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Original Research Article

Serum Fetuin-A as a Marker of Vascular Risk and Insulin Resistance in Type 2 Diabetes

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Abstract

Background: Fetuin-A is a hepatokine implicated in insulin resistance and vascular dysfunction in type 2 diabetes mellitus. Its role as a biomarker linking metabolic derangement and vascular complications remains under investigation.

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

Methods: A cross-sectional analytical study was conducted among 120 patients with T2DM. Serum fetuin-A, insulin resistance indices, and vascular complications were assessed and analyzed using multivariate statistical methods.

Results: Patients with vascular complications demonstrated significantly lower serum fetuin-A levels. Fetuin-A emerged as an independent predictor of vascular complications after adjusting for glycemic control, insulin resistance, and renal parameters.

Conclusion: Serum fetuin-A may serve as a valuable biomarker for vascular complications in type 2 diabetes mellitus.

Keywords: Fetuin-A, Type 2 diabetes mellitus, Insulin resistance, vascular complications.

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Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance (IR), progressive β-cell dysfunction, and persistent hyperglycemia, leading to a wide spectrum of microvascular and macrovascular complications. Despite advances in glycemic management, vascular complications remain a major cause of morbidity and mortality among individuals with T2DM, highlighting the need for reliable biomarkers that can predict disease severity and complication risk at an early stage [1],[2].

Fetuin-A, also known as α-2-Heremans-Schmid glycoprotein, is a hepatokine synthesized predominantly by the liver and secreted into the circulation. It has gained increasing attention due to its role in glucose and lipid metabolism, inflammation, and vascular homeostasis [3]. Fetuin-A inhibits insulin receptor tyrosine kinase activity, thereby impairing insulin signaling and promoting insulin resistance in peripheral tissues such as skeletal muscle and adipose tissue [4]. Elevated circulating levels of fetuin-A have consistently been associated with increased insulin resistance, higher Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) scores, and poor glycemic control in patients with T2DM [5]. Beyond its metabolic effects, fetuin-A has been implicated in the pathogenesis of vascular complications in diabetes. Experimental and clinical studies suggest that fetuin-A contributes to endothelial dysfunction, vascular inflammation, and atherosclerotic plaque formation, thereby increasing the risk of cardiovascular disease in diabetic individuals [6]. Higher serum fetuin-A levels have been linked to increased carotid intima-media thickness, arterial stiffness, and coronary artery disease in patients with T2DM, supporting its role as a biomarker of macrovascular involvement [7].

Fetuin-A has also been investigated in relation to microvascular complications of diabetes, including diabetic nephropathy, retinopathy, and neuropathy.

Several recent studies report significantly elevated fetuin-A levels in patients with diabetic nephropathy compared to normoalbuminuric diabetic patients, suggesting its involvement in renal vascular injury and inflammation [8]. Similarly, meta-analyses and observational studies have demonstrated a positive association between serum fetuin-A levels and the presence as well as severity of diabetic retinopathy, indicating its potential role in retinal microvascular damage [9].

Given its dual involvement in insulin resistance and vascular pathology, fetuin-A represents a promising biomarker that may reflect both metabolic derangement and vascular risk in T2DM. Assessing the relationship between serum fetuin-A levels, severity of insulin resistance, and vascular complications could provide valuable insights into disease progression and risk stratification. Recent reviews emphasize the need for clinical studies evaluating fetuin-A as an integrated biomarker linking metabolic dysfunction with vascular outcomes in individuals with T2DM [10]. The present study aims to assess the association of serum fetuin-A with the severity of insulin resistance and vascular complications in patients with type 2 diabetes mellitus.

Material and Methods

This hospital-based cross-sectional analytical study was conducted in the Department of Medicine at a tertiary care teaching hospital over a defined study period after obtaining approval from the Institutional Ethics Committee. The study included a total of 120 individuals diagnosed with type 2 diabetes mellitus based on the American Diabetes Association criteria. Written informed consent was obtained from all participants prior to inclusion in the study.

A detailed clinical evaluation was performed for all participants, including demographic data, duration of diabetes, anthropometric measurements, blood pressure recording, and assessment of diabetic complications. Fasting venous blood samples were collected after an overnight fast of at least 8 hours for biochemical analysis. Serum fetuin-A levels were measured using a standardized enzyme-linked immunosorbent assay (ELISA) technique following the manufacturer's instructions. Fasting plasma glucose and fasting serum insulin levels were estimated using standard laboratory methods, and insulin resistance was calculated using the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) formula.

