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ORIGINAL RESEARCH

Urinary Ferritin as an Early Indicator of Tubular Injury in Diabetic Kidney Disease: Insights from NHANES and Clinical Cohorts

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Objective: To investigate the association between iron metabolism disorders and diabetic kidney disease (DKD) and to evaluate the potential of urinary ferritin as an early marker of tubular injury in diabetic patients.

Methods: This study utilized data from 1,306 diabetic patients and 1,306 propensity score-matched non-diabetic controls from the NHANES (2017–March 2020) dataset. Diabetic participants were classified into Non-DKD (n = 923) and DKD (n = 383) groups based on the urinary albumin-to-creatinine ratio (UACR). Binary logistic regression and restricted cubic spline models were used to evaluate the association between iron metabolism indicators and DKD risk. Additionally, renal tissue samples from 12 patients (6 with T2DM and 6 non-diabetic controls) undergoing nephrectomy were analyzed for iron accumulation and tubular injury markers. Clinical data from 35 T2DM patients (with and without DKD) and 20 matched healthy controls were included to assess urinary ferritin and tubular injury markers. Finally, 120 T1DM patients were stratified by disease duration to assess correlations between urinary ferritin and renal injury biomarkers.

Results: Decreased serum iron (OR = 0.962, P = 0.037) and increased serum ferritin (OR = 1.001, P = 0.024) were identified as independent risk factors for DKD. Diabetic patients exhibited higher renal iron, urinary ferritin, and tubular injury markers, with significant correlations between renal iron and urinary ferritin levels. Urinary ferritin levels also increased with T1DM duration, significantly correlating with tubular injury markers.

Conclusion: Impaired iron metabolism, characterized by low serum iron and high serum ferritin, is an independent risk factor for DKD. Urinary ferritin may serve as a biomarker of early tubular injury in diabetic patients, even in the absence of albuminuria.

Keywords: iron metabolism, diabetic kidney disease, tubular injury, urinary ferritin

Introduction

Diabetic kidney disease (DKD) is one of the most common and serious chronic complications of diabetes mellitus (DM).[1] The classic diagnosis of DKD primarily relies on persistent albuminuria, though a discrepancy often exists between clinical presentation and morphological damage, leading to underdiagnosis in its early stages.[2] Previous studies from our lab have shown that tubular injury is present even at the stage of normal albuminuria in diabetic mouse models.[3] Numerous studies suggest that tubular injury, particularly in the proximal tubule, plays a crucial role in the initiation and progression of DKD, with this process not merely secondary to glomerular damage.[4] Thus, the renal tubule may be a potential target for DKD prevention and treatment, and clarifying the mechanisms underlying early tubular injury holds practical significance for DKD management.

Approximately 60% of diabetic patients meet current criteria for iron deficiency.[5] In DM, iron deficiency is typically unrelated to inadequate dietary intake or gastrointestinal blood loss but rather stems from impaired iron mobilization.[6]

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Since inflammation, often exacerbated by obesity, increases hepcidin and ferritin levels, inflammation-mediated iron sequestration is a primary driver of functional iron deficiency in diabetes, explaining why diabetes is a major cause of anemia in chronic diseases.[7] Increasing attention is being given to the association between iron metabolism disorders and DKD, with iron metabolism indicators—such as serum iron, ferritin, transferrin, and hepcidin—being closely linked to the occurrence and progression of DKD. Our research team previously conducted a retrospective analysis and Mendelian randomization study involving 1,398 patients with type 2 diabetes, confirming a causal relationship between iron deficiency anemia and DKD. Further bioinformatics analysis suggested that iron deficiency anemia may increase DKD susceptibility by enhancing oxidative stress and altering small molecule transport.[8] Diabetes induces extensive inflammation and oxidative stress, which may lead to iron retention in the renal tubules and subsequent tubular damage through iron overload.[9,10] Our previous studies found that the ubiquitination and degradation of SLC40A1 result in iron overload within tubular epithelial cells, activating ferroptosis pathways in diabetic kidney injury.[3] This study aims to investigate the association between disturbances in circulating and tubular iron metabolism and diabetic kidney injury, which is essential for understanding DKD's underlying mechanisms and advancing early prevention and treatment strategies.

Materials and Methods

Data of NHANSE Participants

The National Health and Nutrition Examination Survey (NHANES), conducted by the Centers for Disease Control and Prevention (CDC) in the United States, is a nationwide, cross-sectional study designed to evaluate the health and nutritional status of both adults and children. Publicly accessible through the CDC's National Center for Health Statistics (NCHS), this study utilized NHANES data collected from 2017 to March 2020 (pre-pandemic), encompassing 15,561 eligible participants. The study selection process is illustrated in the flow diagram in Figure 1. Multiple imputation was applied to address missing data, yielding a final sample of 1,306 diabetes (DM) participants and an equal number of non-diabetic individuals matched by 1:1 propensity score matching (PSM). The DM group was further categorized by urinary albumin-to-creatinine ratio (UACR) as Non-DKD (N=923) or DKD (N=383). Iron metabolism indicators were then analyzed for associations with DKD across these groups.

