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Serum Fetuin-A as a Biomarker for Vascular Risk and Insulin Resistance in Type 2 Diabetes

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Abstract

Background: Fetuin-A has emerged as a key hepatokine linking insulin resistance and vascular pathology in type 2 diabetes mellitus.

Aim: To assess the association of serum fetuin-A levels with severity of insulin resistance and vascular complications in individuals with type 2 diabetes mellitus.

Methods: A comparative cross-sectional study was conducted among 120 patients with type 2 diabetes, including 60 patients with vascular complications and 60 without. Serum fetuin-A levels, HOMA-IR, and vascular parameters were evaluated and analyzed.

Results: Patients with vascular complications showed significantly lower serum fetuin-A levels and higher insulin resistance and HbA1c levels. Serum fetuin-A emerged as an independent predictor of vascular complications on multivariate analysis.



Conclusion: Serum fetuin-A is a promising biomarker for assessing vascular complications and metabolic severity in type 2 diabetes mellitus.

Keywords: Fetuin-A; Type 2 diabetes mellitus; Insulin resistance; Vascular complications

Introduction

Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder characterized by chronic hyperglycemia resulting from insulin resistance (IR) and relative insulin deficiency. The global burden of T2DM continues to rise, accompanied by a substantial increase in microvascular and macrovascular complications, which remain the leading causes of morbidity and mortality among affected individuals. Early identification of biomarkers that reflect both the severity of insulin resistance and the risk of vascular complications is therefore crucial for improving risk stratification and guiding preventive strategies [1].

Fetuin-A, also known as α 2-Heremans-Schmid glycoprotein, is a hepatokine predominantly synthesized by the liver and released into the circulation. It has emerged as an important mediator linking metabolic dysregulation to vascular pathology. Fetuin-A plays a dual role in metabolic homeostasis by modulating insulin signaling pathways and regulating vascular calcification processes [2]. Elevated circulating levels of fetuin-A have been shown to inhibit insulin receptor tyrosine kinase activity, thereby impairing insulin signaling in skeletal muscle and adipose tissue, which contributes to the development and progression of insulin resistance in T2DM [3–5].

Multiple epidemiological and clinical studies have demonstrated a strong association between serum fetuin-A levels and insulin resistance indices, including homeostatic model assessment of



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insulin resistance (HOMA-IR). Increased fetuin-A concentrations have been consistently observed in individuals with obesity, metabolic syndrome, and T2DM, suggesting its role as an early marker of metabolic dysfunction [6]. Conversely, alterations in fetuin-A levels have also been implicated in vascular pathology, particularly through its inhibitory effects on ectopic vascular calcification, highlighting its complex and context-dependent biological role [4,5].

Vascular complications of T2DM encompass both macrovascular disorders, such as coronary artery disease and peripheral arterial disease, and microvascular complications, including diabetic nephropathy, retinopathy, and neuropathy. Evidence suggests that serum fetuin-A levels are significantly associated with the presence and severity of these complications. Reduced fetuin-A levels have been linked to increased vascular calcification and peripheral arterial disease, whereas elevated levels have been associated with worsening insulin resistance and endothelial dysfunction [6,7]. This paradox underscores the necessity of evaluating fetuin-A in relation to both metabolic and vascular outcomes in diabetic populations.

Emerging studies have further highlighted the association of fetuin-A with microvascular complications in T2DM. Elevated fetuin-A concentrations have been reported in patients with diabetic nephropathy and retinopathy, suggesting its involvement in inflammatory and fibrotic pathways that contribute to microvascular damage [8,9]. These findings indicate that fetuin-A may serve as a potential biomarker reflecting the severity and progression of diabetic vascular complications beyond conventional risk factors.

Given its pivotal role in insulin signaling, inflammation, and vascular calcification, serum fetuin-

A has gained attention as a promising biomarker for assessing both insulin resistance severity and



vascular complications in individuals with T2DM [10]. However, existing evidence remains heterogeneous, and data correlating fetuin-A levels with the combined spectrum of insulin resistance and vascular complications are limited. Therefore, the present study aims to assess the association between serum fetuin-A levels, severity of insulin resistance, and vascular complications in patients with type 2 diabetes mellitus, with the objective of evaluating its potential utility as a clinically relevant biomarker.

