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The correlation of serum Asprosin with diabetic nephropathy

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Abstract: Asprosin, a recently identified adipokine, promotes glucose synthesis in the liver. Diabetic nephropathy (DN) is the primary cause of end-stage renal disease. Asprosin has been linked to inflammation and insulin resistance, both critical to DN development. This study aimed to investigate the correlation between serum asprosin levels and DN in patients with type 2 diabetes (T2DM). A total of 180 participants were included in this study: 129 patients with T2DM and 51 healthy controls. Patients were divided into three groups based on their urine albumin to creatinine ratio (UACR): DN0 group (UACR < 30 mg/g), DN1 group (30 ≤ ACR < 300 mg/g), and DN2 group (≥ 300 mg/g). T2DM patients had greater serum asprosin levels than members of the control group. Looking at the various forms of diabetic nephropathy, the DN2 group had notably more asprosin in their blood than the DN0 and DN1 groups. Furthermore, more asprosin was present in the blood of the DN1 group than in the DN0 group. Serum asprosin levels were also strongly correlated with the duration of the disease, blood pressure, increasing blood sugar, glycated hemoglobin, total cholesterol, triglycerides, low-density lipoprotein cholesterol, urea, creatinine, and UACR. Conversely, high-density lipoprotein cholesterol and estimated glomerular filtration rate (eGFR) were negatively correlated very substantially. As DN deteriorated, asprosin levels in the blood increased. Apart from that, asprosin had a negative connection with eGFR and a positive one with UACR.

Keywords: *Asprosin, Diabetic nephropathy, Type 2 diabetes mellitus.*

1. Introduction

Diabetic nephropathy (DN) is one of the most serious complications of type 2 diabetes mellitus (T2DM) and is the primary cause of end-stage renal disease (ESRD) worldwide [1]. It is associated with high morbidity and mortality, having a major effect on patient outcomes. Notably, DN develops in approximately 40% of individuals with type 2 diabetes after a disease duration of 10 years [2]. The pathogenesis of DN is multifactorial, with multiple factors contributing to its onset and progression. These factors include glucose and lipid metabolism disorders, insulin resistance (IR), dysregulation of several cytokines, chronic inflammation, and endothelial dysfunction [3-5]. Asprosin is a newly discovered adipokine. It is C-terminal cleavage peptide produced by profibrillin and encoded by the FBN1 gene. It is released from white adipose tissue and transported primarily to the liver. During starvation, this hormone causes liver cells to release glucose via G protein-cAMP-PKA, preventing hypoglycemia [6]. Another study that looked at how things work showed that asprosin could also get through the blood-brain barrier. Plasma asprosin directly triggers orexigenic neurons in the brain through a cAMP-dependent signal. This makes people gain weight and eat more.It has also been shown that asprosin is linked to inflammation (JNK phosphorylation TLR4-dependent pathway) [7] and endoplasmic reticulum (ER) stress (ER stress/inflammation-dependent pathways) [8]. A lot of research has been done on the link between asprosin and diabetes mellitus and insulin resistance in people. These studies showed a link between the amount of asprosin in the blood and HOMA-IR. People with T2DM

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had higher amounts of asprosin in their blood [8-11]. Asprosin amounts in the blood were going to be looked at in people with and without T2DM, as well as in healthy people who were not diabetes. We also looked into the link between asprosin and the urine albumin-to-creatinine ratio (UACR) and the estimated glomerular filtration rate (eGFR).

2. Materials and Methods

2.1. Subjects

The 180 people who took part in this case-control study included 129 people with T2DM who were identified according to the 2024 American Diabetes Association (ADA) standards [12]. Based on the urinary albumin to creatinine ratio (ACR) measurements, the patients were then put into three groups: DN0 (normal to mildly increased, ACR < 30 mg/g; 39 patients), DN1 (moderately increased, 30 mg/g to 300 mg/g; 40 patients), and DN2 (severely increased, ACR ≥ 300 mg/g; 50 patients). A group of fit adults (n=51) was chosen as a reference.

Exclusion criteria included : Diabetes type 1, heart disease, liver failure, and cancer are some of the most common problems that can happen after having type 1 diabetes. They did the study at four hospitals in Basra, Iraq, from February to July 2024. These were Al-Fayhaa Teaching Hospital, Al-Mawani Teaching Hospital, Basra Teaching Hospital, and Al-Sadr Teaching Hospital. Because they were in line with the Declaration of Helsinki, the methods were okay with the Ethics Committee of Human Experimentation of Affiliated Hospitals. Everyone who is taking part in this study has signed a written permission form.