Human Renal Specimens

We included 12 patients who underwent kidney tumor surgery and were subsequently diagnosed with clear cell carcinoma. Among these patients, three received an initial diagnosis of T2DM during their hospitalization, while the other three did not have diabetes. None of them had previously used glucose-lowering medications. Exclusion criteria encompassed diabetic ketoacidosis, severe infections, urinary albumin-to-creatinine ratio (UACR) exceeding 30 mg/gCr, or eGFR below 60 $mL•min^{-1}•(1.73m^2)^{-1}$. Additionally, comorbid hypertension or the use of renin – angiotensin - aldosterone system inhibitors (RAASi) were grounds for exclusion, other kidney diseases potentially impacting renal function and/or proteinuria, such as urinary tract infections, as were severe underlying conditions such as tumors, hepatitis, connective tissue diseases. All patients provided informed consent and adhered strictly to the guidelines of the Ethics Committee of the First Affiliated Hospital of the University of Science and Technology of China (Approval Number: 2022KY490). After the surgical procedures, we collected normal kidney tissues adjacent to the tumors for further examination.

Data of T2DM Patients

A total of 35 patients with type 2 diabetes mellitus (T2DM) were recruited from the Endocrinology Department of the First Affiliated Hospital of the University of Science and Technology of China (Anhui Provincial Hospital) between February 2023 and July 2023. All patients met the diagnostic criteria for T2DM as outlined in the WHO guideline for the prevention and treatment of T2DM.[11] None of these patients had used glucose-lowering medications within the past three months, and their eGFR was ≥ 60 $mL•min^{-1}•(1.73\ m^2)^{-1}$. Patients were classified into two groups: the T2DM group and the DKD group, based on either their prior UACR or the UACR measured during hospitalization (with DKD diagnosed on the basis of two UACR readings above the 30 mg/gCr threshold). Remaining exclusion criteria were consistent with

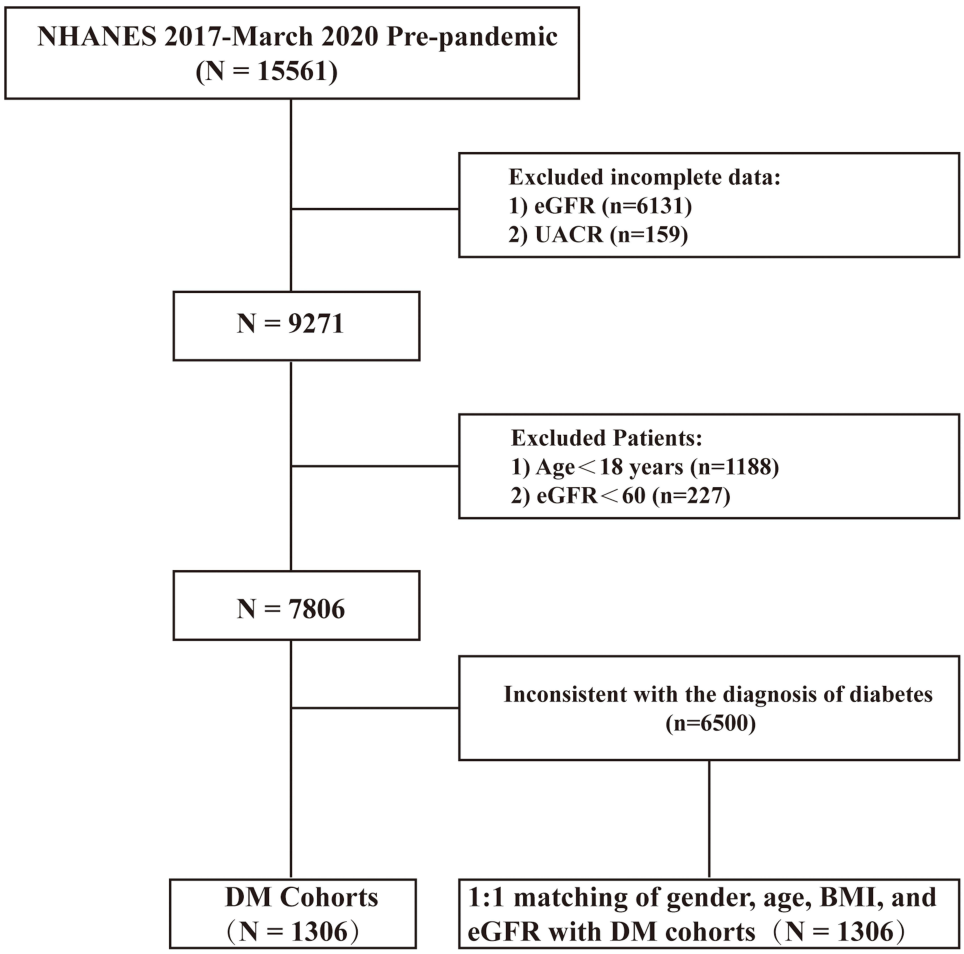

Figure 1 Flowchart of participant selection.

