

SHORT COMMUNICATION

PERIOPERATIVE MEDICINE

Serum netrin-1 level in patients with type 2 diabetes mellitus and its relationship with diabetic complications

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ABSTRACT

Background & objective: Diabetes mellitus is a metabolic disorder, which is becoming more prevalent. It results from a defect in insulin secretion, or insulin action, or both, which is associated with increases risk of developing microvascular and macrovascular complications. Netrin-1 is originally considered an axon guidance protein, With a structure similar to laminine. It has been linked to the growth of numerous tissues, including the pancreas. During the initial phases of the formation of several tissues, such as pancreatic tissue, netrin-1 plays a critical function in controlling cell motility, cell-cell interactions, and cell-extracellular tissue binding. We studied the levels of netrin-1 in the blood of people with type 2 diabetes (T2DM) and if there was a correlation between those levels and certain sociodemographic factors, glycemic control, and lipid profiles.

Methodology: We enrolled 160 participants in this study, and split them into two groups; 81 people with T2DM in the first group, and 79 healthy, normoglycemic people in the second group. Both groups were matched for age and sex. The weight, height, and waist circumference of every participant were recorded. After at least 8 h of fasting, blood samples were obtained. and the levels of netrin-1, lipid profile, fasting blood glucose, and glycated hemoglobin were estimated, among other biochemical indicators.

Result: This study revealed that T2DM patients had significantly higher serum netrin-1 levels than the control group. There was a significant positive correlation between netrin-1 and fasting blood sugar, HbA1c, triglycerides, and very-low-density lipoprotein (VLDL-C); however, a negative association was seen between netrin-1 and high-density lipoprotein-cholesterol (HDL-C).

Conclusion: In comparison to controls, T2DM patients had a significantly higher mean serum netrin-1 concentration, and higher value among patients was reported among those with poor glycemic control, suggesting that serum netrin-1 might serve as a biomarker for therapeutic response. However, further studies are required to assess its role in the development of microvascular and macrovascular complications.

Abbreviations: DCC - Deleted Receptors; FBS - fasting blood sugar; HDL-C-High-Density Lipoprotein-Cholesterol; T2DM - Type 2 Diabetes Mellitus; UNC5 - Uncoordinated 5 Receptors; VLDL-C - Very-Low-Density Lipoprotein;

Keywords: Diabetic complications; Diabetes mellitus; Netrin-1; Receptors

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1. INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder described by high blood glucose level due to inadequate insulin production, impaired action of insulin, or both. Chronic high blood sugar has a close association with relatively long-term microvascular diseases that affect the kidneys, eyes, and blood vessels, as well as an increase in the prevalence of cardiovascular disease (CVD).¹ Globally, 8.8 percent of people aged 20 to 79 y have DM.² Approximately 439 million individuals will have diabetes by 2030, up from the previously estimated 366 million people.^{3,4}

In Iraq, diabetes is prevalent in about 1.4 million Iraqis, ranging from 8.5 percent to 13.9 percent.⁵ In Basra city, the prevalence of diabetes was 19.7 percent.⁶ Netrin-1 was originally considered an axon guidance protein, with a structure similar to laminine.¹ On chromosome 17p13.1 of the genetic code, the NTN1 gene, which codes for the protein Netrin-1.⁷ The complete transcript has seven exons and is transformed into a protein with a length of 604 amino acids with molecular mass of 50–75 kD.^{7,8} The deleted receptors in colorectal cancer (DCC) and the uncoordinated 5 (UNC5) receptors are two widely established receptor families that regulate the biological functions of netrin.^{9,10} Netrin-1 plays a vital role in the initial development of different tissues, including the nervous system, vascular system, pulmonary system, pancreatic system, muscular system, and mammary gland. It controls cell movement, cell-cell contacts, and cell-extracellular tissue adhesion. Netrin-1 has also been linked to tissue rejuvenation, control of inflammatory conditions, and leukocyte migration in peripheral organs.¹¹

Both endocrine and exocrine cells expressed netrin-1. In the pancreas, neogenin was highly expressed, which suggests that netrin-1 is involved in pancreatic development, remodeling of tissue, migration of islet cells, and also rejuvenation.¹² When the β -cells were treated with external Netrin-1 and -4, caspase-3 was discovered to be downregulated.¹³ Neogenin and UNC5-A receptor amounts also decreased along with the decrease in caspase-3 cleavage. However, neogenin and UNC5 receptors have shown the capacity to trigger cell death without netrin while inhibiting it when they bind with netrin-1; this discovery highlights netrin's contribution to β -cell prosurvival.¹³ The retention and migration of dysfunctional adipose tissue are supported by increased netrin-1 expression accelerates the development of persistent inflammation, insulin resistance, and metabolic disorders.¹⁴

The stimulating effect of netrin-1 on insulin release from β -cells was reported, through activation of the Ca^{2+} influx stimulation and cAMP signaling pathway.⁹ The

purpose of this study is to estimate serum netrin-1 levels in T2DM patients and correlate it's with sociodemographic characteristics and glycated hemoglobin (HbA1c), Fasting blood sugar and lipid profile.

