



Estimation of the Association between Serum Fibulin-1 Levels and Diabetic Nephropathy

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ABSTRACT

Background: One of the most dangerous side effects of diabetes is diabetic nephropathy, which can result in end-stage renal failure. Fibulin-1, an extracellular matrix component, is believed to be involved in renal and vascular disorders. This study aims to elucidate the potential of serum fibulin-1 levels as a biomarker for the early detection and progression assessment of diabetic nephropathy, providing a novel insight beyond previously established associations.

Methods: The study included 90 participants, comprising 50 patients diagnosed with diabetic nephropathy and 40 healthy individuals serving as the control group. Fibulin-1 levels, Glycated hemoglobin (HbA1c), fast blood glucose (FBG), creatinine, urea, components of the lipid profile (total cholesterol, triglycerides, high density lipoprotein "HDL" and low density lipoprotein "LDL"), and were among the biochemical studies performed on blood samples. SPSS version 26.0 and Graph Pad Prism version 6 were used to analyze the data.

Results: The results demonstrated that patients with diabetic nephropathy exhibited significantly elevated levels of Fibulin-1, FBG, HbA1c, creatinine, urea, and LDL compared to the control group ($p < 0.001$). A positive correlation was identified between serum Fibulin-1 levels and both creatinine and LDL; however, no significant association was observed between Fibulin-1 and either HbA1c or BMI. Furthermore, the diagnostic potential of Fibulin-1 was assessed using Receiver Operating Characteristic (ROC) curve analysis, which revealed a strong area under the curve (AUC) value of 0.848 ($p < 0.001$), indicating high diagnostic accuracy. The analysis demonstrated good sensitivity (70%) and excellent specificity (95%), reinforcing Fibulin-1 as a promising biomarker for diabetic nephropathy detection.

Conclusion: The fibulin-1 increased significantly ($p < 0.001$) in diabetic nephropathy patients with a very good area under the curve (0.848). From these results, fibulin-1 may be a possible indicator of diabetic nephropathy progression, given its association with markers of renal dysfunction.

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1. INTRODUCTION

Diabetic nephropathy (DN), one of the most prevalent and dangerous side effects of diabetes mellitus (DM), is associated with increased rates of morbidity and mortality in diabetics [1]. From over 40,000 in 2000 to over 50,000 in 2014, the number of diabetic individuals in the US beginning End-stage renal disease (ESRD) treatment has increased significantly [2]. If the treatment strategy for DN prevention does not

immediately improve, the incidence of DN is expected to rise along with the prevalence of diabetes [3]. According to a significant longitudinal cohort study conducted by the United Kingdom Prospective Diabetes Study (UKPDS) center [4], approximately one-third of diabetes patients develop kidney damage as a consequence of the condition [4]. Obesity, smoking, and metabolic syndrome are additional vascular risk factors that worsen these consequences [5].

The pathophysiology of DN remains highly intricate and not yet fully understood, contributing to suboptimal therapeutic outcomes. Research indicates that conventional treatment—primarily focusing on rigorous blood pressure and blood glucose management [3]—fails to halt the progression of DN to end-stage renal disease (ESRD) and does not significantly reduce DN-related mortality [6]. Advancing new therapeutic approaches necessitates a deeper understanding of the underlying mechanisms of diabetic nephropathy (DN). Current research suggests that multiple pathways and mediators—including oxidative stress, angiotensin II (Ang-II), and inflammatory responses—play a crucial role in the progression and development of DN [3,7]. Increased glomerular capillary pressure and permeability (resulting in proteinuria), stimulation of renal cell proliferation and hypertrophy, synthesis of cytokines and extracellular matrix (ECM), and encouragement of macrophage infiltration and inflammation are some of the effects of internal Ang-II that may advance kidney injury [3].

One such group of ECM proteins is the fibulin proteins family[8].Fibulins are a family of extracellular matrix (ECM) proteins, comprising the members fibulin-1 to 8, and they are associated with vasculature and elastic tissues [9].It was named after the latin word fibula, which means clasp or buckle [10]. Fibulins, found in connective tissue fibers, basement membranes, and blood clots, have been linked to tissue organogenesis, vasculogenesis, fibrogenesis, and tumorigenesis due to their role in the elaboration and stabilization of the extracellular matrix [11].

