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Determinants of Uromodulin Levels among Patients with Type 2 Diabetes Mellitus

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Abstract

General Background: Uromodulin, a kidney-specific glycoprotein, is associated with renal function and is frequently reduced in diabetes and chronic kidney disease. **Specific Background:** In type 2 diabetes mellitus, metabolic disturbances contribute to tubular injury, with declining uromodulin levels observed during disease progression. **Knowledge Gap:** However, the relationships between uromodulin levels and demographic and clinical determinants such as age, gender, body mass index, glycemic control, and duration of diabetes remain insufficiently clarified. **Aims:** This study aimed to evaluate the association between uromodulin levels and these variables in patients with type 2 diabetes mellitus. **Results:** A case-control study involving 176 participants demonstrated significant variations in uromodulin levels ($p<0.001$), with lower concentrations associated with advancing age, higher body mass index, longer duration of diabetes, worsening glycemic control, and increased disease severity, particularly in advanced diabetic nephropathy stages (DN2 and DN3). Females generally exhibited higher uromodulin levels compared to males. **Novelty:** This study provides integrated evidence linking multiple demographic and metabolic determinants with uromodulin variation across different stages of diabetic kidney disease. **Implications:** The findings suggest that reduced uromodulin levels may serve as a biomarker for disease progression and risk stratification, supporting its potential utility in clinical monitoring and early identification of high-risk patients with type 2 diabetes mellitus.

Highlights:
- Uromodulin levels decline progressively across advanced diabetic nephropathy stages
- Demographic and metabolic factors show significant associations with biomarker variation
- Lower concentrations observed in prolonged disease duration and poor glycemic status

Keywords: Uromodulin, Type 2 Diabetes Mellitus, Diabetic Kidney Disease, Glycemic Control, Body Mass Index

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Introduction

Type 2 diabetes mellitus (T2DM) represents a major global health challenge, frequently leading to diabetic nephropathy (DN), a leading cause of end-stage renal disease [1]. Uromodulin, also known as Tamm-Horsfall protein, is a kidney-specific glycoprotein produced exclusively by tubular epithelial cells in the thick ascending limb of Henle's loop and early distal convoluted tubule, playing key roles in renal protection, salt balance, and prevention of urinary tract infections [2],[3]. In type 2 diabetes mellitus (T2DM), metabolic disturbances such as hyperglycemia promote interstitial inflammation, which contributes to interstitial fibrosis and tubular atrophy, and induces tubular cell hyperplasia and hypertrophy [4]. As diabetic nephropathy progresses, tubular injury occurs before glomerular damage. The early stages of diabetic nephropathy are characterized by decreased serum uromodulin levels [5][6][7].

So, this study aimed to investigate the change in serum uromodulin levels in relation to risk factors such as age, gender, BMI, duration of diabetes and glycemic control.

Methodology

A case-control study was conducted at three hospitals in Najaf, Iraq in the period from April 2025 to August 2025 at the Al Najaf Specialized Centre for Diabetic and Endocrinology, Al Hakeem General Hospital, Al Sadar Teaching Hospital. The study included 176 participants, including 120 patients diagnosed with type 2 diabetes mellitus (T2DM) based on the American Diabetes Association (ADA) criteria (60 males and 60 females) and 56 healthy control participants (28 males and 28 females). We divided patients according to UACR into three groups. Four groups of participants: 40 patients with type2 diabetes without nephropathy, with ACR values below 30 mg/g (DN1), 40 patients with type-2 diabetes and nephropathy with ACR values between 30–300 mg/g (DN2) and another 40 patients with type-2 diabetes and nephropathy with ACR values over 300 mg/g (DN3), and the control group of 56 healthy and matched subjects (men and women). Exclusion criteria were; type 1 diabetes, gestational diabetes or acute complications including hyperosmolar hyperglycemic state, diabetic ketoacidosis or lactic acidosis. Patients who also experienced heart disease, liver failure, malignancies or kidney disease other than diabetes mellitus were also excluded. Uromodulin concentrations were measured with (Cloud Clone Human uromodulin kit EKHU-3077) from China and ELISA-Human Reader HS from Germany.