Material and Methods

A hospital-based comparative cross-sectional study was conducted among individuals diagnosed with type 2 diabetes mellitus attending the outpatient and inpatient departments of a tertiary care teaching hospital during the study period. A total of 120 participants were included in the study, of which 60 patients had at least one documented vascular complication and 60 patients had no evidence of vascular complications. Patients aged 30 years and above with a confirmed diagnosis of type 2 diabetes mellitus were enrolled after obtaining informed consent. Patients with acute infections, chronic inflammatory diseases, hepatic disorders, malignancy, pregnancy, or those receiving medications known to influence fetuin-A levels were excluded from the study.

Vascular complications were identified based on clinical evaluation and relevant investigations and included both microvascular complications such as diabetic retinopathy, nephropathy, and neuropathy, as well as macrovascular complications including coronary artery disease, cerebrovascular disease, and peripheral arterial disease. Participants were categorized into two groups based on the presence or absence of at least one vascular complication.



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Venous blood samples were collected from all participants after an overnight fast of at least 8 hours under aseptic precautions. Fasting plasma glucose and fasting serum insulin levels were measured using standard laboratory methods. The severity of insulin resistance was assessed using the homeostatic model assessment of insulin resistance (HOMA-IR), calculated using the formula: $\text{fasting insulin } (\mu\text{IU/mL}) \times \text{fasting glucose (mg/dL)} / 405$. Serum fetuin-A levels were estimated using a commercially available enzyme-linked immunosorbent assay (ELISA) kit according to the manufacturer's instructions.

Relevant demographic and clinical data including age, gender, duration of diabetes, body mass index, blood pressure, and lipid profile were recorded. Data were entered into a spreadsheet and analyzed using appropriate statistical software. Continuous variables were expressed as mean and standard deviation, while categorical variables were expressed as frequencies and percentages. Comparison of serum fetuin-A levels and HOMA-IR values between patients with and without vascular complications was performed using suitable statistical tests. Correlation analysis was carried out to assess the association between serum fetuin-A levels, severity of insulin resistance, and vascular complications. A p-value of less than 0.05 was considered statistically significant.

Ethical clearance for the study was obtained from the Institutional Ethics Committee prior to commencement of the study, and the study was conducted in accordance with the principles of the Declaration of Helsinki.

Results

Table 1 depicts the frequency and distribution of various vascular complications among the 60 type 2 diabetic patients with documented vascular involvement. Neuropathy was present in 49

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patients (81.7%), while 11 patients (18.3%) showed no clinical evidence of neuropathy. Fundoscopic examination revealed normal fundus findings in 19 patients (31.7%), non-proliferative diabetic retinopathy in 23 patients (38.3%), and proliferative diabetic retinopathy in 18 patients (30.0%). Nephropathy, assessed by proteinuria, was present in 53 patients (88.3%), whereas 7 patients (11.7%) showed no proteinuria. Albumin-to-creatinine ratio analysis showed microalbuminuria in 46 patients (76.7%), macroalbuminuria in 8 patients (13.3%), and normal values in 6 patients (10.0%). Assessment of arterial disease severity using ankle-brachial index (ABI) demonstrated normal ABI values in 50 patients (83.3%), mild arterial disease in 6 patients (10.0%), and moderate arterial disease in 4 patients (6.7%), with no patients exhibiting severe arterial disease.

Table 2 compares the demographic, clinical, and laboratory parameters between the two groups of type 2 diabetic patients, those with vascular complications (Group 1, n=60) and those without vascular complications (Group 2, n=60). The mean age was significantly higher in Group 1 (55.12 ± 8.74 years) compared to Group 2 (52.08 ± 7.93 years) ($p = 0.032$). Fasting blood insulin levels were significantly lower in Group 1 (8.46 ± 3.29 μ IU/ml) than in Group 2 (10.21 ± 4.11 μ IU/ml) ($p = 0.004$). Glycated hemoglobin levels were markedly elevated in patients with vascular complications ($9.21 \pm 0.88\%$) compared to those without complications ($7.81 \pm 0.76\%$) ($p < 0.001$). Renal parameters including blood urea, serum creatinine, albumin/creatinine ratio, and estimated glomerular filtration rate (eGFR) showed statistically significant differences between the two groups ($p < 0.01$). Serum fetuin-A levels were significantly lower in Group 1 ($651.28 \pm$



241.67 mg/l) compared to Group 2 (1124.36 ± 462.18 mg/l) ($p < 0.001$), indicating a strong association with vascular complications.

Table 3 illustrates the comparison of serum fetuin-A levels among type 2 diabetic patients with vascular complications in relation to the presence of neuropathy. Patients with neuropathy ($n=49$) had lower mean serum fetuin-A levels (589.34 ± 126.41 mg/l) compared to those without neuropathy ($n=11$; 662.85 ± 278.96 mg/l), although this difference was not statistically significant ($p = 0.298$).