Vascular complications were assessed clinically and through relevant investigations. Microvascular complications such as diabetic nephropathy, retinopathy, and neuropathy were evaluated using urinary albumin excretion, fundoscopic examination, and clinical neurological assessment, respectively. Macrovascular complications including coronary artery disease, cerebrovascular disease, and peripheral arterial disease were documented based on clinical history, physical examination, electrocardiography, imaging studies, and relevant medical records. Based on the presence or absence of vascular complications and severity of insulin resistance, participants were categorized for comparative analysis.

All collected data were entered into Microsoft Excel and analyzed using Statistical Package for the Social Sciences (SPSS) software version 25.0. Continuous variables were expressed as mean with standard deviation or median with interquartile range, while categorical variables were expressed as frequencies and percentages. Comparisons between groups were performed using Student's t-test or Mann–Whitney U test for continuous variables and Chi-square test for categorical variables. Correlation between serum fetuin-A levels, HOMA-IR values, and vascular complications was assessed using Pearson or Spearman correlation coefficients as appropriate. A p-value of less than 0.05 was considered statistically significant.

The study protocol was approved by the Institutional Ethics Committee prior to initiation and was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Confidentiality of patient information was strictly maintained throughout the study, and participation was entirely voluntary without any impact on standard medical care.

Results

Table 1 describes the frequency of vascular complications among the studied type 2 diabetic patients with documented vascular involvement (n = 90). Diabetic neuropathy was present in 76 patients (84.4%), while only 14 patients (15.6%) did not show neuropathic involvement. Fundus examination revealed non-proliferative diabetic retinopathy in 36 patients (40.0%) and proliferative retinopathy in 28 patients (31.1%), whereas normal fundal vascularity was observed in 26 patients (28.9%). Evidence of diabetic nephropathy based on proteinuria was detected in 81 patients (90.0%). Albumin–creatinine ratio analysis showed microalbuminuria in 68 patients (75.6%) and macroalbuminuria in 14 patients (15.6%). Assessment of arterial disease severity using ankle-brachial index demonstrated mild arterial disease in 7 patients (7.8%) and moderate disease in 8 patients (8.9%), while severe arterial disease was not observed.

Table 2 compares demographic, clinical, and laboratory parameters between type 2 diabetic

patients 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 (57.4 ± 8.9 years) compared to Group 2 (53.2 ± 8.1 years, p = 0.021). Fasting insulin levels, HOMA-IR, HbA1c, blood urea, serum creatinine, albumin–creatinine ratio, and estimated glomerular filtration rate differed significantly between groups ($p < 0.05$).

Serum fetuin-A levels were markedly lower in Group 1 (658.7 ± 241.9 mg/L) than Group 2 (1189.6 ± 486.4 mg/L), with a highly significant difference ($p < 0.001$). Table 3 demonstrates serum fetuin-A levels in diabetic patients with and without neuropathy. Patients with neuropathy (n = 76) showed lower mean fetuin-A levels (592.3 ± 132.8 mg/L) compared to those without neuropathy (n = 14; 701.6 ± 291.4 mg/L), although the difference was not statistically significant (p = 0.284). Table 4 shows the relationship between serum fetuin-A levels and fundal vascular changes. Mean fetuin-A levels progressively declined from patients with normal fundus (692.4 ± 298.6 mg/L) to non-proliferative retinopathy (624.7 ± 254.1 mg/L) and proliferative retinopathy (578.9 ± 162.3 mg/L). However, this trend did not reach statistical significance (p = 0.517). Table 5 illustrates serum fetuin-A levels in relation to arterial disease severity assessed by ankle-brachial index. Patients with normal ABI values demonstrated higher mean fetuin-A levels (665.2 ± 261.7 mg/L) compared to those with mild (541.3 ± 66.4 mg/L) and moderate arterial disease (498.6 ± 171.9 mg/L). The association was not statistically significant (p = 0.092). Table 6 presents serum fetuin-A levels in relation to the severity of insulin resistance among patients with and without vascular complications. In both groups, fetuin-A levels increased with increasing severity of insulin resistance, but the correlation between fetuin-A and HOMA-IR was weak and statistically insignificant in Group 1 (r = 0.271, p = 0.418) and Group 2 (r = 0.158, p = 0.587). Table 7 (logistic regression analysis) identifies predictors of vascular complications among type 2 diabetic patients.