Statistical analysis

SPSS (version 27) was utilized for data analysis. The normality of the data was examined through Shapiro-Wilk tests, and homogeneity of variance was assessed using Levene's test. The results indicated a deviation from normal distribution; therefore, we resorted to non-parametric methods, specifically the Kruskal-Wallis test for group comparisons, Mann–Whitney U test between two groups Comparison, A p-value of less than 0.05 was considered statistically significant.

Results

Comparison of uromodulin Levels among Different Age Groups in Controls and Cases

Uromodulin levels displayed considerable variation across the different groups ($p<0.001$). Analysis revealed a consistent decline in uromodulin concentrations with advancing age, with individuals aged 60 and older exhibiting the lowest levels compared to their younger counterparts. Additionally, uromodulin concentrations were significantly reduced in the later stages of the disease (DN2 and DN3) in comparison to earlier stages (DN1) as well as control subjects.

Table 1: Mean ± SD Values of uromodulin (ng/ml) Across Age Categories and Disease Stages

Age (Years)	uromodulin (Mean ± SD) (ng/ml)				P-value (Between groups)
	Controls N=56	Cases N=120			
		DN1	DN2	DN3	
40-50 years	29.8±4.2	26.9±3.2	24.2±1.8	8.3±4.8	<0.001
51-60 years	29.4±4.6	25.4±3.5	22.3±4.5	5.7±2.8	<0.001
61-70 years	22.4±3.5	22.4±2.2	20.6±3.7	3.6±1.7	<0.001

Significant value: $p < 0.05$, Non-significant value: $p \geq 0.05$

Comparison of uromodulin Levels between Genders in Controls and Cases

The findings of the study indicated substantial differences in uromodulin concentrations when comparing genders and various groups ($p<0.001$). Specifically, female subjects exhibited higher uromodulin levels than males in the DN1, DN3 and control groups. While DN2 showed the opposite.

Table 2: Mean ± SD Values of uromodulin (ng/ml) by Gender and Disease Stages

Gender	uromodulin (Mean ± SD) (ng/ml)				P-value (between groups)
	Controls N=56	Cases N=120			
		DN1	DN2	DN3	

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Male	26.9±5	24.9±3.7	24.3±3.3	4.7±2.9	<0.001
Female	30.2±4.3	26.3±3.3	20.8±3.6	5.4±3.4	<0.001
P-value	<0.001	<0.001	<0.001	<0.001	<0.001

Significant value: p < 0.05 , Non-significant value: p ≥ 0.05

Comparison of uromodulin Levels by BMI Categories in Controls and Cases

The results revealed significant variations in uromodulin levels across different BMI categories within the examined groups (p<0.001). Furthermore, a marked decrease in uromodulin levels was observed as the disease progressed from stage DN1 to the more severe stages, DN2 and DN3.

Table 3: Mean ± SD Values of uromodulin (ng/ml) Across Different BMI Categories and Disease Stages

BMI	uromodulin (Mean ± SD) (ng/ml)				P-value (between groups)
	Controls N=56	Cases N=120			
		DN1	DN2	DN3	
Normal weight (18.5-24.9)	28.9±4.7	26.2±3.6	23±3.2	4.83±4	<0.001
Overweight (25-29.9)	26.4±5.9	25.6±3.4	22.4±4.8	5±2.8	<0.001
Obese ≥30	-	23.9±3.9	22.2±3.2	5.1±3.7	<0.001

Significant value: p < 0.05, Non-significant value: p ≥ 0.05

Comparison of uromodulin Levels Based on Duration of Diabetes Mellitus in Cases

The findings indicated substantial differences in uromodulin levels across groups based on the duration of diabetes (p<0.001). In particular, individuals with a diabetes history longer than 10 years exhibited the lowest average serum uromodulin concentrations when compared to those whose diabetes lasted between 5 to 10 years and those with durations shorter than 5 years.

Table 4: Mean ± SD Values of uromodulin (ng/ml) Across Different Durations of Diabetes and Disease Stages

Duration of DM	uromodulin (Mean ± SD) (ng/ml)			P-value (Between groups)
	Cases N=120			
	DN1	DN2	DN3	
< 5 years	27.4±2.9	24.3±5.7	-	<0.001
5 - 10 years	26.8±3.1	22.8±3.8	6.4±3.9	<0.001
≥ 10 years	22.4±2.4	22.2±3.9	3.9±1.7	<0.001

Significant value: p < 0.05, Non-significant value: p ≥ 0.05

Comparison of uromodulin Levels Based on Glycemic Control in Cases

Results show significant variations in uromodulin levels associated with glycemic control across glycated hemoglobin (HbA1c) levels (p<0.001). Patients with HbA1c < 7% showed significantly higher serum uromodulin levels than the acceptable range of 7–8% and those with poor control > 8%.