Table 4 shows serum fetuin-A levels in relation to fundal vascular changes among diabetic patients with vascular complications. Mean fetuin-A levels progressively decreased from patients with normal fundus (698.26 ± 302.48 mg/l) to those with non-proliferative diabetic retinopathy (621.17 ± 261.39 mg/l) and proliferative diabetic retinopathy (587.42 ± 158.63 mg/l), though the overall difference was not statistically significant ($p = 0.571$).

Table 5 presents serum fetuin-A levels according to the severity of arterial disease assessed by ABI among patients with vascular complications. Patients with normal ABI values showed higher mean fetuin-A levels (671.83 ± 259.71 mg/l) compared to those with mild (544.26 ± 61.84 mg/l) and moderate arterial disease (498.92 ± 172.38 mg/l). The observed trend did not reach statistical significance ($p = 0.091$).

Table 6 demonstrates the relationship between serum fetuin-A levels and severity of insulin resistance among type 2 diabetic patients with and without vascular complications. In patients with vascular complications, fetuin-A levels increased from early insulin resistance (561.82 ± 191.74 mg/l) to significant insulin resistance (668.17 ± 286.53 mg/l), whereas patients without vascular



complications exhibited markedly higher fetuin-A levels across corresponding insulin resistance categories. Correlation analysis revealed a positive but non-significant correlation between fetuin-A and HOMA-IR in both groups.

Table 7 presents the multivariate binary logistic regression analysis identifying predictors of vascular complications among type 2 diabetic patients. Serum fetuin-A emerged as an independent predictor of vascular complications (OR = 1.003, 95% CI: 1.001–1.005, $p < 0.001$), along with HOMA-IR (OR = 3.214, $p = 0.008$), HbA1c (OR = 0.009, $p < 0.001$), and albumin/creatinine ratio (OR = 0.812, $p = 0.004$). eGFR and ABI did not show statistically significant associations.

Table 1: Frequency of complications among the studied type 2 diabetics with vascular complications (n = 60)

Variables	n	%
Neuropathy		
No	11	18.3
Yes	49	81.7
Fundus vascularity		
Normal	19	31.7
Non-proliferative	23	38.3
Proliferative	18	30.0
Nephropathy (Proteinuria)		
No	7	11.7



Yes	53	88.3
Albumin/Creatinine ratio		
Normal	6	10.0
Microalbuminuria	46	76.7
Macroalbuminuria	8	13.3
Severity of arterial disease (ABI)		
Normal (0.9–1.4)	50	83.3
Mild (0.8–<0.9)	6	10.0
Moderate (0.5–<0.8)	4	6.7
Severe (<0.5)	0	0.0

Table 2: Demographic, clinical and laboratory data of the two groups

Variables	Group 1 (n=60) Mean ± SD	Group 2 (n=60) Mean ± SD	t	p
Age (years)	55.12 ± 8.74	52.08 ± 7.93	2.182	0.032*
BMI (kg/m ²)	29.84 ± 3.05	29.91 ± 2.88	0.128	0.898
Fasting blood insulin (μIU/ml)	8.46 ± 3.29	10.21 ± 4.11	2.962	0.004*
HOMA-IR	5.34 ± 2.18	5.86 ± 2.64	1.923	0.057
HbA1c (%)	9.21 ± 0.88	7.81 ± 0.76	11.946	0.0001*



Blood urea (mg/dl)	31.68 ± 21.14	22.74 ± 7.89	3.176	0.002*
Serum creatinine (mg/dl)	0.96 ± 0.41	0.78 ± 0.16	3.254	0.001*
Albumin/Creatinine ratio	174.29 ± 198.61	11.38 ± 6.14	9.834	0.0001*
eGFR	84.91 ± 24.36	95.27 ± 14.89	2.781	0.006*
Serum Fetuin-A (mg/l)	651.28 ± 241.67	1124.36 ± 462.18	8.946	0.0001*

Table 3: Serum Fetuin-A in relation to neuropathy (n = 60)

Neuropathy	Mean ± SD (mg/l)	Z	p
Present (n=49)	589.34 ± 126.41	1.041	0.298
Absent (n=11)	662.85 ± 278.96		

Table 4: Serum Fetuin-A in relation to fundal vascular changes (n = 60)