those set for the aforementioned renal surgery patients. For a healthy control group, 20 individuals matched by gender, age, and BMI were selected from the general health examination population. All participants provided informed consent and strictly followed the Ethics Committee guidelines of the First Affiliated Hospital of the University of Science and Technology of China (2022KY490). Recorded data included gender, age, diabetes duration, and body mass index (BMI). Fasting venous blood and morning urine samples were collected the following day for analysis of glycated hemoglobin (HbA1c), uric acid (UA), creatinine (Cr), lipid metabolism indicators (total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol), proteinuria-related markers (UACR, immunoglobulin G, retinol-binding protein, transferrin, α-1 microglobulin, β-2 microglobulin), and urinary ferritin levels.

Data of T1DM Patients

A total of 120 patients with type 1 diabetes mellitus (T1DM) were included in the study, comprising 68 males and 52 females, with an average age of 28.7 years. The patients were recruited from the Endocrinology Department of the First Affiliated Hospital of the University of Science and Technology of China (Anhui Provincial Hospital) between May 2020 and May 2023. All patients were receiving insulin therapy for glycemic control, and their diagnosis of T1DM adhered to the diagnostic criteria outlined in the WHO guideline for the diagnosis and treatment of T1DM,[12] and other exclusion criteria resemble those of the aforementioned population. All patients provided informed consent and adhered strictly to the guidelines of the Ethics Committee of the First Affiliated Hospital of the University of Science and Technology of China (2022KY490). Patients were categorized into three groups based on the duration of diabetes: Group A (duration ≤ 1 year), Group B (1 year < duration ≤ 10 years), and Group C (duration > 10 years). Differences in the above-mentioned indicators among these groups were analyzed.

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Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics 22.0 (IBM Co., Armonk, NY, USA). Missing values in this study were entirely random, and with a univariate missing rate of <10%, multiple imputations were applied before analysis. Two-tailed P-values <0.05 were considered statistically significant. Descriptive statistics for continuous variables are presented as means (SDs) or medians (interquartile ranges), depending on distribution, while categorical variables are shown as frequencies (percentages). For comparisons among the three groups, one-way analysis of variance, chi-square tests, or Mann–Whitney *U*-tests were employed as appropriate. Logistic regression models were used to estimate odds ratios with 95% confidence intervals to analyze risk factors associated with DKD, adjusting for statistically significant confounders identified through univariate tests. Restricted cubic splines were used to assess nonlinear associations between serum iron, serum ferritin, and DKD risk.

Results

Characteristics of Participants in NHANES

The median diabetes duration among the 1,306 enrolled diabetic patients was 7 years, with an average HbA1c of 7.49%. As shown in Table 1, based on UACR results, participants were divided into the non-DKD group (n=923) and the DKD group (n=383). Significant differences were observed between the two groups in terms of gender, age, diabetes duration, UACR, glycohemoglobin, FPG, ALP, GGT, HDL, and ferritin (all $p < 0.05$). A 1:1 propensity score matching (PSM) was performed, matching 1,306 non-diabetic patients by gender, age, BMI, and eGFR as a control group. A linear trend

Table 1 The Clinical and Biochemical Characteristics of the Participants in NHANES

