripheral neuropathy, diabetic mellitus and healthy control groups (60.50 ± 11.22) (59.52 ± 8.90) (55.37 ± 11.25) (LSD=4.857) ($p=0.072$), respectively.

But the mean values of BMI for males and females is a highly significant difference in the healthy controls group compared with patients with diabetic peripheral neuropathy and patients with diabetic Mellitus group, (23.89 ± 2.50)(29.82 ± 7.06)(29.54 ± 4.40) (LSD=2.223) ($p=0.0001$), respectively. As illustrated in the **Table (2)**.

Table 2. Mean of Age and BMI of males and females in all the studied groups

Groups	Mean \pm SD	
	Age (year)	BMI (kg/m ²)
Diabetic Peripheral Neuropathy (No=40)	60.50 \pm 11.22 a	29.82 \pm 7.06 a
Diabetic Mellitus (No=40)	59.52 \pm 8.90 a	29.54 \pm 4.40 a
Control (No=40)	55.37 \pm 11.25 a	23.89 \pm 2.50 b
LSD value	4.857 NS	2.223 **
P value	0.072	0.0001
Means having with the different letters in same column differed significantly. ** (P \leq 0.01).		

Table (3) showed the levels of lipid profile and uric acid in Diabetic Peripheral Neuropathy, diabetic patients and the control group in this study.

Table 3. Mean \pm SE of lipid profile and uric acid tests of all the studied groups in female and male

Group	Diabetic Peripheral Neuropathy (No=40)	Diabetic Mellitus (No=40)	Control (No=40)	LSD (P value)
Cholesterol	181.20 \pm 7.83 a	175.27 \pm 5.89 a	152.47 \pm 3.86 b	17.105 ** (0.0028)
Triglyceride	224.82 \pm 30.19 a	153.95 \pm 9.66 b	113.20 \pm 3.09 b	51.50 ** (0.0002)
HDL	55.65 \pm 3.91	51.77 \pm 2.77	54.87 \pm 3.02	9.16 NS (0.676)
VLDL	45.00 \pm 6.02 a	29.97 \pm 1.83 b	22.60 \pm 0.61 b	10.23 ** (0.0001)
LDL	86.87 \pm 5.90 ab	92.17 \pm 4.97 a	76.90 \pm 3.77 b	13.89 * (0.0313)
Uric Acid	4.85 \pm 0.23	4.42 \pm 0.18	4.48 \pm 0.18	0.566 NS (0.259)
Means having with the different letters in same column differed significantly. * (P \leq 0.05), ** (P \leq 0.01).				

Table (4) shows the levels of Visfatin, and HbA1C of the studied groups in male and female. The mean + SD of Visfatin and HbA1C, respectively, there are highly significant differences

between diabetic Peripheral Neuropathy, diabetic patients and control groups in male and female ($p= 0.0001$), where the mean values for DPN and DM are higher than the control group in Visfatin cumbered with HbA1C. As shown in **Table (4)**.

Table 4. Levels of Visfatin and HbA1C in all the studied groups

Groups	Mean \pm SD	
	Visfatin	HbA1C
Diabetic Peripheral Neuropathy (No=40)	4.47 \pm 1.37 a	9.54 \pm 2.07 a
Diabetic Mellitus (No=40)	3.86 \pm 1.38 b	9.16 \pm 1.92 a
Control (No=40)	1.25 \pm 0.55 c	4.85 \pm 0.53 b
LSD value	0.519 **	0.736 **
P value	0.0001	0.0001

Table (5) shows the coefficient correlation of Visfatin with each of HbA1C, Cholesterol, Triglyceride, HDL, VLDL, Uric acid, and BMI in Diabetic Peripheral Neuropathy and Diabetic Miletus groups, respectively. The results indicate that Visfatin does not correlate with all the studied parameters in two patient groups depending on the p values that are recorded in **Table (5)**.

Table 5. Correlation coefficient of Visfatin with the different studied variables in Peripheral Diabetic Neuropathy and diabetic groups.

Variables	Diabetic Peripheral Neuropathy (n=40)		Diabetic Miletus (n=40)	
	r	P .value	r	P .value
BMI(kg/m ²)	0.11	0.487	0.09	0.541
Age (years)	-0.26	0.099	-0.14	0.359
HbA ₁ C	-0.20	0.207	0.24	0.124
S. Cholesterol(mg/dl)	-0.008	0.957	0.08	0.638
S. Triglyceride (mg/dl)	0.28	0.070	-0.07	0.664
S.HDL (mg/dl)	-0.32 *	0.043	-0.26	0.092
S.LDL (mg/dl)	0.13	0.403	0.24	0.126
S.VLDL (mg/dl)	0.28	0.069	-0.15	0.334
S. Uric acid (mg/dl)	-0.005	0.973	0.09	0.543

Analysis of Visfatin reveals the area under the curve (AUC) of ROC in value of (0.966). The best cut-off point derived from the ROC curve shows a sensitivity of (92.5 %) and specificity of (100.0 %), and it is found to be (>2.034 ng/ml). That means the test value of more than 2.034 ng/ml represents the abnormal case, whereas the value less than 2.034 ng/ml refers to the healthy case as shown in **Figure(2)**.The significance level is obtained at ($P = 0.6647$). As illustrated in **Figure (2)**.

