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Original Article

Study of level of netrin-1 in serum of patients with type 2 diabetic nephropathy

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Abstract

Diabetic nephropathy is among the devastating outcomes of diabetes. An essential part of slowing its development is early detection. The goal was to determine the impact of netrin-1 on microalbuminuria and early detection of nephropathy type 2 DM. This trial was conducted on 120 patients divided equally into four groups: group (1) Healthy normal persons; group (2) patients with type 2 DM without albuminuria (albumin/creatinine ratio <30 mg/gm), group (3) patients with type 2 DM with microalbuminuria (albumin creatinine ratio 30–299 mg/gm), and group (4) patients with type 2 DM with overt proteinuria (albumin creatinine ratio ≥300 mg/gm). All participants were subjected to complete history taking, full clinical examination, routine labs, and Netrin-1 level. The highest level of Netrin-1 was found in group 4 (56.2±20.5), followed by group 3 (43.2±22.4), group 2 (36±13.4), and group 1 (33.2±10.8) (P-value <0.001). In addition, there was a significantly higher Netrin-1 level in diabetic nephropathy patients (49.7±22.3) than in patients without nephropathy (34.6±12.1) (P-value <0.001). Plasma netrin-1 level is significantly elevated in patients with diabetic nephropathy, whether micro or macro proteinuria, and there is a future hope for the possibility of using netrin 1 as an early predictor for the diagnosis of diabetic nephropathy.

Keywords: diabetes mellitus, diabetic nephropathy, serum netrin-1, albuminuria.

Introduction

Type 2 diabetes mellitus (T2DM) is becoming more common all over the globe. Society has been hit hard by the increased incidence of type 2 diabetes, both emotionally and monetarily. Complicating the selection of anti-hyperglycemic treatments, patients with type 2 diabetes often exhibit a constellation of comorbidities, including cardiovascular disease, hypertension, dyslipidemia, diabetic foot ulcers, and renal failure [1].

World Health Organization data indicates that diabetic nephropathy (DN) is one of the leading causes of end-stage renal disease (ESRD) globally. Diabetic complications, such as end-stage renal disease (ESRD), may be avoided with prompt diabetes diagnosis and treatment. Damage to the glomeruli and tubules may happen before microalbuminuria ever occurs [2].

Embryonic development relies on axons and cells guided by netrins, an extracellular protein family that is very conserved. Netrin-1, netrin-3, netrin-4, netrin G1, and netrin G2 are the five known varieties of netrins. The cell membrane secretes netrins 1-4, whereas netrins G1 and G2 are bound to the cell membrane by means of two glycosylphosphatidylinositols [3].

For the heart and blood vessels, Netrin1 is an essential protein. New research has shown that netrin-1 has anti-inflammatory, pro-angiogenic, and anti-apoptotic characteristics. Furthermore, it has been shown that netrin1 has a role in the regulation of inflammation-based diseases, tissue regeneration, and leukocyte migration to peripheral organs. Two groups of receptors have been associated with axonal activities related to Netrin1: the Unc5s family, which includes Unc5A, and the deleted in colorectal cancer (DCC) family,

which includes DCC and its orthologue Neogenin-1. However, research evaluating netrin1 as a biomarker for diabetes and its long-term consequences is still in its infancy [4].

The researchers set out to determine if there is a correlation between netrin-1 and microalbuminuria, as well as how netrin-1 affects renal problems in type 2 diabetics. In addition, we want to find out what variables influence serum netrin-1 levels in individuals whose albuminuria is severe.

Material and methods

Study design and patients

This was a randomized controlled clinical trial conducted in the clinics of the internal medicine department and Endocrinology clinic at Beni-Suef University Hospital between September 2021 and March 2023. The study was performed on 120 patients and divided into four groups: group (1) 30 Healthy normal persons with age and sex-matched; group (2) 30 patients with type 2 diabetes mellitus without albuminuria (albumin creatinine ratio in urine <30 mg/gm), group (3) 30 patients with type 2 diabetes mellitus with microalbuminuria (albumin creatinine ratio in urine 30–299 mg/gm), and group (3) 30 patients with type 2 diabetes mellitus with overt proteinuria (albumin creatinine ratio in urine ≥300 mg/gm).