Characteristics	Control (n=1306)	Non-DKD (n=923)	DKD (n=383)	P value[#]	P for trend[&]
General Data					
Gender (Male/Female)	700/606	473/450	232/151	0.002	0.257
Age (year)	61.32 ± 14.26	59.98 ± 13.03	61.81 ± 13.07	0.022	0.537
BMI (kg/m^2)	32.32 ± 8.37	32.94 ± 7.77	32.49 ± 7.56	0.338	0.712
Diabetes-related indicators					
Duration of diabetes	-	5 (0, 14)	10 (2, 18)	< 0.001	-
UACR (mg/gCr)	7.37(5.10, 11.81)	8.8 (5.86, 14.37)	82.02 (46.96, 193.28)	< 0.001	< 0.001
HbA1c (%)	5.63 ± 0.37	7.24 ± 1.4954	8.0971 ± 1.9903	< 0.001	< 0.001
FPG (mmol/L)	5.91 ± 0.71	8.55 ± 3.04	10.01 ± 4.27	< 0.001	< 0.001
Biochemical indicators					
ALT (U/L)	18 (14, 26)	19 (14, 27)	20 (14, 28)	0.702	0.001
AST (U/L)	20 (17, 24)	19 (15, 24)	19 (15, 25)	0.505	0.137
ALP (U/L)	77 (64, 91)	80 (65, 96)	83 (67.5, 103)	0.005	< 0.001
GGT (U/L)	22 (15, 32)	25 (17, 40)	27 (19, 46)	0.008	< 0.001
Alb (g/L)	40.12 ± 3.17	39.99 ± 3.26	39.67 ± 3.63	0.111	0.014
Total Bilirubin (umol/L)	6.84 (5.13, 10.26)	6.84 (5.13, 9.405)	6.84 (5.13, 10.26)	0.654	0.596
eGFR (mL/min/1.73 m²)	107.28 (91.07, 127.64)	108.73 (88.29, 132.33)	105.14 (83.95, 134.13)	0.214	0.209
Uric acid (umol/L)	321.2 (273.6, 380.7)	321.2 (267.7, 386.6)	327.1 (267.7, 398.5)	0.363	0.545
Lipid metabolism indicators					
TG (mmol/L)	1.10(0.76, 1.55)	1.28 (0.90, 1.75)	1.34 (0.93, 2.04)	0.106	< 0.001
LDL-c (mmol/L)	2.91 ± 0.89	2.60 ± 1.03	2.56 ± 1.08	0.405	0.054
HDL-c (mmol/L)	1.33(1.11, 1.63)	1.19 (1.01, 1.45)	1.14 (0.98, 1.34)	0.001	< 0.001
Iron metabolism indicators					
Ferritin (ng/mL)	126 (69.3, 220)	120 (55.63, 214.75)	132 (64, 244)	0.014	< 0.001
Serum iron (umol/L)	15.2 (11.6, 18.8)	14 (10.6, 17.65)	13.4 (10.4, 17.2)	0.097	< 0.001

Notes: # *P*: DKD Group vs Non-DKD Group & *P*: Linear Trend Analysis Across Three Groups.

Abbreviations: BMI, Body Mass Index; UACR, Urinary Albumin-to-Creatinine Ratio; HbA1c, Hemoglobin A1c; FPG, Fasting Plasma Glucose; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; ALP, Alkaline Phosphatase; GGT, Gamma-Glutamyl Transferase; eGFR, Estimated Glomerular Filtration Rate; TG, Triglycerides; LDL-c, Low-Density Lipoprotein Cholesterol; HDL-c, High-Density Lipoprotein Cholesterol.

analysis across the three groups revealed that with disease progression, UACR, FPG, HbA1c, ALT, ALP, GGT, TG, and serum ferritin showed an increasing trend, while ALB, HDL-c, and serum iron demonstrated a significant decreasing trend (all p for trend < 0.05). No significant trend was observed for the other indicators.

Iron Metabolism Disorder as a Relative Independent Risk Factor for DKD in DM Patients

Variables with P-values less than 0.1 from the DKD vs non-DKD group comparison (excluding UACR) were included in a binary stepwise logistic regression analysis. The results indicated that diabetes duration (OR=1.019), HbA1c (OR=1.291), and ferritin (OR=1.001) were risk factors for DKD, while serum iron (OR=0.962) was a protective factor (Figure 2A). Elevated ferritin or reduced serum iron levels indicate a decrease in bioavailable iron, the primary iron metabolism disorder observed in diabetic patients. Using restricted cubic spline curves, we then assessed the relationship between ferritin and serum iron levels and DKD progression. After adjusting for diabetes duration, serum iron, and HbA1c, results showed a non-linear association between ferritin levels and DKD risk, with a turning point at 124 μg/L for an Odds Ratio of 1 (Figure 2B). Conversely, serum iron levels demonstrated a statistically significant linear inverse correlation with DKD risk (Figure 2C).

Iron Metabolism and Diabetic Renal Tubular Injury

To further elucidate the early signs of renal tubular damage in diabetes and the role of iron overload, we selected 12 individuals who underwent kidney tumor surgery (baseline data are provided in Supplementary Table 1). HE staining revealed that, compared to the control group, diabetic patients exhibited glomerular enlargement accompanied by tubular dilation and increased infiltration of inflammatory cells in the glomeruli and interstitium (Figure 3A). PAS staining further demonstrated glomerular expansion, thickening of the tubular basement membrane, and loss of brush border in diabetic patients (Figure 3B). Figure 3C shows the mRNA levels of tubular damage markers—Kim-1, Ngal, and PAL1—which were significantly elevated in diabetic patients compared to controls. Immunohistochemistry indicated that FTH1 expression was markedly higher in the T2DM group than in controls (Figure 3D). Similarly, analysis of renal tissues showed elevated Fe2+ concentrations in diabetic patients (Figure 3E). Morning urinary ferritin levels were also significantly higher in diabetic patients than in the control group (Figure 3F), with a strong positive correlation between urinary ferritin and renal tissue Fe2+ levels (Figure 3G). These findings suggest that significant pathological changes occur in both the glomeruli and renal tubules in the early stages of diabetes, with no evident chronological order. Traditional glomerular markers, such as urinary albumin, may lag in assessing glomerular damage, highlighting the necessity of tubular markers for a comprehensive early diagnosis of diabetic kidney injury. Urinary ferritin could serve as a potential indicator of renal iron metabolism.