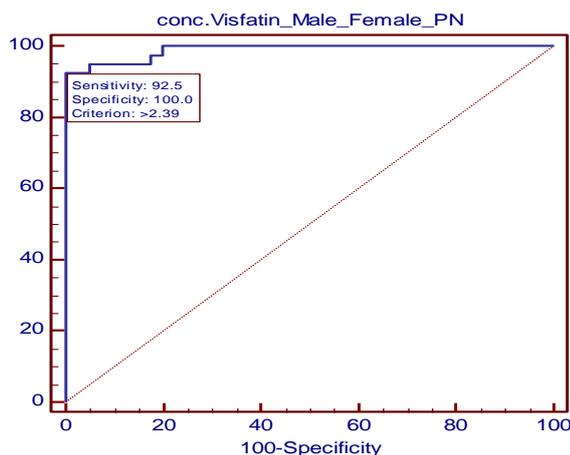


Figure 2. The Roc curve for Visfatin

4. Discussion

Because axons don't make cholesterol, it must be transported to the tips and Schwann cells of regenerating axons by axonal transport or HDL-C and LDL-C. This may explain group dynamics. Statins reduce cholesterol levels available for axonal regeneration on two pathways, resulting in a different composition of lipids in the cholesterol-rich myelin sheath of Schwann cells. This causes nerve swelling due to reactive thickening of the myelin sheath, similar to hereditary disorders in cholesterol metabolism. An increase in lipid-equivalent nerve lesions and nerve volume, both correlated with a decrease in HDL-C and LDL-C, would represent nerve swelling due to an altered composition of lipids in Schwann cells due to insufficient cholesterol supply to regenerating neurites after neuropathic damage, resulting in decreased nerve conduction. [23]

The current analysis confirms Lorenzo et al.[24] Murwan et al.[25], Agha et al.[26], Satish et al.[27], Renuka & Vasantha[28]. T2DM, DPN patients have higher blood cholesterol and Triglyceride levels than healthy controls. Lorenzo et al. [24], Gunjan et al.[29], and Sujaya et al.[30] found that HDL levels were considerably lower in T2DM (G2) than in controls. Several authors have shown elevated triglycerides with normal HDL-C in diabetic patients: Khursheed et al. [31], Ahmed et al. [32], Yassin et al. [33].

Renuka & Vasantha [14] and Lorenzo et al. [24] found that serum LDL was greater in T2DM and DPN patients than in controls. Johann et al. [29] found that DPN patients had lower LDL values than T2DM patients [23].

Diabetes raises blood lipid levels by mobilising free fatty acids from adipose tissue. Reduced insulin action converts excess blood fatty acids to triglycerides, phospholipids, and cholesterol in the liver [34].

Visfatin was utilised to identify visceral fat in mice and humans from subcutaneous fat. Visfatin in perivascular and epicardial fat may affect the heart. Adipocytes and inflammatory cells, such as activated macrophages, emit visfatin in adipose tissue. Obesity increases adipose tissue inflammation, especially macrophages. Visfatin contains the intrinsic enzyme nicotinamide phosphoribosyltransferase (Nampt) (2002). NAD⁺ is crucial in physiology. Nampt catalyses the rate-limiting step in the NAD⁺ synthesis pathway in mammals. Mixing 5-pyrophosphoribosyl-1-pyrophosphate with nictinamide yields NMN and inorganic pyrophosphate (PRPP). Nmnat converts NMN to NAD in a second step. Nampt has two animal forms. iNampt maintains NAD-dependent enzyme activity and is associated to cell metabolism, maturation, and survival. Several cell types release extracellular Nampt (eNampt). Encamps are considered to provide a way for

organs to communicate[35]. Previous research by Buyukaydin et al. [36] revealed no relationship between Visfatin results and biochemical parameters, oxidative stress biomarkers, or thiol-disulphide levels.

Visfatin may be implicated in endothelial dysfunction, according to Alghasham and Barakat [37]. Liang and Dong [38] found reduced serum visfatin levels in diabetic macroangiopathy. Visfatin, a proangiogenic adipokine, may be involved in diabetic retinopathy, say Wang et al. Visfatin levels in diabetic retinopathy patients' blood and vitreous increase with disease severity [39].

Mageswari R et al. found that diabetic nephropathy biomarkers increase with disease severity [40]. Lee et al. Visfatin levels were much greater in rheumatoid arthritis patients than in healthy controls[41]. Mousavi, Zohreh, and colleagues connected visfatin levels to non-alcoholic fatty liver disease categorization. Autocrine or paracrine processes may be at work when visceral adipose tissue secretes visfatin [42].

Visfatin levels are greater in type 2 diabetics with atherosclerotic plaques than in those without plaques. Males with atherosclerotic plaques increased the most. Visfatin levels were higher in T2DM patients with carotid plaques than femoral or no plaques [19].

5. Conclusion

Diabetics have high lipid levels due to adipose tissue mobilisation. Reduced insulin activity causes the liver to convert extra fatty acids into triglycerides, phospholipids, and cholesterol. Visfatin in perivascular and epicardial fat may damage the cardiovascular system. Adipocytes and activated macrophages generate and release visfatin in adipose tissue. Obesity promotes inflammatory macrophages in adipose tissue. Visfatin is a Nampt enzyme.

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