Exclusion criteria for this research were as follows: other endocrine diseases that affect glucose metabolism and lipid metabolism, *e.g.*, Cushing disease and familial hypertriglyceridemia. Also, patients with chronic hepatitis, primary kidney disease, pregnancy, and a history of drug abuse. In addition, patients with advanced stage of diabetic nephropathy with eGFR<15.

Laboratory, anthropometric and clinical data collection

All participants were subjected to complete history taking, including duration of diabetes in the case of diabetic patients, symptoms, treatment compliance, other drug history, and other comorbidities. Clinical examination was performed on all the participants, focusing on vital signs, general examination, and signs of diabetic complications.

Laboratory investigation performed included CBC, Urea, Creatinine, and eGFR using CKD-EPI creatinine equation (2021), Albumin/creatinine ratio in urine, HbA1c, Na, and K levels. The serum level of Netrin-1 was analyzed by using Human Netrin-1 (Ntn1) ELISA Kit supplied by SinoGeneClon Biotech Co.,Ltd. Catalog No: SG-11227 according to the user's manual.

Statistical analysis

The data was analyzed using SPSS v. 25 for Windows, which stands for Statistical Package for the Social Sciences. The variables were shown in a mean, and standard deviation was used to describe quantitative variables (SD). We used percentages and numbers (No.) to express the qualitative elements. When comparing the three groups on nonparametric scale variables, the Kruskal Wallis test was used; however, when comparing groups on normally distributed variables, the One-Way ANOVA test was employed. The Chi-square test was used to compare groups regarding categorical variables. ROC curve was used to predict optimal cut-off in Netrine 1 in the prediction of macroproteinuria, macroproteinuria, and diabetic nephropathy. Correlations were done between numeric variables. Multivariable binary logistic regression analysis for prediction of diabetic nephropathy in the presence of Netrine 1 after adjustment for other variables. The significance level was evaluated using a P-value when P-value<0.05.

Results

Baseline characteristics of the studied participants

The age of patients was matched in all groups with a mean age in group 1 (53.07±8.4 years), group 2 (51.3±8.6 years), group 3 (54.2±9.5 years), and group 4 (55.1±7.4 years) (P-value 0.36). Also, the majority of the patients were females in all groups with no significant differences (P-value 0.21). The duration of the disease was significantly longer in group 4 (14.1±5.7 years) compared to group 3 (8.4±4.03 years) and group 2 (2.6± 1.7 years) (P-value<0.001) (Table 1).

Laboratory investigations of the studied participants

Patients in all groups showed normal levels in terms of Hb, WBC count, platelet count, and sodium level. Comparison between all groups revealed no significant differences between all groups regarding Hb level (P-value 0.678), WBC count (P-value 0.716),

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Table 1: Baseline characteristics of the studied participants.

Variables	Group (1) (no=30)	Group (2) (no=30)	Group (3) (no=30)	Group (4) (no=30)	P-value
Age (years) [Mean±SD]	53.07±8.4	51.3±8.6	54.2±9.5	55.1±7.4	0.36
Sex [No. (%)]					
Male	9 (30%)	11 (36.7%)	4 (13.3%)	9 (30%)	0.21
Female	21 (70%)	19 (63.3%)	26 (88.7%)	21 (70%)	
Disease duration (years) [Mean±SD]	-	2.6±1.7	8.4±4.03	14.1±5.7	**<0.001***

Note: * – P-value is significant.

Platelet count (P-value 0.80), and sodium level (P-value 0.763). Higher serum creatinine (1.4±0.6 mg/dl), urea (55.6±18.8 mg/dl), K+ (4.4±0.3), HbA1c (9.1±1.6) and A/C ratio (993.5±626.2) were observed in group 4 compared to other groups (P-value<0.001). On the other hand, eGFR (54.3±20.2) was significantly lower in group 4 compared to other groups (P-value<0.001).