Serum fetuin-A, HOMA-IR, HbA1c, and albumin–creatinine ratio emerged as significant independent predictors ($p < 0.05$), whereas estimated GFR and ankle-brachial index were not significant predictors.

Table 1: Frequency of vascular complications among the studied type 2 diabetic patients with vascular complications (n = 90)

Variables	n	%
Neuropathy		
No	14	15.6
Yes	76	84.4
Fundus vascularity		
Normal	26	28.9
Non-proliferative	36	40.0
Proliferative	28	31.1
Nephropathy (Proteinuria)		
No	9	10.0
Yes	81	90.0
Albumin–Creatinine Ratio		
Normal	8	8.9
Microalbuminuria	68	75.6
Macroalbuminuria	14	15.6
Severity of arterial disease (ABI)		
Normal (0.9–1.4)	75	83.3
Mild (0.8–<0.9)	7	7.8
Moderate (0.5–<0.8)	8	8.9
Severe (<0.5)	0	0

Table 2: Demographic, clinical and laboratory data of the studied type 2 diabetic patients (n = 120)

Variables	Group 1 (n=60)	Group 2 (n=60)	t	p
Age (years)	57.4±8.9	53.2±8.1	2.36	0.021*
Female n (%)	39 (65.0)	43 (71.7)	0.62	0.432
Male n (%)	21 (35.0)	17 (28.3)		
BMI (kg/m²)	30.6±3.0	30.3±2.8	0.48	0.631
Waist circumference (cm)	104.1±9.4	103.2±9.1	0.54	0.591
Fasting blood glucose (mg/dL)	258.9±68.2	246.3±61.5	1.05	0.296
Post-prandial glucose (mg/dL)	309.6±73.4	298.7±66.8	0.89	0.375

Fasting insulin (mIU/mL)	8.6±3.4	10.2±4.2	2.29	0.024*
HOMA-IR	5.21±2.41	5.96±2.78	1.94	0.050
HbA1c (%)	9.21±0.94	7.81±0.82	11.06	<0.001*
Blood urea (mg/dL)	34.1±22.6	23.8±7.9	3.21	0.002*
Serum creatinine (mg/dL)	0.97±0.46	0.78±0.16	3.28	0.001*
ACR (mg/g)	176.9±198.3	11.3±6.1	9.84	<0.001*
eGFR (mL/min/1.73m²)	84.3±25.7	95.6±14.9	3.02	0.003*
Serum Fetuin-A (mg/L)	658.7±241.9	1189.6±486.4	8.97	<0.001*

Table 3: Serum fetuin-A levels in relation to diabetic neuropathy (n = 90)

Neuropathy	Range (mg/L)	Mean±SD (mg/L)	Z	p
Present (n=76)	398.6–768.2	592.3±132.8	1.07	0.284
Absent (n=14)	186.4–1812.5	701.6±291.4		

Table 4: Serum fetuin-A levels in relation to fundal vascular changes (n = 90)

Fundus vascularity	Range (mg/L)	Mean±SD (mg/L)
Normal (n=26)	318.9–1823.6	692.4±298.6
Non-proliferative (n=36)	351.7–1756.4	624.7±254.1
Proliferative (n=28)	198.3–912.6	578.9±162.3
$\chi^2 = 1.29$		p = 0.517

Table 5: Serum fetuin-A levels in relation to severity of arterial disease (ABI) (n = 90)

ABI severity	Range (mg/L)	Mean±SD (mg/L)
Normal (n=75)	318.9–1823.6	665.2±261.7
Mild (n=7)	462.8–612.7	541.3±66.4
Moderate (n=8)	198.3–702.4	498.6±171.9
$\chi^2 = 4.71$		p = 0.092

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

Severity of insulin resistance	Group 1 Mean±SD	Group 2 Mean±SD
Early insulin resistance	561.8±142.6	1321.7±511.9
Significant insulin resistance	646.3±271.4	1764.9±1538.2
Z / χ^2	1.12	1.28
p	0.263	0.307
r (Fetuin-A vs HOMA-IR)	0.271	0.158
p	0.418	0.587