Characteristics of Urinary Renal Injury Biomarkers in T2DM Patients

Ferritin, as a reflection of body iron stores, has a large molecular weight and is not readily filtered by the renal barrier. In individuals with an intact renal filtration barrier, urinary ferritin levels likely reflect secretion or release from tubular cells. This

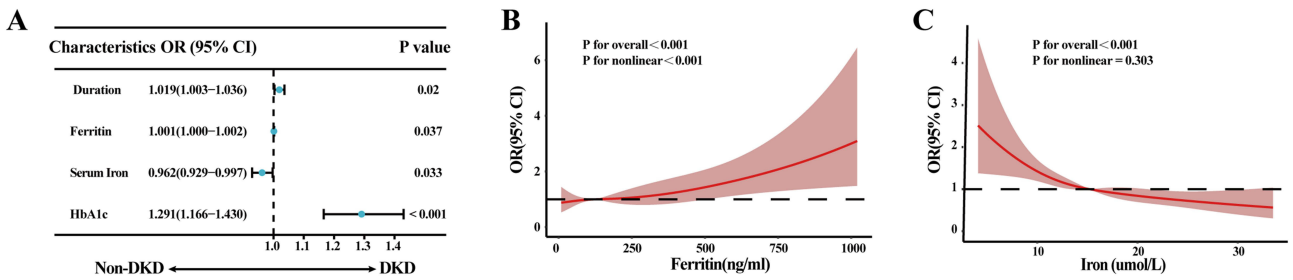

Figure 2 Iron Metabolism Disorder as a Relative Independent Risk Factor for DKD in DM Patients. (**A**) Relative risk factors influencing DKD development; (**B**) Non-linear relationship between ferritin levels and DKD risk, adjusted for duration, serum iron, and HbA1c, evaluated by restricted cubic splines; (**C**) Linear inverse relationship between serum iron levels and DKD risk, adjusted for duration, ferritin, and HbA1c, evaluated by restricted cubic splines.

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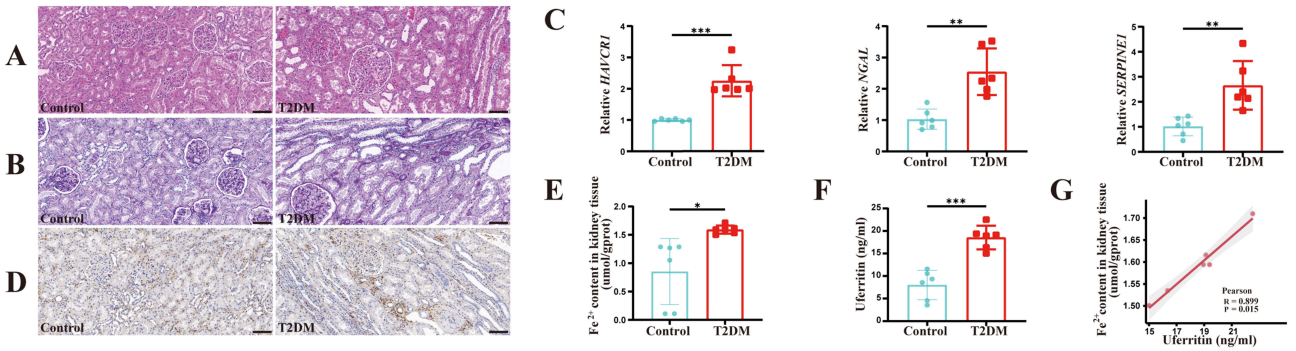

Figure 3 Iron Metabolism and Diabetic Renal Tubular Injury. (**A**) HE staining. (**B**) PAS staining. (**C**) RT-PCR results for KIM1, Ngal, and PAI-1 in kidney tissues. (**D**) Immunohistochemistry staining of FTH1. (**E**) Measurement of Fe^{2+} content in kidney tissue. (**F**) Urinary Ferritin. (**G**) Correlations between Uferritin and kidney Fe^{2+} content. Values represent the mean±SD; N=6 patients in both the T2DM group and control group, respectively. *p < 0.05, **p < 0.01, ***p < 0.001.

study further evaluates the relationship between urinary biomarkers, including urinary ferritin, and diabetic kidney injury.We selected 35 T2DM patients who were not using antidiabetic medications and had no history of hypertension. Patients were classified into the T2DM and DKD groups based on prior or admission UACR assessments. Additionally, 20 healthy individuals matched for gender, age, and BMI served as a control group (Supplementary Table 2 for baseline characteristics). Compared to the control group, the T2DM group showed no significant differences in glomerular injury markers, including UACR (Figure 4A), urinary IgG (Figure 4B), and urinary transferrin (Figure 4C). Trend analyses for UACR and urinary IgG also revealed no statistically significant differences (all P trend > 0.05). However, urinary tubular injury markers, including Uα1MG (Figure 4D) and URBP (Figure 4E), demonstrated significant differences among the three groups, with consistent trend analysis indicating statistical significance (all P < 0.001). Further analysis of urinary ferritin levels (Figure 4F) showed significant differences across the three groups (p < 0.01, P trend < 0.001). These findings suggest that tubular damage is an early indicator of diabetic kidney injury, with iron overload potentially involved in its pathogenesis.