Post hoc pairwise comparison between the 4 groups revealed that there were significantly higher creatinine and potassium levels in the macro-proteinuria group than in the other 3 groups. There was a significantly higher urea level in the macro-proteinuric group than the other 3 groups and between the micro-albuminuric and the other 2 diabetic groups. There was a significant difference between all of the studied groups, except between diabetic non-proteinuric and diabetic micro-proteinuric groups, regarding the eGFR. There was a significant difference between all diabetic groups and controls regarding the HbA1c. There was a significant difference between all of the studied groups and the macro-proteinuric group regarding the A/C ratio (Table 2).

Assessment of Netrin-1 level in the studied participants

Assessment of Netrin-1 level among the studied participants showed that the highest level was found in group 4 (56.2±20.5), followed by group 3 (43.2±22.4) and group 2 (36±13.4). In contrast, the healthy control patients in group 1 had the lowest level (33.2±10.8) with significant differences between all groups (P-value <0.001). There was a significant difference between all of the studied groups and the macro-proteinuric group regarding the Netrin 1 level. There was an insignificant difference between the control group, the diabetic non-proteinuric group, and the diabetic micro-albuminuric group.

Comparison between non-nephrotic patients (Control group and diabetic group without proteinuria) and

Table 2: Laboratory investigations of the studied participants.

Items (mean±SD)	Group (1) (no=30)	Group (2) (no=30)	Group (3) (no=30)	Group (4) (no=30)	P-value
Hb gm/dl	12.3±1.2	12.1±1.1	11.9±1.3	11.9±1.2	0.678
WBCs	6190±1824.9	6493.3±2021	6017±1296.7	6123.3±1406.3	0.716
PLT X 10^3	252753.3±79355	245366±70964	277133±69437	233033±41966	0.80
Creatinine	0.9±0.1	0.9±0.2	0.9±0.2	1.4±0.6	
Pairwise comparison		P1=0.963	P2=0.723	**P3<0.001***	**<0.001***
		P4=0.941	**P5<0.001***	**P6<0.001***	
Urea	23.6±6.2	26.9±5.9	35.1±6.7	55.6±18.8	
Pairwise comparison		P1=0.661	**P2<0.001***	**P3<0.001***	**<0.001***
		P4=0.002*	**P5<0.001***	**P6<0.001***	

Table 2: Continued.

Items (mean±SD)	Group (1) (no=30)	Group (2) (no=30)	Group (3) (no=30)	Group (4) (no=30)	P-value
Sodium	139.7±2	140±2.2	139.5±1.8	139.7±1.7	0.763
K+	4.1±0.2	4.1±0.2	4.1±0.2	4.4±0.3	
Pairwise comparison		P1>0.999	P2=0.998	**P3=0.003***	**<0.001***
		P4=0.999	**P5=0.003***	**P6=0.002***	
eGFR	101.5±20.7	87.2±18.7	76.3±18.7	54.3±20.2	
Pairwise comparison		**P1=0.029**	**P2<0.001***	**P3<0.001***	**<0.001***
		P4=0.147	**P5<0.001***	**P6<0.001***	
HbA1c	5.1±0.2	7.8±1.1	8.5±1.5	9.1±1.6	
Pairwise comparison		**P1<0.001***	**P2<0.001***	**P3<0.001***	**<0.001***
		P4=0.134	**P5<0.001***	P6=0.169	
A/C ratio	16.5±4.8	20.2±5.7	114±30.5	993.5±626.2	
Pairwise comparison		P1=0.999	P2=0.629	**P3<0.001***	**<0.001***
		P4=0.658	**P5<0.001***	**P6<0.001***	

Note: * – P-value is significant. Post hoc Pairwise comparison: P1 group 1 *vs*. group 2, P2 group 1 *vs*. group 3,P3 group 1 *vs*. group 4, P4 group 2 *vs*. group 3, P5 group 2 *vs*. group 4, P6 group 3 *vs*. group 4.

nephrotic patients (diabetic group with micro-albuminuria and macro-albuminuria) revealed that there was a significantly higher Netrin 1 level in patients with diabetic nephropathy (49.7±22.3) compared to subjects without nephropathy (34.6±12.1) (P-value<0.001) (Tables 3 and 4).