2. METHODOLOGY

This case-control study was carried out in Al-Muane Teaching Hospital, in the southern Iraqi province of Basrah, from November 2022 to November 2023. The Basrah Faculty of Medicine's ethics review committee approved the study and informed written consent was taken from every participant.

2.1. Study population

A total of 160 participants were enrolled and divided into two separate groups. There were 81 patients with T2DM in one group and 79 apparently healthy people, matched with the cases with respect to age or sex, were in the second group. Every participant visited the hospital, whether it was for a checkup or a medical consultation. Exclusion criteria included type 1 DM, pregnant and lactating women, chronic liver diseases, patients with heart, hepatic, and renal impairment, patients with hormone replacement therapy and patients with hypertension. A detailed questionnaire included demographic characters, type of treatment and family history of diabetes was filled for every participant. Anthropometric characteristics like height, BMI, body weight, and waist circumference (WC) were also recorded.

2.2. Blood collection

Venous blood 5 mL was drawn after an overnight fast of at least eight hours from each participant. Two mL was dispensed into an EDTA tube for the estimation the HbA1c%. The remainder of the blood was used in a serum separator tube (SST). A portion of the serum was utilized for the estimating the biochemical parameters. The remaining portion was placed into Eppendorf tubes and preserved at $-20^{\circ}C$ for later determination of serum netrin-1. Estimation of netrin-1 was done by a sandwich enzyme-linked immunosorbent assay (ELISA) kit (Sunlong Biotech, China, REF SL1249Hu). The inter-assay precision value was less than 10%, but the intra-assay precision value was less than 8%. A kit from Roche Diagnostics GmbH, Germany, was used to automatically measure fasting blood sugar (FBS) (REF 04404483190), total cholesterol (REF 03039773190), triglycerides (REF 20767107190), high-density lipoprotein cholesterol (HDL-C) (REF 07528566190), and low-density lipoprotein cholesterol (LDL-C) (REF 07005717190). The measurement of glycated hemoglobin was conducted utilizing ion exchange high-performance liquid chromatography with the utilization

Table 1: Sociodemographic and biochemical parameters of patients and controls.

Age (y)	Netrin-1 (pg/ml)		P value*
	Cases (n = 81)	Controls (n = 79)	
30-39 y	185.54 ± 37.29	95.94 ± 13.96	< 0.001
40-49 y	185.75 ± 28.14	96.15 ± 11.22	< 0.001
50-59 y	185.94 ± 37.06	96.69 ± 13.38	< 0.001
60-69 y	186.00 ± 37.94	96.98 ± 11.96	< 0.001
>70 y	186.91 ± 36.66	97.06 ± 6.89	< 0.001

Data presented as (Mean ± SD); P < 0.05 was considered as significant

of the Variant II Turbo HbA1c Kit-2.0, which was supplied by Bio-Rad, USA, (REF 220-0220).

2.3. Statistical analysis

Statistical Package for Social Science (SPSS) version 28 was used to analyze the data. The findings are displayed as numbers and percentages, as well as mean ± standard deviation (SD). An independent t-test was used to analyze continuous data, while the Chi-square test (χ^2 test) was used to analyze categorical data. The correlation coefficient (r-value) between the parameters was found using the bivariate Pearson correlation.

3. RESULTS

Table 1 showed the sociodemographic characters and biochemical parameters of the of the patients and controls. No statistically significant differences were seen between the patients and the control group with

respect to BMI, WC, total cholesterol, LDL-C, and HDL-C (P > 0.05). There was a significant difference between patients and controls with respect to FBS, HbA1c, triglycerides, and VLDL-C. The mean value of serum netrin-1 was significantly higher in patients in comparison to the control group (P < 0.001).

After the stratification of the patients and controls into five groups, Comparison of the serum netrin-1 among patients and controls was shown in Table 2. There was a significant difference between patients and controls in all age groups (P < 0.001).