Fibulin-1 is found in the major vessels, coronary arteries, brain, choroid plexus, meninges, and other connective tissues such as the kidney, lung, and liver [11]. Correlations have been seen between indicators of decreasing kidney function and rising serum fibulin-1 concentrations [12]. In the given circumstance, it is proposed that decreased renal function may be linked to damaged kidney structures, resulting in an increased amount of free fibulin-1 accumulating in circulation. This discovery would be interesting to place in a broader context that includes other extracellular matrix proteins associated with kidney dysfunction, such as elastin and collagen, which have been described as potential indicators and therapeutic targets for renal problems [13].

2. Methods

The study included 90 samples, divided into two groups. The first group comprised 50 patients diagnosed with diabetic nephropathy by a specialist physician at Baqubah Teaching Hospital in Diyala Province. The second group consisted of 40 healthy volunteers, serving as the control group. Samples were collected by drawing 5 ml of venous blood from each participant using plastic medical syringes. The collected blood samples were divided into two portions: the first was placed in EDTA tubes for HbA1c testing, while the second was stored in gelatin tubes for further analysis. To extract the serum, the gelatin tubes were centrifuged at 3000 rpm for 10 minutes to separate the serum for each sample, which was then splitted into two portions in tiny tubes. The first part is used to make blood tests, which ncludes TG, TC, HDL-C, albumin, urea, creatinine, uric acid, and CRP, whereas the second part, which is kept at -20°C, is used later to perform Fibulin-1 tests.

3. Statistical analysis

The scale's numerical parameters were first tested for normality using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Those that passed both tests (no significant difference) were given as mean $\pm$ standard deviation (SD), and the ANOVA test was used to compare the groups. The other parameters (nominal) were given as percentage frequencies, and the Pearson-Chi-square test was used to determine whether there were significant differences between the frequencies. The Graph Pad Prism version 6 and the statistical package SPSS version 26.0 were used to conduct these analyses.

4. Results

4.1. Comparison of Age, BMI, Duration, FBG and HbA1c parameters of two group

Table 1 presents a comparative analysis of age (years), BMI (kg/m²), disease duration (years), FBG (mg/dL), and HbA1c (%) between two groups: 50 diabetic nephropathy (DN) patients and 40 healthy individuals serving as the control group. The DN patients had a significantly higher mean age of 63.70 years compared to 56.35 years in the control group, which is statistically significant ($p < 0.001$). Additionally, DN patients had a noticeably increased body mass index (BMI) 30.14 versus 25.84 in the control group, indicating overweight or obesity in DN patients. The duration of diabetes in DN patients was 14.98 years, while there was no history of diabetes in the control group (0.0 year). This reflects the strong association between long duration of diabetes and development of diabetic nephropathy. FBG were significantly higher ($p < 0.001$) in DN patients, averaging 240.3 mg/dL compared to 105.5 mg/dL in the control group. Also, HbA1c was significantly higher ($p < 0.001$) in DN patients, 8.15% versus 5.68%, reflecting poor glucose control in patients with diabetic nephropathy.

Table 1. Comparison of Age, BMI, Duration, FBG and HbA1c parameters of two groups

Variable	Mean±SD 50DN Patients	Mean±SD 40Control group	P value
Age (years)	63.70 ± 11.50	56.35 ± 9.36	< 0.001**
BMI (kg/m ²)	30.14 ± 4.82	25.84 ± 2.83	< 0.001**
Duration (years)	14.98 ± 8.27	0.0 ± 0.0	< 0.001**
FBG (mg/dL)	240.3 ± 121.5	115.5 ± 14.98	< 0.001**
HbA1c (%)	8.15 ± 2.0	5.68 ± 0.75	< 0.001**

