PTM-Fetuin-A: A Novel Biomarker for Early Detection of Diabetic Kidney Disease.

Abstract

Chronic kidney disease (CKD) is a significant public health issue with a rising prevalence globally. Diabetic kidney disease (DKD), a leading cause of CKD, necessitates improved biomarkers for early detection and effective management. Traditional markers such as serum creatinine, estimated glomerular filtration rate (eGFR), and albuminuria have notable limitations in sensitivity and specificity, especially for early detection. Fetuin-A, specifically its post-translationally modified form (PTM-Fetuin-A), has emerged as a potential novel biomarker for DKD.This study evaluates PTM-Fetuin-A in a cohort of Bulgarian patients with type 1 and type 2 diabetes, assessing its correlation with traditional markers such as albuminuria and eGFR. Significant correlations were observed between PTM-Fetuin-A and these indicators (e.g., Pearson's $r = 0.447$, $p = 0.025$ for albuminuria), highlighting its ability to detect early kidney function decline. Furthermore, PTM-Fetuin-A demonstrated potential as a non-invasive tool for identifying normoalbuminuric DKD, addressing gaps left by conventional biomarkers. By offering additional prognostic value, PTM-Fetuin-A could improve the early diagnosis and clinical management of diabetic patients, reducing the burden of CKD.

Keywords: CKD, DKD, PTM-Fetuin-A, prevention, biomarkers, renal function.

Introduction

Chronic kidney disease (CKD) is a significant public health problem worldwide, with an increasing prevalence often described as a global pandemic. CKD affects approximately 10% of the global population, causing substantial morbidity and mortality, especially among individuals with comorbidities such as diabetes and hypertension [1,2]. Its progression frequently leads to end-stage renal disease (ESRD), which necessitates dialysis or kidney transplantation—both resource-intensive treatments that impose a considerable burden on healthcare systems. Additionally, CKD has a profound economic impact, with high healthcare costs stemming from the treatment of advanced stages and associated complications [2].

Diabetic kidney disease (DKD), a prevalent complication of diabetes mellitus, is the leading cause of CKD and accounts for nearly half of all ESRD cases [3,4]. The global rise in diabetes incidence underscores the critical need for early identification and effective strategies to slow DKD progression and reduce the associated healthcare burden.

Currently, kidney function assessment in diabetic patients primarily relies on traditional biomarkers such as serum creatinine, estimated glomerular filtration rate (eGFR), and albuminuria. However, these markers have limitations in detecting early renal changes, particularly in normoalbuminuric patients, and their sensitivity and specificity are influenced by factors such as age, sex, and muscle mass [5,6]. Therefore, there is an urgent need for novel biomarkers capable of providing earlier and more accurate detection of kidney dysfunction, especially in diabetic patients at high risk of progression to ESRD.

Limitations of Current Biomarkers

Traditional biomarkers used for monitoring kidney function each have significant limitations that reduce their effectiveness, particularly in the early detection of DKD. Serum creatinine, one of the most widely used markers, is affected by factors such as muscle mass, age, and sex, making it an imperfect indicator of kidney health. Creatinine has a "blind spot area" in early kidney damage due to tubular secretion, meaning its levels may not rise until substantial kidney damage has occurred, limiting its utility for early detection [6]. Estimated glomerular filtration rate (eGFR), derived from serum creatinine levels, provides a general estimate of kidney function but is subject to similar confounding factors that impact creatinine levels, such as variations in muscle mass and ethnicity. Additionally, eGFR is calculated using formulas such as the Modification of Diet in Renal Disease (MDRD) equation or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, both of which have limitations in accuracy for certain populations, including those with extremes in body mass or age [7].

Albuminuria, which measures the presence of albumin in the urine, is another commonly used marker for assessing kidney damage. It is more sensitive than serum creatinine for detecting early kidney damage, particularly in diabetic patients. However, not all patients with ongoing DKD will have elevated levels of albumin in their urine. This condition, known as normoalbuminuric DKD, complicates the early diagnosis and risk stratification of patients, as albuminuria alone may fail to capture early pathophysiological changes in the kidney [8]. Furthermore, albuminuria can be influenced by factors such as hydration status, exercise, and infection, which can lead to variability in measurements and reduce its reliability as a standalone marker.

Given these limitations, there is a critical need for more specific and sensitive biomarkers that can accurately reflect early kidney damage and predict disease progression. Such biomarkers would ideally detect subtle renal changes before significant structural damage occurs, allowing for timely intervention and improved patient outcomes [9, 10].