2.2. Data Collection

Anthropometric parameters including height and weight were recorded. The body mass index (BMI) was determined by the formula weight/height^2. Blood pressure (BP) was measured. The glomerular filtration rate (GFR) was calculated using the Cockroft-Gault formula. A biochemistry automated analyzer [COPAS INTEGRA 400 plus (Roche Diagnostics, Mannheim, Germany)] was used to measure Fasting blood sugar, serum lipids and renal function parameters. Glycated hemoglobin (HbA1c) was measured using an ion-exchange high performance liquid chromatography (HPLC) (Bio-Rad Variant™ Il Turbo analyzer). The ACR was tested three times, and the average score was used. An ELISA kit from Melsin Medical Co., Limited in China was used to check blood samples for asprosin.

2.3. Statistical Analysis

The data were examined using SPSS version 26 and provided as Mean ± SD and percentages. The ANOVA (continuous variables) or chi-squared test (categorical variables) was used to assess the variations across groups. A P value less than 0.05 helped to define the threshold of significance. Using Pearson correlation, the correlation coefficient (r-value) between asprosin and biochemical parameters, together with other study population variables, was assessed.

3. Results

3.1. Baseline Characteristics of the Study Population

The present study included 180 participants (51 controls and 129 cases divided into 3 groups DN0 39, DN1 40, and DN2 50). As shown in Table 1, compared with the control group, the diabetic patient groups expressed significantly higher BMI, systolic BP, diastolic BP, FBS, HbA1c, total cholesterol (TC), triglyceride (TG), low-density lipoprotein-cholesterol (LDL-C), very low-density lipoprotein-cholesterol (VLDL), urea, creatinine (Cr) and UACR and lower high-density lipoprotein-cholesterol (HDL-C) and eGFR. With further comparison, DN2 patients showed the most pronounced abnormalities compared to controls, DN0, and DN1 groups ($p<0.001$).

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3.2. Asprosin Levels in Different Subgroups

The asprosin levels in the blood were checked in three groups of T2DM patients and healthy people. The levels were 14.45 ± 0.73 ng/mL for DN0, 17.18 ± 1.38 ng/mL for DN1, 22.32 ± 1.41 ng/mL for DN2, and 10.71 ± 0.87 ng/mL for controls. In Table 1, you can see that there is a statistically significant difference between the groups (P< 0.001).

Table 1.
Clinical characteristics of the study population.

Parameters		T2DM			
	Control (n=51)	DN0 (n=39)	DN1 (n=40)	DN2 (n=50)	P value
Age	49.14 ± 12.27	53.33 ± 13.86	50.28 ± 12.36	50.48 ± 12.44	0.476
Gender M/F	25/26	19/20	18/22	26/24	0.934
BMI	21.76 ± 1.45	27.22 ± 2.02[a]	28.86 ± 2.38[ab]	32.67 ± 2.49[abc]	<0.001
SBP (mmHg)	118.02 ± 9.19	124.41 ± 2.68[a]	132.48 ± 2.87[ab]	135.38 ± 5.77[abc]	<0.001
DBP (mmHg)	77.63 ± 2.63	78.77 ± 2.40[a]	84.15 ± 2.91[ab]	89.76 ± 2.52[abc]	<0.001
Duration of DM	-	3.41 ± 1.81	6.65 ± 3.57[b]	6.96 ± 4.29[b]	<0.001
FBS (mg/dL)	87.96 ± 10.26	189.72 ± 18.48[a]	253.85 ± 47.06[ab]	308.60 ± 65.22[abc]	<0.001
HbA1c (%)	4.56 ± 0.39	7.82 ± 0.55[a]	9.61 ± 0.70[ab]	10.60 ± 0.78[abc]	<0.001
Urea (mg/dL)	25.76 ± 6.68	27.28 ± 7.10	99.03 ± 22.71[ab]	135.64 ± 23.19[abc]	<0.001
Cr (mg/dL)	0.64 ± 0.16	0.65 ± 0.15	1.97 ± 0.29[ab]	5.00 ± 0.79[abc]	<0.001
UACR (mg/g)	7.22 ± 3.61	14.64 ± 5.07	93.55 ± 33.33[ab]	509.42 ± 115.41[abc]	<0.001
eGFR (mL/min/1.73m^2)	127.20 ± 46.6	124.35 ± 46.45	31.12 ± 1.08[ab]	11.28 ± 2.68[abc]	<0.001
Asprosin (ng/mL)	10.71 ± 0.87	14.45 ± 0.73[a]	17.18 ± 1.38[ab]	22.32 ± 1.41[abc]	<0.001
TC (mg/dL)	163.80 ± 15.81	214.28 ± 12.79[a]	227.98 ± 16.82[ab]	268.02 ± 14.85[abc]	<0.001
HDL-C (mg/dL)	52.12 ± 4.45	44.26 ± 2.51 [a]	35.88 ± 3.48[ab]	35.62 ± 3.53[ab]	<0.001
LDL-C (mg/dL)	90.81 ± 16.14	135.66 ± 11.32[a]	156.99 ± 15.28[ab]	179.42 ± 12.37[abc]	<0.001
VLDL (mg/dL)	20.87 ± 5.81	34.36 ± 3.02[a]	35.10 ± 1.85[a]	52.98 ± 4.03[abc]	<0.001
TG (mg/dL)	104.27 ± 29.09	171.82 ± 15.11 [a]	175.53 ± 9.25 [a]	264.90 ± 20.19 [abc]	<0.001