4.2. Comparison of Urea, Creatinine, Uric acid, Albumin and eGFR in two groups

The results of Table 2 below showed that DN patients suffered from significant deterioration in renal function. Creatinine level in DN patients was significantly higher, averaging 4.66 mg/dL compared to 0.68 mg/dL in the control group, a highly significant difference ($p < 0.001$), indicating impaired renal function. Also, urea was significantly elevated in DN patients, reaching 133.8 mg/dL compared to 37.67 mg/dL in the control group, and the difference was highly significant ($p < 0.001$). DN patients had substantially higher uric acid levels 7.07 mg/dL compared to the control group 5.70 mg/dL, indicating a greater risk of hyperuricemia, which can aggravate renal issues and infections. Albumin level was lower in DN patients, reaching 3.36 g/dL compared to 4.17 g/dL in the control group, which may indicate protein loss through urine (proteinuria) due to deterioration of kidney function, but the difference was not significant ($p > 0.05$). Glomerular filtration rate (eGFR) was sharply lower in DN patients, reaching 19.71 ml/min/1.73m² compared to 97.14 ml/min/1.73m² in the control group, indicating an advanced stage of renal failure in diabetic nephropathy patients ($p < 0.001$).

Table 2. Comparison of Urea, Creatinine, Uric acid, Albumin and EGFR parameters of two groups

Variable	Mean±SD 50DN Patients	Mean±SD 40Control group	P value
Urea (mg/dL)	133.8 ± 74.09	37.67 ± 10.59	< 0.001**
Creatinine (mg/dL)	4.66 ± 2.84	0.68 ± 0.21	< 0.001**
Uric acid (mg/dL)	7.07 ± 3.15	5.70 ± 1.35	<0.01*
Albumin(g/dL)	3.36 ± 1.53	4.17 ± 0.64	> 0.05
EGFR(ml/min/1.73m ²)	19.71 ± 16.16	97.14 ± 19.37	< 0.001**

4.3. Comparison of lipid profiles and of serum in two groups

In Table 3, DN patients had significantly higher total cholesterol levels 189.7 mg/dL compared to the control group 122.5 mg/dL, with a very significant difference ($p < 0.001$). Triglycerides were also considerably greater, reaching 163.3 mg/dL in DN patients compared to (89.93 mg/dL) in the control group, with a very significant difference ($p < 0.001$). As for bad cholesterol (LDL), it was greater in DN patients, reaching 104.9 mg/dL compared to 53.27 mg/dL, and the difference was very significant ($p < 0.001$), which raises the risk of heart disease. Additionally, DN patients had greater levels of very low-density lipoprotein (VLDL), reaching 32.69 mg/dL as opposed to 17.99 mg/dL this difference was highly significant ($p < 0.001$).

Good cholesterol (HDL) levels in the two groups were 47.90 mg/dL in DN patients and 51.33 mg/dL in the control group; however, this difference was not statistically significant ($p > 0.05$).

Table 3. Comparison of lipid profiles of serum in two groups

Variable	Mean±SD 50DN Patients	Mean±SD 40Control group	P value
Cholesterol (mg/dL)	189.7± 51.73	122.5± 19.05	< 0.001**
Triglycerides (mg/dL)	163.3±53.71	89.93±16.58	< 0.001**
HDL (mg/dL)	47.90±11.26	51.33±7.47	> 0.05
LDL (mg/dL)	104.9 ±41.27	53.27 ±20.50	< 0.001**
VLDL (mg/dL)	32.69±10.74	17.99±3.31	< 0.001**

4.4. Comparison of CRP and FBLN-1 in two groups

In Table 4, the CRP level 4.93 mg/L was higher in DN patients compared to the control group 2.71 mg/L, but it was not statistically significant ($p < 0.05$). The Fibulin-1 level was higher in DN patients, reaching 7.07 ng/ml compared to the control group 5.70 ng/ml, and the difference was highly significant ($p < 0.001$), which may indicates the role of this protein in the development of diabetic nephropathy.