Table 5: Mean ± SD Values of uromodulin (ng/ml) Across Different Glycemic Control Levels and Disease Stages

Glycemic control	uromodulin (Mean ± SD) (ng/ml)			P-value
	Cases N=120			
	DN1	DN2	DN3	
Optimal control <7	27.1±2.8	26.1±3.1	4.5±4.4	<0.001
Acceptable control 7 – 8	25.9±3.6	19.9±3.6	4.5±2.2	<0.001
Poor control >8	24.7±3.6	22.7±3.7	5.2±3.3	<0.001

Significant value: p < 0.05, Non-significant value: p ≥ 0.05

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Discussion

In this study, the mean serum uromodulin levels across different age groups were significantly lower in patients with type 2 diabetes compared to their age-matched controls ($p < 0.001$). Moreover, uromodulin concentrations showed a progressive decline with advancing age and disease progression, consistent with previous findings that demonstrated a significant negative correlation between serum uromodulin and age [8].

The current study's findings demonstrated that, across all groups except for DN2, the mean value of uromodulin levels in female participants was greater than that of male participants, these results are in line with the previous study that indicated Serum uromodulin levels are higher in healthy female participants than healthy male participants, they suggested that Estrogen increases uromodulin production, likely because of noncanonical and half estrogen response elements in the uromodulin gene.[9]

The study results revealed significant differences in serum uromodulin in relation to BMI categories, these results are in contrast with the results indicated that revealed there was no significant correlation between serum uromodulin and Body Mass Index [10].

The study results indicated a significant difference in serum uromodulin in relation to duration of diabetes with lower results being with more duration mainly above 10 years, these results disagree with a study that showed there was no significant correlation between serum uromodulin and duration of DM, that suggests there is no relationship between uromodulin and duration of DM [8].

As for the serum uromodulin correlation with glycemic control, serum uromodulin was significantly reduced with worsening glycemic control >8, these results are consistent with the various previous studies that indicated a significant negative correlation between serum uromodulin and glucose metabolism, under hyperglycemic conditions, damage to the thick ascending limb (TAL) may lead to uromodulin leakage into the renal interstitial space, thereby reducing its serum concentration [10][11][12][13][14]. Consequently, low serum uromodulin levels may reflect advanced stages of diabetic nephropathy and diminished renal cell mass [3][15].

Conclusion

Conclusion Serum uromodulin is an independent biomarker of renal and metabolic deterioration and this study shows that that uromodulin concentrations correlate positively and negatively with multiple demographic and clinical determinants in a population of patients with type 2 diabetes mellitus. Results showed age-independent decrease of uromodulin with increasing severity and duration of disease, BMI and poor glycemic control, significantly lowered in advanced stage of diabetic nephropathy (DN2 and DN3). Interestingly, the authors also identified differences between sexes, as females generally had higher levels of uromodulin than those of males, providing some evidence that uromodulin expression could be modulated by hormones. These findings support the notion of early tubular impairment in DKD, where decreased uromodulin is a marker of impaired tubular mass and of impaired renal protective measures, respectively. These findings have important clinical implications; serum uromodulin may provide a means of identifying very high-risk individuals earlier in the course of their disease process, it may also aid in risk stratification, allowing for a more targeted approach to glycemic and metabolic management. Moreover, measuring uromodulin in the daily clinical practice could improve early treatment strategies to conserve renal function in patients with type 2 diabetes. Larger multicenter prospective cohorts are required to confirm our findings and to understand the mechanistic basis by which uromodulin may lead to metabolic and renal injury,

and if similar relationships can be observed to predict long-term renal and cardiovascular outcomes in diabetic populations.

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Ethical approval

The Scientific Committee of the College of Medicine at the University of Basrah granted ethical clearance. Additionally, the hospital ethics board approved this study. All participants provided written informed consent after obtaining detailed information about the study's aims and methodologies.

Author contributions

The conception, design and manuscript preparation of the study was contributed equally by all authors.

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