The Role of Fetuin-A in Chronic Kidney Disease

Fetuin-A, also known as alpha-2-Heremans-Schmid glycoprotein (AHSG), is primarily synthesized in the liver and released into circulation, playing a role in processes such as calcium regulation, inhibition of ectopic calcification, and modulation of insulin signaling pathways

[9,10]. Elevated levels of fetuin-A are linked to insulin resistance, metabolic syndrome, and cardiovascular risk, which are common comorbidities in diabetes and CKD [11,12,13].

Post-translationally modified fetuin-A (PTM-Fetuin-A) has emerged as a promising biomarker for early detection of renal dysfunction, particularly in patients with diabetes. PTM-Fetuin-A is a modified form of the protein that reflects underlying molecular changes associated with kidney injury and inflammation. Recent studies have demonstrated that PTM-Fetuin-A levels correlate with markers of renal dysfunction, such as albuminuria and eGFR, and may provide additional prognostic value beyond traditional biomarkers [14, 15]. The ability of PTM-Fetuin-A to detect early changes in renal function, even in patients with normoalbuminuric DKD, suggests that it could serve as an important tool for improving the early diagnosis and management of diabetic kidney disease.

Musolino et al. (2024) conducted a pilot study on PTM-Fetuin-A in patients with CKD of both diabetic and non-diabetic etiology, demonstrating that PTM-Fetuin-A levels were significantly elevated in patients with DKD compared to those with other causes of CKD. The authors suggested that PTM-Fetuin-A could be used as a non-invasive biomarker to differentiate between diabetic and non-diabetic CKD, particularly in cases where renal biopsy is not feasible [15]. This finding aligns with earlier work by Kumar Bandi et al. (2022), who reported a significant correlation between PTM-Fetuin-A and albuminuria, with PTM-Fetuin-A showing superior performance in predicting CKD stages compared to traditional markers like UACR [16].

Studies by Chuanga et al. (2024) further explored the potential of PTM-Fetuin-A as a biomarker capable of predicting kidney function decline in patients with type 2 diabetes from different ethnic backgrounds. Their findings indicated that high PTM-Fetuin-A levels were associated with a higher risk of renal function decline, independent of other traditional risk factors such as albuminuria, eGFR, and HbA1c levels [17,18]. The additive predictive power of PTM-Fetuin-A over traditional markers suggests that it may be a valuable tool for early identification of patients at risk for DKD progression.

Based on the existing evidence regarding PTM-Fetuin-A as a potential biomarker, our study aims to further evaluate its role in the early detection and monitoring of diabetic kidney disease. Specifically, we investigated PTM-Fetuin-A levels in a cohort of Bulgarian patients with type 1 and type 2 diabetes, with and without low-grade albuminuria. By comparing PTM-Fetuin-A with traditional markers such as albuminuria and eGFR, we sought to determine its potential as non-invasive tool for early identification of DKD and to assess its prognostic value in predicting kidney function decline [19,20].

Materials and Methods

This study was designed as a cross-sectional observational analysis involving 70 patients with diabetes mellitus, both type 1 and type 2. Participants were recruited from a single healthcare center in Bulgaria, and the primary aim was to assess the levels of post-translationally modified fetuin-A (PTM-Fetuin-A) as a biomarker for diabetic kidney disease (DKD). The analysis also compared PTM-Fetuin-A levels with traditional kidney function markers such as albuminuria and estimated glomerular filtration rate (eGFR) to evaluate its potential for early detection and prognostic value in renal function decline.

The participants included 25 individuals with type 1 diabetes and 45 with type 2 diabetes, with an age range of 19 to 88 years and a mean age of 53.5 years. Inclusion criteria required patients to have a confirmed diagnosis of diabetes, regardless of disease duration, and the presence or absence of low-grade albuminuria. Patients were further categorized based on the duration of diabetes into groups of less than 5 years, 5–10 years, and over 10 years.All 70 participants were evaluated at three distinct time points: baseline (V0), the third month (V3), and the sixth month (V6).

Urine samples were collected from each participant at three distinct time points: baseline (V0), the third month (V3), and the sixth month (V6). The samples were centrifuged and stored at -80°C until analysis. Biomarkers including serum creatinine, albuminuria, eGFR, body mass index (BMI), and ratios such as albumin/creatinine (UACR) and fetuin/creatinine (FCR) were measured at the same intervals. The PTM-Fetuin-A levels were determined using a commercially available enzyme-linked immunosorbent assay (ELISA) kit, following the manufacturer's instructions. All samples were processed in duplicate to ensure accuracy, and frozen urine samples were analyzed in a single batch to minimize variability.