The predictive role of Netrin-1 levels in diabetic nephropathy

To evaluate the role of Netrin 1 in the prediction of diabetes (without proteinuria), the ROC curve analysis showed that there was an insignificant role (P-value 0.413) of Netrin 1 in the prediction of diabetes (without proteinuria), at a cut-off>32.3 with sensitivity, specificity, PPV, and NPV, 50%, 56.67%, 53.6%, and 53.1%, respectively.

To evaluate the role of Netrin 1 in the prediction of diabetes (with microproteinuria), the ROC curve analysis showed that there was a significant role (P-value 0.031) of Netrin 1 in the prediction of diabetes with microproteinuria at a cut-off>36.4 with sensitivity, specificity, PPV, and NPV, 60%, 73.3%, 69.2%, and 64.7%, respectively.

Table 3: Comparison between the studied groups regarding their Netrin 1 level.

Items (mean±SD)	Group (1) (no=30)	Group (2) (no=30)	Group (3) (no=30)	Group (4) (no=30)	P-value
Netrin 1	33.2±10.8	36±13.4	43.2±22.4	56.2±20.5	
Pairwise comparison		P1=0.923	P2=0.125	**P3<0.001***	**<0.001***
		P4=0.389	**P5<0.001***	**P6=0.024**	

Note: * – P-value is significant.

Table 4: Comparison between the non-nephropathic and nephropathic groups regarding their Netrin 1 level.

Items (mean±SD)	Non-nephropathy (no=60)	Nephropathy (no=60)	P-value
Netrin 1	34.6±12.1	49.7±22.3	**<0.001***

Note: * – P-value is significant.

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Table 5: Cut off, sensitivity, specificity, PPV, and NPV of Netrin 1 in the prediction of diabetes (without proteinuria), diabetes with microproteinuria, diabetes with microproteinuria, diabetic nephropathy

Items	Diabetes without proteinuria	Diabetes with microproteinuria	Diabetes with microproteinuria	Diabetic nephropathy
Area under curve	0.561	0.653	0.852	0.733
P-value	0.413	0.031*	<0.001*	<0.001*
Cut off	>32.3	>36.4	>36.4	>36.4
Sensitivity (95%CI)	50.00 (31.3–68.7)	60.00 (40.6–77.3)	86.67 (69.3–96.2)	73.33 (60.3–83.9)
Specificity (95%CI)	56.67 (37.4–74.5)	73.33 (54.1–87.7)	73.33 (54.1–87.7)	68.33 (55.0–79.7)
Positive predictive value (95%CI)	53.6 (40.1–66.5)	69.2 (53.7–81.3)	76.5 (63.9–85.7)	69.8 (60.8–77.6)
Negative predictive value (95%CI)	53.1 (41.3–64.6)	64.7 (52.9–74.9)	84.6 (68.3–93.4)	71.9 (61.9–80.1)

To evaluate the role of Netrin 1 in the prediction of diabetes (with macroproteinuria), the ROC curve analysis showed that there was a significant role (P-value <0.001) of Netrin 1 in the prediction of diabetes with macroproteinuria at a cut-off>36.4 with sensitivity, specificity, PPV, and NPV, 86.67%, 73.3%, 76.5%, and 84.6%, respectively.

To evaluate the role of Netrin 1 in the prediction of diabetic nephropathy, the ROC curve analysis showed that there was a significant role (P-value<0.001) of Netrin 1 in the prediction of diabetic nephropathy group at a cut-off>36.4 with sensitivity, specificity, PPV, and NPV, 73.3%, 68.3%, 69.8%, and 71.9%, respectively (Table 5).

Multivariable analysis

This regression model is the best model that can explain the change in the probability of diabetic nephropathy. Table 6 showed that after adjustment for age, sex, and HbA1c in the presence of Netrin 1 for prediction of diabetic nephropathy, it was detected that the increase of patient's age one year increases the probability of acquisition of D. nephropathy with 1.087 times, every increase in Netrin 1 with one unit increases the D. nephropathy with 1.06 times. Every increase in HbA1c with one unit increases the D. nephropathy with 2.226 times.

Discussion

Although some studies have shown that diabetes may be slowed or stopped altogether if therapy begins sooner, it is difficult to anticipate and detect diabetic complications in their early stages. One example is the lack of a definite diagnosis method for diabetic retinopathy. Even when diagnostic techniques do exist, they often have inadequate sensitivity and specificity when it comes to additional problems [5].