Table 4. Comparison of CRP and FBLN-1 in two groups

Variable	Mean±SD 50 DN Patients	Mean±SD 40 Control group	P value
CRP(mg/L)	4.93 ± 5.94	2.71 ± 1.69	< 0.05
FBLN-1 (ng/ml)	7.07 ± 3.15	5.70 ± 1.35	< 0.001**

4.5. Correlations

Fibulin-1 exhibits a weak and statistically insignificant correlation with BMI, suggesting that body mass index does not influence fibulin-1 levels in patients with diabetic nephropathy. While FBG, HbA1c, urea, creatinine, Uric acid, and albumin all have a moderately positive significant correlation ($p < 0.05$), which means that increased FBLN-1 may be associated with increased blood levels of these factors, which may be related to metabolic processes and kidney functions. Total cholesterol, triglycerides, VLDL, and HDL all have a weak positive insignificant correlation with FBLN-1, which means that this protein does not significantly affect lipid levels in diabetic nephropathy patients. LDL exhibits a positive but statistically insignificant correlation ($r = 0.280$, $p > 0.05$) with Fibulin-1 levels. This finding suggests a potential association between elevated Fibulin-1 and increased LDL levels, which may contribute to cardiovascular disease risk in patients with diabetic nephropathy. Additional research is required to validate and further explore this potential association.

eGFR has a weak positive non-significant correlation (0.187) with FBLN-1 as shown in table 5.

Table 5. Correlations of FBLN-1 with tested biochemical parameters of diabetic nephropathy patients calculated by Pearson correlation

Parameters	FBLN-1	Parameters	FBLN-1
BMI	r 0.153	Cholesterol	r 0.207
	p > 0.05		p > 0.05
FBG	r 0.442*	Triglycerides	r 0.142
	p < 0.05		p > 0.05
HbA1c	r 0.430*	HDL	r 0.056
	p < 0.05		p > 0.05
Urea	r 0.420*	LDL	r 0.280
	p < 0.05		p > 0.05
Creatinine	r 0.504*	VLDL	r 0.141
	p < 0.05		p > 0.05
Uric acid	r -0.351*	EGFR	r 0.187
	p < 0.05		p > 0.05
Albumin	r 0.209		
	p > 0.05		

4.6. Receiver operating characteristic curve

The results of receiver operating characteristic (ROC) curve statistical analysis for FBNL-1 in patients, demonstrated Area Under the Curve(AUC) (0.848). This value reflects the accuracy of the test. The closer it is to 1, the better the test is at distinguishing between patients and healthy individuals. A value of (0.848) indicates very good accuracy. Standard Error (Std. Error) (0.040) this shows how variable the estimated AUC value is, and a small value means that the estimating is reliable. (P-value < 0.001) this value indicates that the results are statistically significant, i.e. the test has a real ability to distinguish between groups. Sensitivity (70%) refers to the ability of the test to detect infected patients. That is, 70% of true patients were correctly classified. Specificity (95%) refers to the ability of the test to exclude healthy individuals. That is, 95% of non-infected individuals were correctly classified. The graph in figure 1 shows the ROC curve, where the higher the curve and the further away from the diagonal line (red line), the more accurate the test is. The diagonal line represents a random guess (AUC = 0.5), and since the actual curve is clearly above it, this means that the FBLN-1 test is effective in distinguishing between disease and non-disease cases. as shown in table 6.

Table 6. Statistical analysis of receiver operating characteristic curve for fibulin-1 in DN patients

Variables	AUC	Std. Error ^a	P value	Sensitivity %	Specificity %
FBLN-1	0.848	0.040	< 0.001	70 %	95 %