Triglycerides (TG), blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI), and type 2 diabetes mellitus (T2DM) are all terms used in this study. LDL-C (low-density lipoprotein cholesterol), HDL-C (high-density lipoprotein cholesterol), and VLDL-C (very low-density lipoprotein cholesterol) are the different types of cholesterol that can be found in the blood. In this test, we measure Cr creatinine, UACR (urine albumin to creatinine ratio), and eGFR (estimated glomerular filtration rate). A big difference compared to the control group; B a big difference compared to the DN0 group; C a big difference compared to the DN1 group

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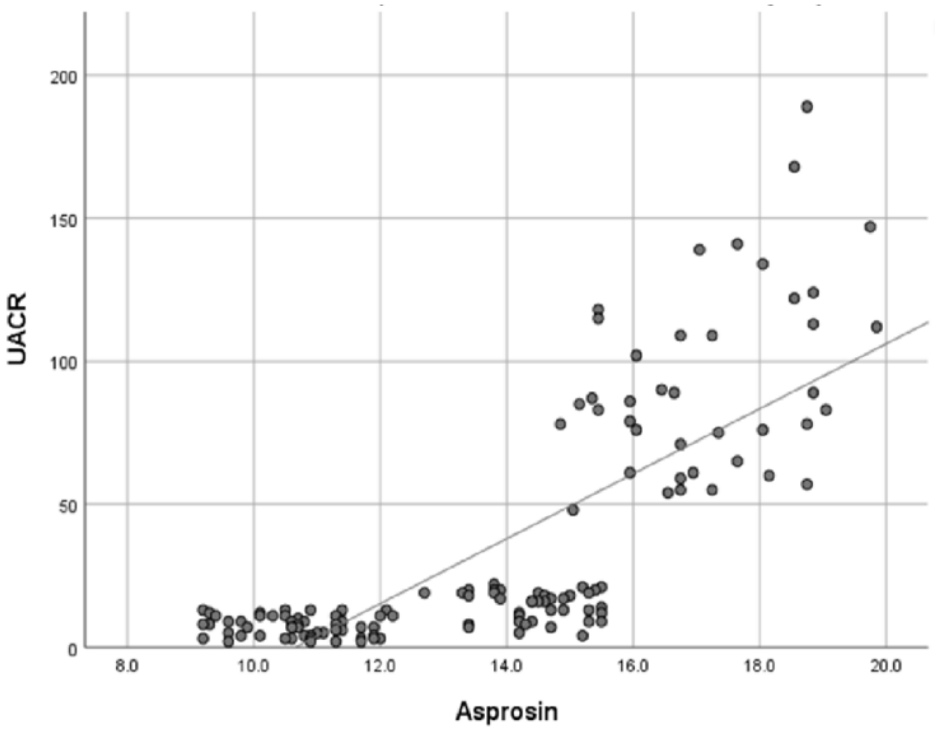

Figure 1.
Correlation of asprosin levels with UACR in T2DM patients (Pearson r =0.893, p < 0.001).