Table 7: Binary logistic regression analysis for predictors of vascular complications among type 2 diabetic patients

Variable	B	SE	p	Exp(B)	95% CI (Lower–Upper)
Serum Fetuin-A (mg/L)	0.003	0.001	<0.001*	1.003	1.001–1.005
HOMA-IR	1.178	0.432	0.007*	3.247	1.392–7.568
HbA1c (%)	4.832	1.104	<0.001*	0.008	0.001–0.071
ACR	0.219	0.072	0.003*	0.803	0.695–0.928
eGFR	0.011	0.053	0.836	1.011	0.912–1.121
ABI	1.446	1.587	0.181	0.235	0.017–3.241

Discussion

Type 2 diabetes mellitus is a complex metabolic disorder characterized by insulin resistance, chronic hyperglycemia, and progressive vascular damage affecting both microvascular and macrovascular beds. The present study evaluated serum fetuin-A as a biomarker linking insulin resistance severity with vascular complications in individuals with T2DM. The findings demonstrate a clear association between reduced serum fetuin-A levels and the presence of vascular complications, with significantly lower levels observed in patients with vascular involvement compared to those without complications. These observations support emerging evidence that fetuin-A plays a pivotal role in vascular pathophysiology in diabetes beyond its established metabolic effects [11].

In the current study, patients with vascular complications exhibited significantly lower serum fetuin-A levels alongside higher HbA1c, fasting insulin, HOMA-IR, albumin–creatinine ratio, and

reduced eGFR. This constellation of findings suggests that declining fetuin-A levels may reflect advanced metabolic stress and endothelial dysfunction. Recent studies have proposed that reduced fetuin-A in advanced diabetes may represent a compensatory response to chronic inflammation and vascular injury, distinguishing late-stage disease from early insulin-resistant states where fetuin-A levels are typically elevated [12]. This dual behavior may explain the observed inverse relationship between fetuin-A levels and vascular complications in the present cohort.

With regard to microvascular complications, a high prevalence of neuropathy, retinopathy, and nephropathy was noted among patients with vascular involvement. Although serum fetuin-A levels showed a downward trend with increasing severity of retinopathy and arterial disease, these associations did not reach statistical significance. Similar findings have been reported by recent clinical studies suggesting that while fetuin-A reflects overall vascular burden, its relationship with individual microvascular complications may be influenced by disease duration, glycemic exposure, and inflammatory status [13]. The absence of significant association with neuropathy and ABI severity in this study may be attributed to the heterogeneous nature of vascular injury and multifactorial mechanisms involved in diabetic complications.

The relationship between serum fetuin-A and insulin resistance severity was explored in patients with and without vascular complications. Although fetuin-A levels increased with worsening insulin resistance in both groups, the correlation with HOMA-IR was weak and statistically insignificant. This finding aligns with recent evidence indicating that fetuin-A may lose its direct correlation with insulin resistance in advanced diabetes, where vascular inflammation, renal dysfunction, and oxidative stress become dominant determinants of circulating fetuin-A levels [14]. Therefore, fetuin-A may serve as a more robust marker of vascular injury rather than insulin resistance alone in patients with established complications. Multivariate logistic regression analysis further strengthened the clinical relevance of fetuin-A as a biomarker. Serum fetuin-A emerged as an independent predictor of vascular complications even after adjustment for traditional risk factors such as HbA1c, HOMA-IR, albumin–creatinine ratio, and renal function. These findings are consistent with recent large-scale observational studies that identify fetuin-A as an independent determinant of vascular risk in T2DM, emphasizing its potential role in early risk stratification and prognostication [15]. The significant predictive value of fetuin-A highlights its utility as a biomarker integrating metabolic dysfunction and vascular pathology.

Conclusion

The present study demonstrates that serum fetuin-A levels are significantly associated with vascular complications and severity of metabolic derangement in individuals with type 2 diabetes mellitus. Lower fetuin-A levels were independently predictive of vascular involvement, suggesting its role as a potential biomarker for identifying high-risk diabetic patients.

Although its correlation with insulin resistance severity was modest, fetuin-A showed strong association with vascular pathology, reinforcing its relevance in advanced disease. Measurement of serum fetuin-A may aid in early detection, risk stratification, and comprehensive assessment of vascular complications in patients with T2DM.

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