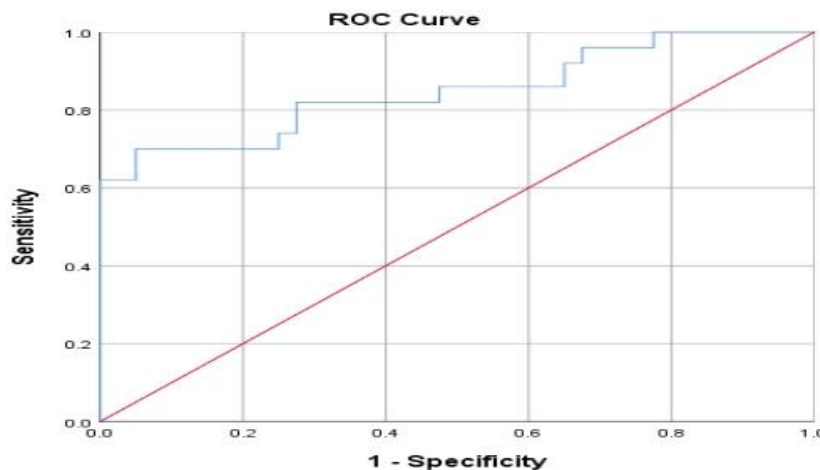


Figure 1. ROC curve of Fibulin-1 in DN patients

5. Discussion

One of diabetes's prevalent and dangerous side effects is diabetic nephropathy (DN). Which has a substantial impact on patients' quality of life and, if left untreated, can result in end-stage renal failure. In order to better understand the connection between fibulin-1 levels and the course of the disease, we examined a number of clinical and biochemical characteristics in patients with diabetic nephropathy these results offer fresh perspectives on the variables linked to diabetes individuals' declining renal function.

In this study, we identified a correlation between serum Fibulin-1 levels and diabetic nephropathy, aligning with previous experimental and clinical research that has established this association. Furthermore, our findings are consistent with a multiproteomic analysis, which demonstrated that elevated serum Fibulin-1 levels are linked to renal impairment and diabetes, suggesting its potential role as a biomarker for renal dysfunction [13].

These findings align with a research that indicated elevated serum fibulin-1 levels were linked to renal failure and diabetes; however, in contrast to our investigation, this study discovered a correlation between fibulin-1 levels and age [12]. Elevated serum fibulin-1 concentrations were also linked to markers of renal impairment, with creatinine acting as an independent predictor [12].

Human fibulin-1 protein was found at considerably greater levels in a group of patients with glomerulonephritis than in controls, as well as in patient samples for all other renal illnesses studied. This implies that serum fibulin-1 levels might serve as a possible measure for monitoring renal dysfunction or kidney injury [13]. Patients with polycystic kidney disease had higher levels of serum fibulin-1, according to another study [14].

Fibulin-1 levels were shown to be positively correlated with LDL cholesterol levels in a statistically significant way. These results contrast with those of the present investigation, which demonstrated a connection between serum fibulin-1 levels and LDL was not significant [12]. Our results are in line with previous studies showing that high HbA1c is linked to the development of diabetic nephropathy and that hyperglycemia is the primary cause of the condition [15] Mishra et al. assessed the fasting blood glucose, serum urea, and serum creatinine levels of 50 type 2 diabetes patients and 50 healthy individuals from Agra's North Indian community. Serum urea, serum creatinine, and fasting blood glucose levels were significantly higher in those with diabetes for a longer period of time ($p < 0.001$) [16]. Senthilkumar et al. found a decrease in mean serum albumin value in their patient group [17] which is consistent with our findings .

Our results agree with the study done by Shaaban et al. who found a decrease in the mean value of eGFR in the patient group as compared with the control group [18]. Russo, G. T et al 2016 (217), who stated that hyperlipidemia is characterized by abnormal lipid profile readings, which may include excessive levels of serum cholesterol and triglycerides [19]. In our study, high TG and low HDL-c were significantly or borderline associated with an increased risk of diabetic nephropathy.

The ROC curve analysis highlights Fibulin-1's diagnostic potential as a biomarker for diabetic nephropathy (DN). The curve demonstrates high diagnostic accuracy, with an Area Under the Curve (AUC) of 0.848 and a statistically significant p-value (< 0.001), indicating its reliability in distinguishing DN patients from healthy individuals. Based on the findings of our study and prior research, it is reasonable to hypothesize that Fibulin-1 plays a role in the disease pathways of diabetic nephropathy, particularly in clinical conditions characterized by elevated serum Fibulin-1 levels, such as diabetes. Moreover, serum fibulin-1 has promise as a diabetic nephropathy biomarker.

6. Conclusion

A recent study revealed elevated levels of Fibulin-1 in the serum of patients with diabetic nephropathy. This increase was correlated with FBG, HbA1c levels, and key renal function indicators, including urea, creatinine, and uric acid. High diagnostic accuracy is indicated by the ROC curve analysis of fibulin-1, which displays an area under the curve of 0.848 with a significant p-value < 0.001 . This validates the potential of fibulin-1 as a DN diagnostic tool.

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