Serum asprosin correlates positively and significantly with FBS, HbA1c, TC, TG, LDL, urea, creatinine, and UACR (p<0.001), Figure 1, while this study showed that there is a negative significant correlation between asprosin with HDL-C, and eGFR (p<0.001), Figure 2.

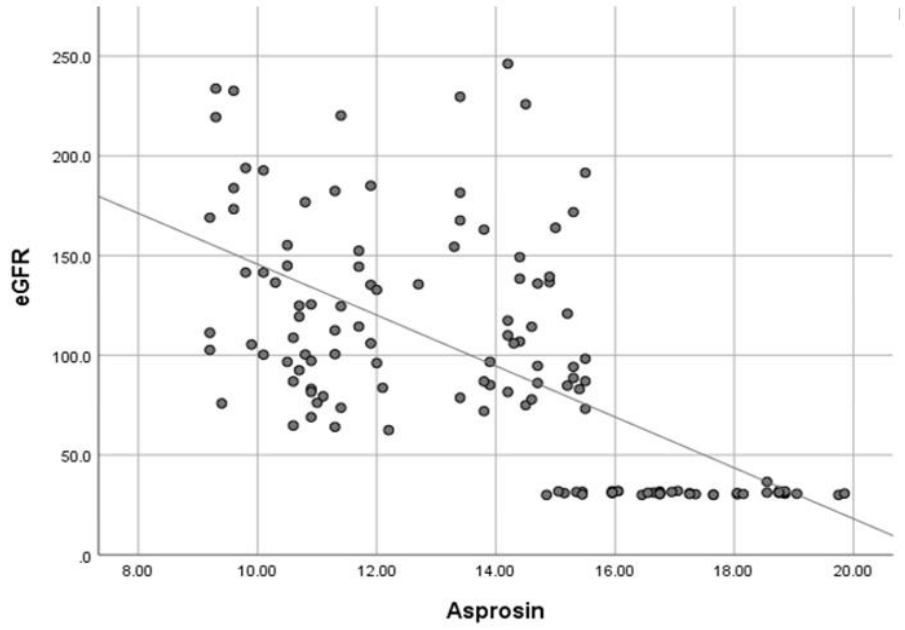

Figure 2.
Correlation of asprosin levels with eGFR in T2DM patients (Pearson r = - 0.778, p < 0.001).

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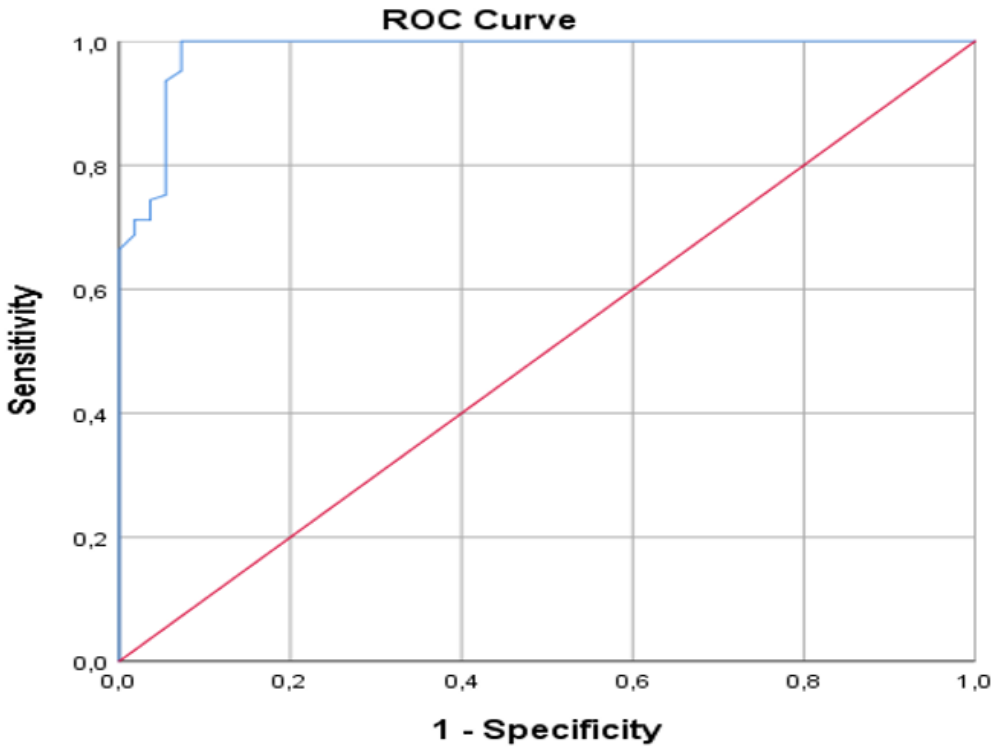

Figure 3.
ROC curve analysis of asprosin's diagnostic capacity to distinguish between T2DM from control.