Table 6: Multivariable binary logistic regression analysis for prediction of diabetic nephropathy in the presence of Netrin 1 after adjustment for other variables.

Independent variables	P-value	OR	95% C.I. for OR	
			Lower	Upper
Age	0.002*	1.087	1.030	1.148
Female sex	0.091	2.922	.841	10.148
Netrin 1	0.004*	1.060	1.019	1.103
HbA1C	0.001*	2.226	1.524	3.250
Model summary		R2=0.651 P-value<0.001*		

Note: * – P-value is significant; OR –odds ratio; CI – Confidence interval.

It would be ideal if diabetic management could be used early on in the course of the illness and directed towards those who would benefit most from the therapeutic intervention in order to slow the advancement of diabetes mellitus. In order to do this, it is crucial to find novel biomarkers that can identify people who are likely to develop diabetes and associated complications. This will allow us to focus our prevention efforts more effectively [6].

Jurgen *et al.*'s clinical trial suggested that Netrin-1 might be a novel biomarker for the early diagnosis of impaired fasting glucose (IFG) or type 2 diabetes. Serum Netrin-1 levels were positively correlated with fasting glucose, HbA1c, HOMA-IR, AST, and ALT; in brief, those with IFG or T2DM had a significantly higher level of serum Netrin-1 than the control group. Additionally, Netrin-1 and HDL cholesterol and eGFR levels were shown to have a statistically adverse association. Furthermore, the presence of either IFG or T2DM was independently linked to serum Netrin-1 [7].

In contrast, Liu *et al.* measured the level of Netrin-1 in diabetic patients by conducting a clinical trial on 56 human subjects; 30 of these participants had newly-onset type 2 diabetes, while the other 36 served as controls. Netrin-1 levels were significantly lower in diabetes patients compared to healthy controls. There was also a negative correlation between Netrin-1 level and homeostasis model insulin resistance, fasting glucose, post-meal plasma glucose, fasting insulin, triglyceride, and hemoglobin A1c levels [8].

Therefore, more research is needed to establish the true association between Netrin-1 level and DM and DN because the results of the two clinical investigations mentioned above were inconsistent.

In these, the majority of study participants had already experienced chronic renal failure (CRF), had damaged renal function, did not have a history of diabetes, or were only participants in animal experiments. At the same time, there was a scarcity of information about the relationship between plasma netrin-1 levels and the onset of diabetic nephropathy. It is uncertain how plasma netrin-1 levels and micro- and macroalbuminuria in diabetes relate to one another.

We set out to examine the potential of plasma netrin-1 level as an early predictor for the diagnosis of diabetic nephropathy, as well as the effects of netrin-1 on type 2 diabetic kidney complications and any associations between netrin-1 and the degree of albuminuria.

We enrolled 120 patients divided into four groups: a healthy control group, a diabetic group with no proteinuria, a diabetic group with micro-albuminuria, and a diabetic group with macroproteinuria. Each of them is 30 patients. There was no statistically significant difference between the four groups as regards age and sex distribution.

Post hoc pairwise comparisons between the four groups and between the non-nephropathic group (healthy control and diabetic not proteinuric) and nephropathic group (diabetic with micro-albuminuria and diabetic with macro proteinuria) for the significant difference in level of plasma netrin 1 level in each group. As predicted, there was a significantly higher creatinine level in the macro-proteinuria group than in the other 3 groups. There was a significant difference between all the studied groups except between diabetic non-proteinuria and diabetic micro-albuminuria regarding the eGFR.

Concerning plasma netrin 1 level in different groups, our study showed that there was a significant difference between all of the studied groups and the macro proteinuria group. There was an insignificant difference between the control group, the diabetic non-proteinuric group, and the diabetic micro-albuminuria group. On comparing the non-nephropathic group (healthy control and diabetic not proteinuria) and the nephropathic group (diabetic with micro-albuminuria and diabetic with macro proteinuria), the study showed that there was a significantly higher Netrin 1 level in patients with diabetic nephropathy compared to subjects without nephropathy.