Characteristics of Urinary Renal Injury Biomarkers in T1DM Patients

To further evaluate the role of iron overload in early renal damage in diabetes, this study collected data from 120 T1DM patients, including 68 males, with an average age of 28.7 years. None of the patients had been diagnosed with DKD. Based on diabetes duration, patients were divided into three groups: Group A (duration ≤ 1 year, N=25), Group B (1 year

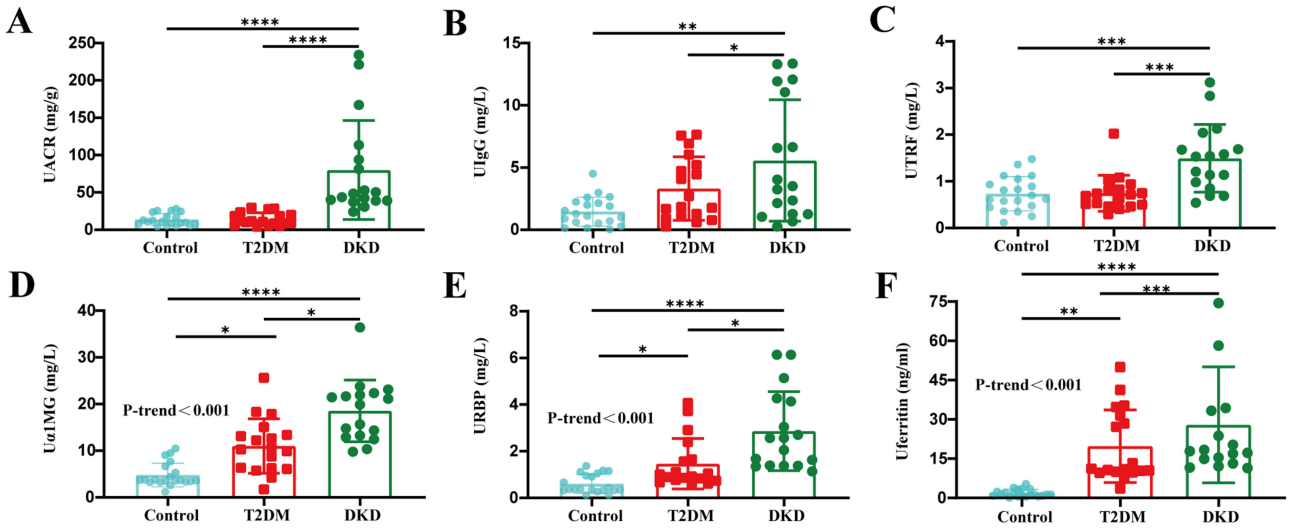

Figure 4 Characteristics of Urinary Renal Injury Biomarkers in T2DM Patients. (**A**) UACR. (**B**) Urinary IgG. (**C**) Urinary Transferrin. (**D**) Urinary α1MG. (**E**) Urinary RBP. (**F**) Urinary Ferritin. Values are presented as mean ± SD in the control group (N=20), T2DM group (N=18), and DKD group (N=17), respectively. *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001.