Comparison of the serum netrn-1 level in relation to disease duration, FBS, and HbA1c are shown in Table 3. The results showed that the mean level of serum netrin-1 was higher in people who had the duration of disease for more than 5 y compared to people who had it for less than or equal to 5 y. However, this difference is statistically not significant (P > 0.05). With respect to

Table 2: The distribution of serum netrin-1 in the different age groups of the patients and controls.

Variables	Cases (n = 81)	Controls (n = 79)	P value	
Age (y)	53.60 ± 9.10	52.60 ± 9.67	NS	
Gender	Male	38 (46.9)	39 (49.4)	NS
	Female	43 (53.1)	40 (50.6)	
BMI (kg/m ²)	30.10 ± 4.78	29.57 ± 5.45	NS	
Family history of DM	65 (80.2)	46 (58.2)	< 0.05	
Duration of disease (y)	1.73 ± 0.45	-----	-----	
FBS (mg/dL)	229.44 ± 85.20	103.51 ± 13.38	< 0.001	
HbA1c (%)	8.59 ± 2.00	5.05 ± 0.55	< 0.001	
Serum total cholesterol (mg/dL)	190.89 ± 57.84	173.97 ± 44.69	NS	
Serum triglycerides (mg/dL)	189.83 ± 67.42	149.57 ± 46.92	< 0.001	
S.HDL-C (mg/dL)	40.16 ± 12.84	41.63 ± 11.04	NS	
S.LDL-C (mg/dL)	111.81 ± 55.16	102.18 ± 42.77	NS	
S.VLDL-C (mg/dL)	38.91 ± 14.72	29.90 ± 9.54	< 0.001	
Netrin-1 (pg/ml)	185.90 ± 34.67	96.57 ± 12.12	< 0.001	

Data presented as (Mean ± SD) or n (%); P < 0.05 was considered as significant

Table 3: Distributions of serum netrin-1 according to the duration of disease, FBS, and HbA1c.

Parameter		Netrin-1 (pg/ml)	P-value
Duration of disease	≤ 5 y	183.54 ± 25.60	NS
	> 5 y	186.68 ± 37.32	
FBS (mg/dL)	≤130	108.23 ± 37.38	< 0.001
	>130	183.87 ± 33.34	
HbA1c%	Good control < 7%	113.20 ± 44.24	< 0.001
	Fair control 7-8%	180.64 ± 30.32	
	Poor control > 8%	181.80 ± 51.81	

Data presented as (Mean ± SD); P < 0.05 was considered as significant

FBS, the results showed that the patients with FBS levels exceeding 130 mg/dL have higher netrin-1 levels as compared to those with FBS levels of ≤ 130 mg/dL and this difference was statistically significant (P < 0.001). This study revealed that patients with poor glycemic control (HbA1c > 8%) had higher levels of serum netrin-1 as compared to those with fair glycemic control (HbA1c 7-8%), and good glycemic control (HbA1c < 7%) respectively.

Table 4: Correlations of serum netrin-1 with FBS and HbA1c.

Netrin-1	Variable	r-value	P-value
	FBS (mg/dL)	0.568 **	< 0.001
	HbA1c (%)	0.628 **	< 0.001

** Correlation is significant at the 0.01 level (2-tailed)

4. DISCUSSION

The most prevalent form of diabetes is type 2 diabetes mellitus, which manifests as a persistent metabolic illness and is characterized by a complex interplay of various factors, its incidence has exhibited a consistent upward trend on a global scale.¹⁵ According to the findings of this study, female patients made up more than half of the patients (53.1%), and that could be because DM has a marginal prevalence in females compared to males in Basra population. More women than men sought medical care because the majority of the them were housewives and are the major attendance of diabetic centers and hospital out-patient's clinics during day time.¹⁶

Netrin-1 is a member of the laminin-related proteins of axon guidance and has been shown to have a variety of roles via its two traditional receptor families, including deletion in colorectal cancer (DCC) and uncoordinated 5 (UNC5).¹⁷ More recent research has focused on netrin-1 as an indicator for Type 2 diabetes and a wider spectrum

of long-term complications. Consequently, netrin-1 could be a predictive biomarker in DM.¹⁸ Netrin-1, which functions as a neuro-immune signaling molecule, has a significant impact on embryonic pancreas development.^{19,20} Rejuvenation, tissue remodeling, islet cell migration, and pancreatic morphogenesis are all impacted by netrin1. Several studies have elucidated the significance of netrin-1 in the pathophysiology of type 2 diabetes, thereby expanding its diagnostic and therapeutic utility.^{9,21,22}

The current study observed a notable elevation in serum netrin-1 levels among individuals diagnosed with diabetes compared to the control group. Several studies revealed the same result,^{9,14,23-25} they stated that these changes may be due to a compensatory reaction to the disease. In general, these differences with respect to the association between netrin-1 and T2DM are unclear, which may be attributed to variation with respect to sample collection, ethnicity, other sociodemographic characteristics of the population sample, sample size, and method of estimation.