3.3. Receiver-Operating Characteristic (ROC) Curve Analysis for Asprosin with T2DM and T2DM with DN in the Study Population

Figures 3 and 4 show the ROC curve analysis that was used to test how well asprosin could tell the difference between disease states. So, asprosin showed a good ability to tell the difference between T2DM (AUC [CI] 0.983[0.965, 1]). There was a significant difference between the controls and T2DM + DN cases (AUC [CI] 0.994 [0.987–1.000], p<0.001, cutoff: (15.32 ng/mL), sensitivity: 96.7% and specificity: 94.4 %).

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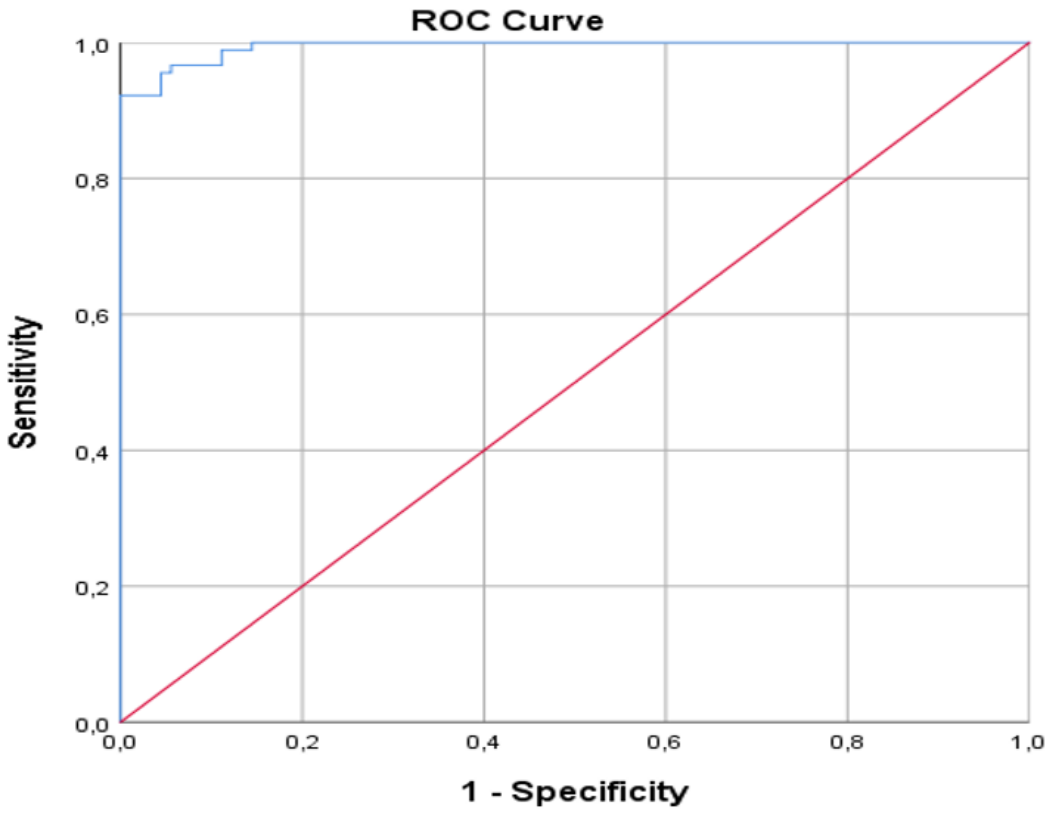

Figure 4.
ROC curve analysis of asprosin's diagnostic capacity to distinguish between T2DM+DN from control.