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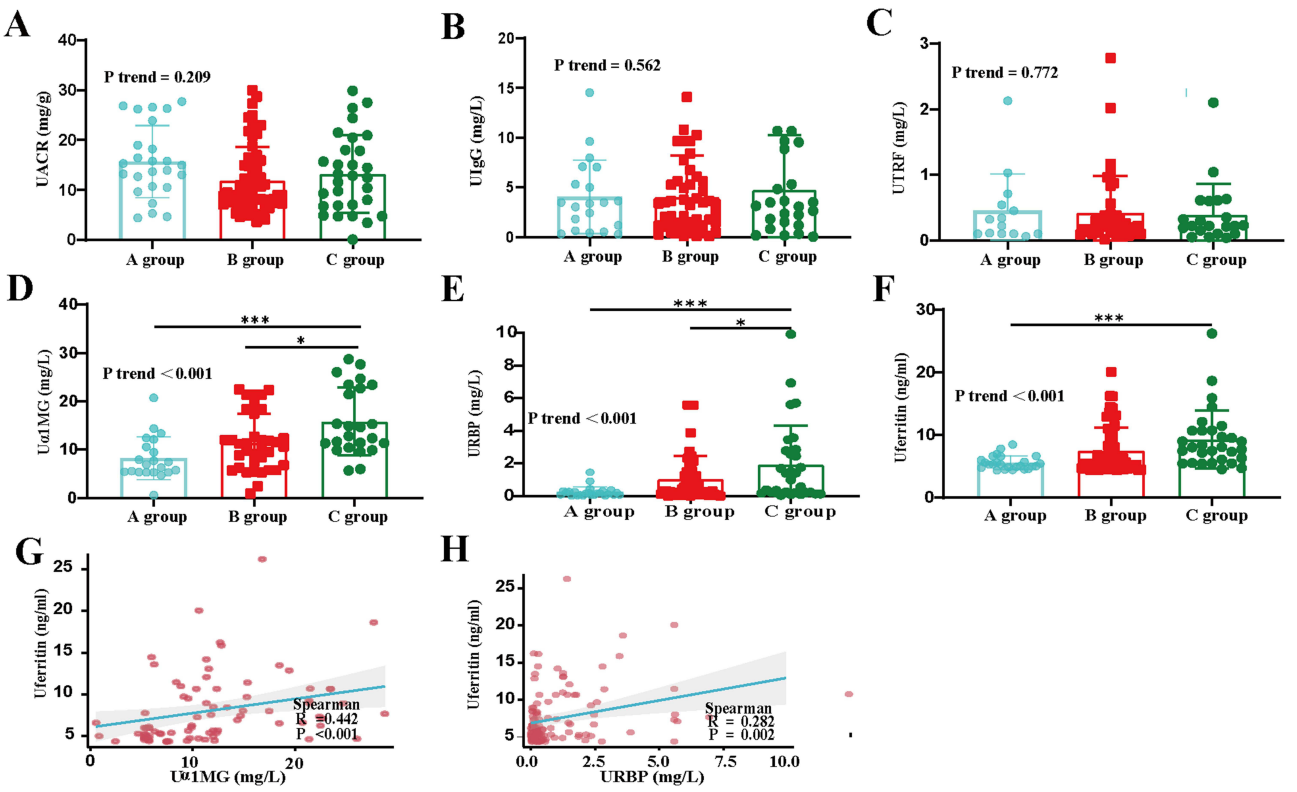

Figure 5 Characteristics of Urinary Renal Injury Biomarkers in T1DM Patients. (**A**) Urinary Albumin-to-Creatinine Ratio. (**B**) Urinary IgG. (**C**) Urinary Transferrin. (**D**) Urinary α1MG. (**E**) Urinary RBP. (**F**) Urinary Ferritin. (**G**) Correlation between Uα1MG and Uferritin. (**H**) Correlations between Uferritin and URBP. Values represent the urinary biomarker levels in Group A (duration ≤ 1 year, N=25), Group B (1 year < duration ≤ 10 years, N=65), and Group C (duration > 10 years, N=30), respectively. *p < 0.05, ***p < 0.001.

< duration ≤ 10 years, N=65), and Group C (duration > 10 years, N=30). Apart from age and disease duration, there were no significant differences in baseline parameters among the groups (Supplementary Table 3). Urinary markers of glomerular and tubular damage were compared across the groups. No significant differences were found for UACR (Figure 5A), urinary IgG (Figure 5B), or urinary transferrin (UTRF) (Figure 5C), and trend analysis showed no correlation with T1DM duration (all P trend > 0.05). However, both Group A and Group B showed significant differences in urinary α1-microglobulin (Uα1MG) (Figure 5D) and urinary retinol-binding protein (URBP) (Figure 5E) levels compared to Group C (all $p < 0.05$). Further trend analysis revealed significant differences in these tubular damage markers, with Figure 5F showing that urinary ferritin levels in Group C were significantly higher than in Group A ($p < 0.001$), and trend analysis confirmed a gradual increase in urinary ferritin levels with T1DM duration ($p < 0.001$). A correlation analysis between tubular damage markers and urinary ferritin indicated that Uα1MG (Figure 5G) and URBP (Figure 5H) were positively correlated with urinary ferritin. These findings suggest that diabetic tubular damage may emerge progressively before clinical diagnosis of DKD, occurring more frequently than glomerular damage, with renal tubular iron overload potentially playing a critical role in this process.

Discussion

Iron is an essential trace element in the human body, acting as a cofactor in various enzymes and participating in numerous metabolic processes A considerable body of evidence has indicated the link between iron and glucose metabolism in diabetes.[13] Iron accumulation or overload can adversely impact glucose metabolism,[14,15] while hyperglycemia may also trigger iron overload and ferroptosis.[16] DKD is among the most common and serious chronic complications of diabetes, with increasing evidence showing that tubular epithelial cell (TEC) injury plays a crucial role in its onset and progression, though the underlying pathological mechanisms remain complex and warrant further study. This study, based on NHANES data analysis, identified decreased serum iron and increased serum ferritin as

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independent risk factors for DKD in diabetic patients. To further elucidate the role of iron metabolism dysregulation in diabetic renal tubular injury, our histological analysis of human kidney specimens suggested that even in the early, proteinuria-free stages of diabetes, tubular injury and iron accumulation are already present, with urinary ferritin levels highly correlated with renal iron content. Additionally, in a local cohort, we confirmed early tubular injury in diabetes, with urinary ferritin levels mirroring trends seen in tubular injury markers. These findings imply that iron dysregulation may contribute to DKD pathogenesis, with urinary ferritin emerging as a potential biomarker for renal tubular iron overload in early diabetes-associated kidney injury.