The findings of the study demonstrated a statistically significant positive correlation between the ages of patients and their serum netrin-1 levels. Also, the mean value of serum netrin-1 levels was higher than those of the control group at comparable ages in all five groups, with a highly significant difference (P < 0.001). This study also demonstrated a positive correlation between the age of the study group and serum netrin-1 (r = 0.054, P = 0.497). These results were consistent with the findings of other studies.^{26,27,28}

Also, there was a significant positive correlation between serum netrin-1 and disease duration. (r = 0.798, P < 0.001). It should be point out that the duration of disease could have relation with serum netrin-1 level or could have no relation because the duration of DM actually was reported since the time of diagnosis, which may not reflect the real duration of disease, because many patients with DM might be diagnosed after years since the occurrence of the disease.

The study revealed that the mean body mass index (BMI) of individuals diagnosed with type 2 diabetes mellitus was higher in comparison to the control group; however, this difference was not statistically significant (P > 0.05). The netrin 1 circulation may be disrupted by obesity; it has been suggested that there is modest upregulation of netrin 1 in the cells of visceral adipose tissue, leading to a circulatory reduction of the netrin 1

level in obesity. The macrophage retention cue of netrin 1 in adipose tissue possibly augments the chronic inflammatory process and insulin resistance that occur subsequently in T2DM.²⁹

With respect to glycemic control, a significant positive correlation was observed between serum netrin-1 levels and HbA1c ($r = 0.628$, $P < 0.001$). The findings of this study indicate a statistically significant positive correlation between the concentrations of netrin-1 and serum glucose ($r = 0.568$, $P < 0.001$). Similar findings were stated by several studies.^{8,23,33} Ay et al.²⁵ concluded that individuals with diabetes with HbA1c levels higher than 8.1% had higher serum netrin-1 levels than the control group. While Liu et al.²⁶, Assi et al.³¹ and ACAR et al.³² observed, patients have lower levels of netrin-1 compared to the control group. Lui et al.²⁶ was stated that there is a negative correlation between serum netrin-1 levels and FBS and HbA1c%. The people involved in his study were patients they diagnosed with type 2 diabetes within the past six months and have mean HbA1c values of (8.5%). Those people have shorter duration of disease and the degree of insulin resistance may vary from patients with longer duration of disease. Similar finding was obtained by Gao et al.,⁹ who demonstrated that netrin-1 directly stimulates the release of insulin in the mouse pancreas by facilitating beta-cell calcium ion influx and the generation of cyclic adenosine 5'-monophosphate (cAMP).

In T2DM netrin 1 may have a role in the pathological mechanism through their effect in inflammatory process.³⁰ It has been stated that netrin 1 may have a regulatory influence on inflammation which may lead to negative regulation of insulin secretion and may have a role in dysfunction of β -cell.²⁸ Netrin-1 overexpression stimulate macrophage differentiation to the M2 phenotype leading to promotion of islet cells remodeling.¹² In addition to that there is an association between netrin 1 level and dysfunction of islet cell in T2DM which in turn it is correlate negatively with hyperglycemia. It is not clear how β -cell degradation may be resulted from repeated exposure and prolonged attack of hyperglycemia, which reduces the stimulatory effect of glucose on insulin secretion and finally leads to apoptosis of β -cell.²⁹

De Breuck, Saskia, et al.¹² stated that netrin 1 might had a vital role in the morphogenesis of regenerating pancreatic tissue. Netrin-1 secretion by the injured β -cell is reduced, which promoting function failure of β -cell.

5. CONCLUSION

In conclusion, the mean serum netrin-1 concentration was significantly higher in patients suffering from Type 2 diabetes mellitus than in controls, and a higher value was reported among those with poor glycemic control, which might suggest that serum netrin-1 could be used as a biomarker for therapeutic response.

6. Data availability

The numerical data generated during this research is available with the authors.

7. Acknowledgement

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8. Conflict of interest

The study utilized the hospital resources only, and no external or industry funding was involved.

9. Authors' contribution

All authors contributed in the conduct of this study, data analysis and drafting the manuscript. All authors approved the final draft for publication.

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