Our findings corroborated those of Elkholy *et al.*, who showed that blood and urine netrin-1 levels were substantially higher in microalbuminuric and macroalbuminuric DN patients compared to normoalbuminuric T2DM patients; the greatest values were found in the macroalbuminuric DN patients [9].

Additionally, Liu *et al.* examined serum netrin-1 levels in relation to the albuminuria stage. They discovered that in the Macro-albuminuria group, the median serum netrin-1 level was significantly higher ($P<0.001$) compared to the normo-albuminuria group (2.45±1.07, 4.13±1.72, and 5.56±4.03 pg/mL, respectively) [10].

In the correlation between Netrin 1 level and all other laboratory data and disease duration with each group, there was a statistically significant linear moderate positive correlation between Netrin 1 and A/C ratio in the micro-albuminuria group and a statistically significant linear strong positive correlation between Netrin 1 and A/C ratio in the macro proteinuria group.

On the other side, when Correlating between Netrin 1 level and all other laboratory data and disease duration in the diabetic nephropathy group (micro and

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macro proteinuria), there was a statistically significant linear positive correlation between Netrin 1 and disease duration, urea level, and A/C ratio.

In predictive data using the Receiver Operating characteristic curve for the prediction of diabetes without proteinuria (compared to the control group), there was an insignificant role of Netrin 1 in the prediction of diabetes (without proteinuria) at a cut-off>32.3 with sensitivity, specificity, PPV, and NPV, 50%, 56.67%, 53.6%, and 53.1%, respectively. On the contrary, for the prediction of diabetes with micro-proteinuria there was a significant role of Netrin 1 in the prediction of diabetes with microproteinuria at a cut-off>36.4 with sensitivity, specificity, PPV, and NPV, 60%, 73.3%, 69.2%, and 64.7%, respectively and also for prediction of diabetes with macro proteinuria there was a significant role of Netrin 1 in prediction of diabetes with macro proteinuria at a cut off >36.4 with sensitivity, specificity, PPV, and NPV, 86.67%, 73.3%, 76.5%, and 84.6%, respectively.

In Multivariable binary logistic regression analysis for the prediction of diabetic nephropathy in the presence of Netrin 1 after adjustment for other variables, our study showed that after adjustment for age, sex, and HbA1c in the presence of Netrin 1 for prediction of diabetic nephropathy, it was detected that the increase of patient's age one year increases the probability of acquisition of D. nephropathy with 1.087 times, every increase in Netrin 1 with one unit increases the D. nephropathy with 1.06 times. Every increase in HbA1c with one unit increases the D. nephropathy by 2.226 times.

There are a number of plausible reasons for the correlation between increased netrin-1 plasma levels and the development of DN, and our clinical investigation lends credence to these findings. As a first step in improving translation, elevated albumin levels stimulate proximal tubular epithelial cell netrin-1 synthesis via the extracellular signal-regulated kinase (ERK) and Akt kinase pathways. Secondly, when early-stage diabetes causes the proximal tubules to have a diminished capacity, the body responds by increasing netrin-1 synthesis. According to current research, the development of DN is mostly influenced by poor tubular reabsorption of albumin. Our findings corroborate previous research showing an upregulation of various tubular damage markers in chronic kidney disease.

The diagnostic accuracy for the utility of Netrin-1 in the diagnosis of diabetic nephropathy in the study of Badran *et al.* revealed that at a cut-off point of less than 103 ng/ml, sensitivity was 33.33%, specificity was 77.97%, and accuracy was 77.97% [11].

Also, Shalaby and El Mancy found in their study that serum nitrin-1 levels at a cut-off value of >368 pg/ml can be used to discriminate between a healthy control group and patients with type 2 DM, with sensitivity of 80%, specificity of 93.3%, PPV 92.3%, and NPV 82.4% (AUC=0.96; p<0.001) [12].

Acute kidney damage was shown to mostly originate from proximal tubular epithelial cells, according to experiments conducted on mice with renal injury. Also, normal tubular epithelial cells in the kidney express very little netrin-1, whereas injured kidney cells express it at high levels [5].