Statistical analyses were conducted using SPSS software (version 25.0). Descriptive statistics, such as mean values, standard deviations, and ranges, were used to characterize PTM-Fetuin-A, eGFR, and UACR across the different groups and time points. One-way ANOVA was performed to compare PTM-Fetuin-A levels between different subgroups, while Pearson’s correlation coefficient and Spearman’s rho were used to explore relationships between PTM-Fetuin-A, eGFR, and UACR. Multiple linear regression was employed to assess the impact of traditional markers (UACR and eGFR) on PTM-Fetuin-A levels over time, with R^2 and p-values indicating the strength and significance of these relationships.

Results

The assessment of the relationship between PTM-Fetuin-A levels in urine, albuminuria, and CKD progression revealed several significant findings. Notably, a positive correlation was observed between baseline PTM-Fetuin-A levels (V0) and albuminuria levels at six months (V6), with Pearson's correlation coefficient $r = 0.447$ and $p = 0.025$. This indicates that higher initial levels of PTM-Fetuin-A may predict an increase in albuminuria over time. (fig. 1)

Fig. 1

		V0 Fetuin A[ng/ml]	V3 Fetuin A	V6 Fetuin A[ng/ml]	V0 Albuminuria	V3 Albuminuria	V6 Albuminuria
V0 Fetuin A[ng/ml]	Pearson's r	—					
	p-value	—					
V3 Fetuin A [ng/ml]	Pearson's r	-0.189	—				
	p-value	0.365	—				
V6 Fetuin A[ng/ml]	Pearson's r	-0.059	-0.116	—			
	p-value	0.780	0.579	—			

Fig. 1

		V0 Fetuin A[ng/ml]	V3 Fetuin A	V6 Fetuin A[ng/ml]	V0 Albuminuria	V3 Albuminuria	V6 Albuminuria
V0 Albuminuria	Pearson's r	-0.257	0.011	0.447 *	—		
	p-value	0.215	0.957	0.025	—		
V3 Albuminuria	Pearson's r	-0.230	0.112	-0.118	0.578 **	—	
	p-value	0.269	0.595	0.574	0.002	—	
V6 Albuminuria	Pearson's r	-0.268	0.193	-0.161	0.658 ***	0.919 ***	—
	p-value	0.196	0.356	0.443	< .001	< .001	—

Note. * p < .05, ** p < .01, *** p < .001

Comparison between patients with type 1 and type 2 diabetes across different time points (V0, V3, V6) showed no statistically significant differences in PTM-Fetuin-A levels. For instance, at V0, the mean PTM-Fetuin-A level was 4.29 ng/ml in type 1 diabetes patients and 3.36 ng/ml in type 2 diabetes patients, with Mann-Whitney U test results of U = 550 and p = 0.88, indicating no significant difference. These results suggest that while PTM-Fetuin-A levels do not significantly differ between diabetes types, their correlation with albuminuria positions PTM-Fetuin-A as a potential biomarker for tracking disease progression. (fig. 2)

Fig. 2

		N	Mean	Median	Std. Dev.	Mann-Whitney U/ p
V0 Fetuin A[ng/ml]	type 1	25	4.29	2.79	5.98	U=550, p=0.88
	type 2	45	3.36	2.43	3.67	
V3 Fetuin A [ng/ml]	type 1	25	4.40	2.88	8.25	U=554, p=0.92
	type 2	45	39.32	2.00	112.84	
V6 Fetuin A[ng/ml]	type 1	25	12.36	1.78	49.09	U=457, p=0.28
	type 2	45	6.03	1.16	26.10	
V0 Albuminuria	type 1	25	68.56	36.00	57.06	U=556, p=0.94
	type 2	45	75.55	48.00	68.27	
V3 Albuminuria	type 1	25	56.20	38.00	46.25	U=531, p=0.69
	type 2	45	55.71	28.00	55.53	
V6 Albuminuria	type 1	25	43.81	26.00	39.56	U=560, p=0.97
	type 2	45	49.69	23.00	52.39	
V0 serum creatinine	type 1	25	90.48	85.90	17.46	U=531, p=0.70
	type 2	45	89.91	86.00	23.65	
V3 serum creatinine	type 1	25	91.54	87.90	22.77	U=522, p=0.61