The kidneys, as key organs of excretion, express various iron metabolism-related proteins, playing a critical role in systemic iron homeostasis through glomerular filtration and tubular reabsorption and secretion.[17] Filtered iron-bound transferrin (TRF) is reabsorbed by proximal tubular epithelial cells (PTEC) through receptor-mediated endocytosis, where it is stored as ferritin, utilized in mitochondria, or exported via SLC40A1.[18] Disruptions in systemic iron balance, including iron overload and deficiency, have detrimental effects on kidney function, and studies have shown increased iron deposition in the TECs of DKD patients compared to healthy individuals. Chronic iron overload may lead to nephrotoxicity, accelerating kidney injury through oxidative stress (via the Fenton reaction), activation of ferroptosis, and stimulation of the renin-angiotensin system.[19] TRF-bound iron is primarily reabsorbed in PTECs via TfR1, and the lower serum TRF levels observed in T2DM patients with DKD may be linked to increased urinary TRF excretion and renal iron deposition.[20] Research has shown that deletion of Tfr1 can mitigate kidney fibrosis in DKD mouse models by inhibiting iron-induced oxidative stress,[21] underscoring the importance of iron homeostasis for kidney health and the potential role of iron overload in DKD progression. Understanding iron regulation mechanisms may offer novel therapeutic targets for kidney damage caused by iron overload.

DKD diagnosis traditionally relies on persistent albuminuria and decreased creatinine clearance. However, diabetes-induced renal pathology often precedes detectable lab abnormalities, resulting in underdiagnosis at early stages.[22] Identifying early mechanisms of diabetic kidney injury and exploring effective strategies to delay or prevent DKD progression is a critical objective in clinical and research settings. TECs, especially PTECs, are pivotal in the kidney's reabsorption functions, and mounting evidence suggests TEC injury as an early initiator in DKD, with urinary TEC damage markers rising earlier than microalbuminuria in diabetic patients.[23] To alleviate iron overload, cells primarily synthesize ferritin or expel iron via SLC40A1. Inflammatory responses and reduced renal clearance in diabetes often lead to elevated serum hepcidin, promoting SLC40A1 degradation and reducing iron mobilization and utilization.[24] Compared to healthy controls, early-stage DKD patients show increased FTH in proximal tubule tissues and reduced SLC40A1.[25] Our previous studies indicated that TEC injury in diabetes is associated with SLC40A1 ubiquitin-mediated degradation leading to iron overload,[3] yet urine-based markers to assess tubular iron content are still lacking. Ferritin has been detected in human urine (or urinary exosomes) and correlates with serum ferritin and body iron stores in healthy individuals.[26] Due to its large molecular size, urinary ferritin in individuals without significant filtration barrier damage reflects tubular cell secretion or damage release, potentially serving as a marker for tubular iron content. Our study on renal tissue specimens from diabetic patients without proteinuria found a strong correlation between urinary ferritin, renal iron content, and kidney injury markers, highlighting its potential as a biomarker for early tubular damage in diabetes.

In summary, iron dysregulation may play a role in DKD pathogenesis, with urinary ferritin offering insights into early tubular damage in diabetes. This has important implications for understanding DKD mechanisms and assessing early tubular injury. However, limitations of this study include: 1) Limited renal biopsy specimens due to the early stage of renal injury studied; 2) Relatively small T1DM and T2DM sample sizes, primarily from the Han population in Hefei, Anhui Province, which may introduce sampling bias; 3) The NHANES dataset lacks comprehensive diabetes-related parameters, such as HOMA-IR and urinary tubular injury markers.Despite substantial efforts in prevention and treatment, DKD remains a major health burden. Our study elucidates the potential mechanisms of early tubular injury in diabetes and suggests strategies targeting tubular iron overload regulation. We believe that combining traditional urinary TEC damage markers with urinary ferritin from the perspective of tubular injury and the pathological feature of iron overload in diabetic tubules could offer a more comprehensive and earlier warning for kidney injury. An evolving kidney protection assessment system based on this approach could provide a more sensitive quantification standard for early DKD prevention and management.

Data Sharing Statement

The datasets analysed during the current study are available from the corresponding author.

Approval of the Research Protocol

The study received ethical approval from the First Affiliated Hospital of the University of Science and Technology of China.

Informed Consent

We have obtained written informed consent from all study participants.All of the procedures were performed in accordance with the Declaration of Helsinki and relevant policies in China.

Approval Date of Registry and the Registration No. of the Study/Trial

2022.10.23, approval Number: 2022KY490

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Disclosure

The authors declare that they have no competing interests in this work.

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