This goes against the findings of Yim *et al.*, who found a correlation between increased blood netrin-1 levels and either IFG or newly diagnosed type 2 diabetes [13]. According to our research, Netrin 1 did not have a major effect on the diabetic group's proteinuria prediction. Nevertheless, further prospective research is required to clarify netrin-1's function in the development of type 2 diabetes, its consequences (such as diabetic nephropathy), and the likelihood of increasing its diagnostic and therapeutic use.

Conclusion

There is strong evidence that plasma netrin 1 level is significantly elevated in patients with diabetic nephropathy, whether micro or macro proteinuria, and there is a future hope for the possibility of using netrin 1 as an early predictor for diagnosis of diabetic nephropathy

Conflict of interest

The authors declare no conflict of interest.

Ethics approval

The approval for this study was obtained from the Ethics Committee of the Faculty of Medicine, Beni-Suef University (approval ID: FMBSUREC/07032021/Naiem).

Consent to participate

Written informed consent was obtained from all the participants.

References

1. Usha A, Sriprajna M, Sudindra R, Menambath DT. Netrin-1 and Insulin Resistance as markers in Type 2 Diabetes Mellitus. Journal of Livestock Science. 2023 Jan 1(14):148-154.
2. Salem HH, Lashin F, El Hai DA, Selim A. The Role of Netrin-1 and Interleukin-6 in Diabetic Nephropathy in Patients with Type 2 Diabetes Mellitus. Journal of Advances in Medicine and Medical Research. 2022 Sep 14;34(22):61-8.
3. Behnoush AH, Khalaji A, Shokri Varniab Z, Rahbarghazi A, Amini E, Klisic A. Urinary and circulatory netrin-1 as biomarker in diabetes and its related complications: a systematic review and meta-analysis. Endocrine. 2024 May;84(2):328-44.
4. Fadel MM, Ghaffar FR, Zwain SK, Ibrahim HM. Serum netrin and VCAM-1 as biomarker for Egyptian patients with type II diabetes mellitus. Biochemistry and Biophysics Reports. 2021 Sep 1;27:101045.
5. Tu Y, Wang H, Sun R, Ni Y, Ma L, Xv F, et al. Urinary netrin-1 and KIM-1 as early biomarkers for septic acute kidney injury. Renal failure. 2014 Nov 1;36(10):1559-1563.
6. Guay C, Regazzi R. Circulating microRNAs as novel biomarkers for diabetes mellitus. Nature Reviews Endocrinology. 2013 Sep;9(9):513-521.
7. Jung HI, Bae J, Han E, Kim G, Lee JY, Kim SR, et al. Circulating Netrin-1 as a novel biomarker for impaired fasting glucose and newly diagnosed type 2 diabetes mellitus. Diabetes. 2018 Jul 1;67(1):1535.
8. Liu C, Ke X, Wang Y, Feng X, Li Q, Zhang Y, et al. The level of netrin-1 is decreased in newly diagnosed type 2 diabetes mellitus patients. BMC endocrine disorders. 2016 Dec;16:1-5.
9. Elkholy RA, Younis RL, Allam AA, Hagag RY, Abdel Ghafar MT. Diagnostic efficacy of serum and urinary netrin-1 in the early detection of diabetic nephropathy. Journal of Investigative Medicine. 2021 Aug;69(6):1189-1195.
10. Liu C, Li Q, Feng X, Li Q. Elevated levels of netrin-1 in the serum of patients with diabetic nephropathy: relationship with renal function and inflammation. European Journal of Inflammation. 2018 Nov;16:1-6.
11. Badran DI, Elkholy EA, Youssef MF. Netrin-1 and 8-Hydroxy-2-Deoxyguanosine as Predictor Biomarkers for Diabetic Nephropathy in Type 2 Diabetes Mellitus. Advances in Environmental and Life Sciences. 2024 Jan 1;5(1):1-9.
12. Shalaby A, El Mancy IM. Study of serum Netrin-1 level in prediabetics and type 2 diabetic Egyptian patients. Al-Azhar International Medical Journal. 2021 Jun 1;2(6):17-22.
13. Yim J, Kim G, Lee BW, Kang ES, Cha BS, Kim JH, et al. Relationship between circulating netrin-1 concentration, impaired fasting glucose, and newly diagnosed type 2 diabetes. Frontiers in endocrinology. 2018 Nov 23;9:691.

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