		N	Mean	Median	Std. Dev.	Mann-Whitney U/ p
	type 2	45	92.14	91.00	18.34	
V6 serum creatinine	type 1	25	84.26	83.00	12.82	U=417, p=0.07
	type 2	45	92.22	93.00	21.13	

A significant positive correlation was also observed between the Fetuin/creatinine ratio (FCR) and UACR, as well as between FCR and eGFR, with varying degrees across type 1 and type 2 diabetes and depending on diabetes duration. For example, for V6, a strong correlation was noted between FCR and UACR in patients with a shorter diabetes duration (less than 5 years), with r = 0.599 and p = 0.009. This finding suggests that increased urinary PTM-Fetuin-A levels are closely related to rising albuminuria, which is a key indicator of kidney damage in diabetic nephropathy. (fig. 3, fig. 4, fig. 5)

Fig. 3

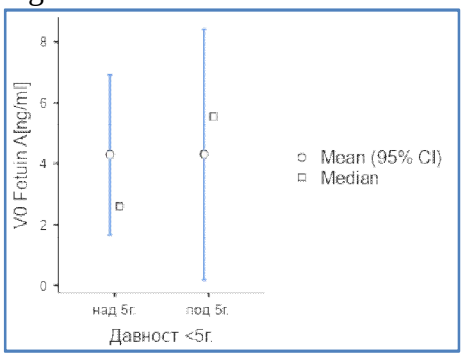


Fig. 4

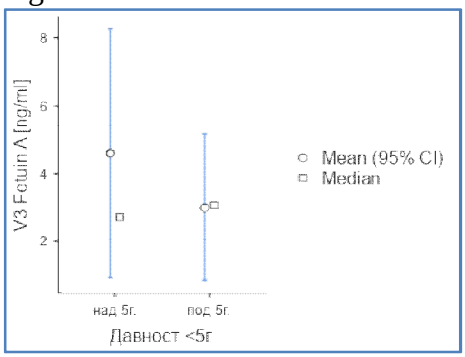
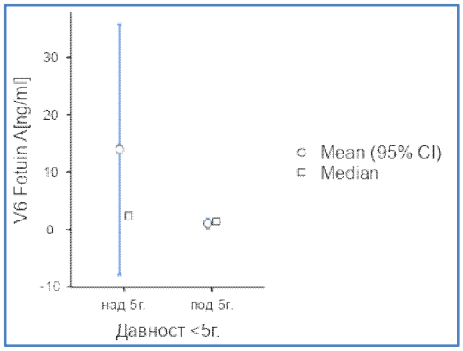


Fig. 5



In patients with type 2 diabetes, correlation analysis showed negative associations between FCR and eGFR at different time points. For V6, a significant negative correlation was observed with r = -0.736 and p < 0.001, indicating that as eGFR decreases (worsening kidney function), FCR levels increase. This supports the relationship between declining kidney function and increasing PTM-Fetuin-A levels.

In patients with a diabetes duration of less than 5 years, a significant negative correlation was found between FCR and eGFR at V0 (r = -0.499, p = 0.035), suggesting that PTM-Fetuin-A may serve as a sensitive marker for worsening kidney function in the early stages of the disease. For patients with diabetes duration over 10 years, the correlations between FCR and eGFR were weaker or absent. For example, no significant correlation was found for V0 eGFR and FCR (r = -0.165, p = 0.432), suggesting that in prolonged kidney damage, other factors may have a greater impact on disease progression. (fig. 6)

Correlation Matrix

		V0 F/Ucr	V3 F/Ucr	V6 F/Ucr	V0 EGFR	V3 EGFR	V6 EGFR	V0 serum crea	V3 serum crea	V6 serum crea
V0 F/Ucr [ng/mg]	Pearson's r	—								
	p-value	—								
V3 F/Ucr [ng/mg]	Pearson's r	-0.144	—							
	p-value	0.569	—							
V6 F/Ucr [ng/mg]	Pearson's r	0.599 **	-0.047	—						
	p-value	0.009	0.852	—						
V0 EGFR	Pearson's r	-0.499 *	-0.121	-0.164	—					
	p-value	0.035	0.634	0.515	—					
V3 EGFR	Pearson's r	-0.307	0.216	-0.226	0.050	—				
	p-value	0.216	0.390	0.368	0.844	—				
V6 EGFR	Pearson's r	-0.166	-0.185	-0.098	0.638 **	0.385	—			
	p-value	0.511	0.463	0.698	0.004	0.115	—			