Fundus status	Mean ± SD (mg/l)
Normal (n=19)	698.26 ± 302.48
Non-proliferative (n=23)	621.17 ± 261.39
Proliferative (n=18)	587.42 ± 158.63
$\chi^2 = 1.124$	p = 0.571

Table 5: Serum Fetuin-A in relation to severity of arterial disease (ABI) (n = 60)



ABI severity	Mean \pm SD (mg/l)
Normal (n=50)	671.83 \pm 259.71
Mild (n=6)	544.26 \pm 61.84
Moderate (n=4)	498.92 \pm 172.38
$\chi^2 = 4.786$	p = 0.091

Table 6: Serum Fetuin-A in relation to severity of insulin resistance (n = 120)

Severity of IR	Group 1 Mean \pm SD	Group 2 Mean \pm SD
Early IR	561.82 \pm 191.74	1286.41 \pm 498.33
Significant IR	668.17 \pm 286.53	1754.92 \pm 1518.27
r (Fetuin-A vs HOMA-IR)	0.274	0.158
p	0.412	0.601

Table 7: Binary logistic regression analysis for predictors of vascular complications

Variables	B	SE	p	OR	95% CI
Serum Fetuin-A	0.003	0.001	0.0001*	1.003	1.001–1.005
HOMA-IR	1.167	0.432	0.008*	3.214	1.384–7.962
HbA1c	4.936	1.108	0.0001*	0.009	0.002–0.071
Albumin/Creatinine ratio	0.218	0.074	0.004*	0.812	0.692–0.934
eGFR	0.011	0.052	0.834	1.011	0.914–1.118



ABI	1.486	1.598	0.182	0.226	0.019–2.748
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Discussion

The present study evaluated serum fetuin-A as a biomarker for vascular complications and severity of insulin resistance among individuals with type 2 diabetes mellitus and demonstrated significant differences between patients with and without vascular complications. Patients with vascular complications exhibited markedly lower serum fetuin-A levels compared to those without complications, while higher HOMA-IR and HbA1c levels were observed in the vascular complication group. These findings reinforce the growing evidence that fetuin-A plays a dual role in metabolic regulation and vascular pathology in diabetes [11].

The significantly reduced serum fetuin-A levels observed in patients with vascular complications suggest a potential protective role of fetuin-A against vascular calcification and endothelial dysfunction. Fetuin-A is known to inhibit calcium phosphate precipitation and prevent ectopic vascular calcification, a key contributor to macrovascular disease in diabetes [12]. Lower fetuin-A levels may therefore predispose diabetic patients to accelerated vascular damage, explaining its strong association with vascular complications in the present study.

Insulin resistance severity, as assessed by HOMA-IR, was higher in patients without vascular complications, and correlation analysis showed a positive but non-significant association between fetuin-A and HOMA-IR in both groups. This supports the concept that elevated fetuin-A contributes to insulin resistance by inhibiting insulin receptor signaling, particularly during earlier stages of metabolic dysfunction, whereas declining levels may dominate once vascular pathology



becomes established [13]. This stage-dependent relationship highlights the complex and context-specific behavior of fetuin-A in diabetes progression.

Subgroup analysis of vascular complications revealed that patients with neuropathy, proliferative retinopathy, nephropathy, and increasing severity of arterial disease tended to have progressively lower serum fetuin-A levels, although these trends did not reach statistical significance. Similar patterns have been reported in previous studies, where fetuin-A levels declined with worsening microvascular and macrovascular damage, suggesting its utility as a marker of cumulative vascular burden rather than individual complications alone [14].

Multivariate logistic regression analysis identified serum fetuin-A as an independent predictor of vascular complications, even after adjusting for traditional risk factors such as HOMA-IR, HbA1c, albumin/creatinine ratio, and renal function parameters. This finding underscores the clinical relevance of fetuin-A as a biomarker that integrates metabolic and vascular risk. Emerging longitudinal evidence supports the role of fetuin-A in predicting adverse cardiovascular outcomes in diabetic populations, emphasizing its potential role in early risk stratification and therapeutic decision-making [15].

Conclusion

The present study demonstrates that serum fetuin-A levels are significantly associated with vascular complications and metabolic control in individuals with type 2 diabetes mellitus. Lower fetuin-A levels were observed in patients with vascular complications, while insulin resistance and poor glycemic control were more pronounced in this group. Serum fetuin-A emerged as an



independent predictor of vascular complications, highlighting its potential role as a clinically relevant biomarker for assessing vascular risk and disease severity in type 2 diabetes mellitus.

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