4. Discussion

In this study, they looked at the link between diabetic nephropathy and asprosin, a new adipokine that changes metabolism in people with type 2 diabetes. This study found that blood asprosin levels were much higher in people with T2DM who had DN 0 (UACR < 30 mg/g), DN1 (UACR 30–299 mg/g), and DN 2 (UACR ≥ 300 mg/g) compared to the control group. Also, higher levels of asprosin in the blood were related to lower eGFR and higher levels of creatinine in the blood, showing a possible link between asprosin and kidney problems in people with T2DM. Furthermore, serum asprosin concentrations showed a positive correlation with UACR, creatinine, urea, and a negative correlation with eGFR. A new study by Zhang, et al. [13] found that people with T2DM who had microalbuminuria had higher amounts of asprosin. These results are similar. The amounts of asprosin were checked in three groups: those with normal glucose tolerance, T2DM without DN, and T2DM with early-stage DN. People with macroalbuminuria, on the other hand, were not allowed to take part in the study. This showed that asprosin had a strong link with early DN. However, it is not possible to tell if asprosin amounts change with albuminuria stages. Still, our results give us some information about this problem. El Kattawy and Ashour [14] conducted an animal study, in which type 2 diabetic rats given an anti-asprosin antibody showed a substantial decrease in creatinine, blood urea, and proteinuria in comparison to control rats. Nevertheless, the investigation of renal pathology demonstrated that the treatment with anti-asprosin antibodies effectively alleviated chronic inflammation in the glomeruli and tubules of the kidneys, thereby significantly reducing kidney injury. These findings indicate that asprosin may influence the onset and progression of diabetic nephropathy. The current study's findings demonstrated that, in comparison to the DN0 group, the TG, TC, and LDL-C levels were greater in the DN1 and DN2 groups, while the HDL-C level was lower. Asprosin also caused higher amounts of TC,

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TG, and LDL-C in the blood of diabetes patients. A positive relationship was seen between the amount of asprosin in the blood and BMI, TC, TG, and LDL-C. A negative relationship was seen with HDL-C. A similar link has been found by other studies as well [15-17]. It is well established that the development of diabetic nephropathy may be facilitated by dyslipidemia [18, 19]. Researchers have found that when people with type 2 diabetes have too many lipids, it can raise the levels of AGEs and inflammatory cytokines in the kidneys. This can cause problems with the endothelium, glomerulosclerosis, and tubule interstitial failure [20-22]. Also, as a result of excessively high blood lipid levels, the blood viscosity increases, decreasing renal blood flow, resulting in hypoxia , ischemia, glomerular capillary destruction, which in turn causes increased permeability and albumin leakage, which aggravates DN [17]. To find out how well asprosin can tell the difference between people with sickness and people who are healthy, we made a ROC curve and calculated the AUC. Asprosin has a high diagnostic ability to distinguish between type 2 diabetes, as evidenced by the AUC of 0.983. The diagnostic sensitivity and specificity for type 2 diabetes were 99.2% and 92.7%, respectively, at the cutoff point of 13 ng/mL. Additionally, asprosin's AUC of 0.994 suggests that it can effectively distinguish diabetic nephropathy. The diagnostic sensitivity was 96.7% and the specificity was 94.4% at the cutoff point of 15.32 ng/mL.

5. Conclusions

T2DM patients at different stages of diabetic nephropathy had significantly higher serum asprosin levels. Asprosin levels showed a positive correlation with BMI, disease duration, blood pressure, FBS, HbA1c, UACR, creatinine, urea, TC, TG, and LDL-C, while demonstrating a negative correlation with eGFR and HDL-C. These findings suggest that serum asprosin levels could serve as a potential indicator for the presence and progression of diabetic nephropathy. Therapeutically focusing on asprosin may also provide novel approaches to treating DN. To clarify the exact mechanism that connect asprosin to renal disease, further research is necessary.

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Institutional Review Board Statement:

Ethical approval was received from the ethical and research committee of the affiliated hospitals (Al-Fayhaa Teaching Hospital, Al-Mawani Teaching Hospital, Basra Teaching Hospital, Al-Sadr Teaching Hospital in Basrah, Iraq). All patients included in this study have signed handwritten consent documents.

Transparency:

The authors confirm that the manuscript is an honest, accurate and transparent account of the study that no vital features of the study have been omitted and that any discrepancies from the study as planned have been explained. This study followed all ethical practices during writing.

Competing Interests:

The authors declare that they have no competing interests.

Authors' Contributions:

All authors contributed equally to the conception and design of the study. All authors have read and agreed to the published version of the manuscript.

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