Correlation Matrix

		V0 F/Ucr	V3 F/Ucr	V6 F/Ucr	V0 EGFR	V3 EGFR	V6 EGFR	V0 serum crea	V3 serum crea	V6 serum crea
V0 serum crea	Pearson's r	0.518 *	-0.066	0.317	-0.721 ***	-0.019	-0.201	—		
	p-value	0.028	0.796	0.200	< .001	0.939	0.425	—		
V3 serum crea	Pearson's r	0.208	-0.314	0.352	0.335	-0.799 ***	0.086	-0.013	—	
	p-value	0.407	0.204	0.152	0.174	< .001	0.734	0.959	—	
V6 serum crea	Pearson's r	0.034	0.117	0.184	-0.273	-0.392	-0.804 ***	0.126	0.234	—
	p-value	0.894	0.643	0.466	0.273	0.108	< .001	0.619	0.349	—

Note. * p < .05, ** p < .01, *** p < .001

Discussion

Our findings align with previous studies that highlight the potential of PTM-Fetuin-A as a biomarker for early detection of diabetic kidney disease (DKD). The positive correlation between baseline PTM-Fetuin-A levels and subsequent albuminuria levels supports the hypothesis that PTM-Fetuin-A can serve as an early predictor of kidney function decline. This is consistent with Musolino et al. (2024), who also reported elevated PTM-Fetuin-A levels in patients with DKD compared to those with non-diabetic CKD, suggesting its utility as a non-invasive biomarker for monitoring renal health [17, 22].

Moreover, the strong correlation observed between the FetuinA/creatinine ratio (FCR) and UACR in patients with a shorter diabetes duration mirrors findings by Kumar Bandi et al. (2022), who demonstrated the superior performance of PTM-Fetuin-A over traditional markers like UACR in predicting CKD stages [21,24]. These results indicate that PTM-Fetuin-A not only correlates well with established markers of kidney damage but may also offer additional prognostic value, particularly in early-stage disease.

Interestingly, our study found no significant differences in PTM-Fetuin-A levels between patients with type 1 and type 2 diabetes, similar to the findings by Chuanga et al. (2024), who observed high PTM-Fetuin-A levels across different ethnic backgrounds without significant variation between diabetes types [19, 23]. This suggests that PTM-Fetuin-A levels may be influenced more by the presence of kidney damage rather than by the type of diabetes itself.

Our correlation analysis between FCR and eGFR further supports the potential role of PTM-Fetuin-A in monitoring kidney function decline. The significant negative correlation between FCR and eGFR in type 2 diabetes patients indicates that as kidney function declines, PTM-Fetuin-A levels increase, which is in line with the general understanding of biomarkers that reflect worsening renal function. This observation adds to the growing body of evidence suggesting that PTM-Fetuin-A could be a reliable indicator of kidney health, particularly in the context of diabetic nephropathy.

However, it is important to note that in patients with longer diabetes duration (over 10 years), the correlations between FCR and eGFR were weaker or absent. This finding suggests that PTM-Fetuin-A may be more effective as a biomarker in the earlier stages of diabetes-related kidney

damage, whereas other factors may play a more dominant role in long-standing disease progression. This highlights the need for a multimodal approach in the assessment of CKD progression, particularly in advanced cases.
In conclusion, our study supports the use of PTM-Fetuin-A as a promising biomarker for early detection and monitoring of DKD. By offering additional prognostic value beyond traditional markers like albuminuria and eGFR, PTM-Fetuin-A could improve the management of patients with diabetes, particularly those at risk of rapid kidney function decline.

Conclusion

In summary, this study provides evidence supporting the potential of PTM-Fetuin-A as an effective biomarker for the early detection and monitoring of diabetic kidney disease (DKD). The significant correlations between PTM-Fetuin-A, albuminuria, and kidney function highlight its value beyond traditional markers like serum creatinine and eGFR, particularly in early disease stages. While our findings align with previous research, they also underscore the need for further studies to confirm the utility of PTM-Fetuin-A in different populations and to explore its role in more advanced cases of CKD. The use of PTM-Fetuin-A in clinical practice could help improve early diagnosis and management of DKD, ultimately reducing the burden of chronic kidney disease among diabetic patients.

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