Research in Molecular Medicine

Research Paper

Uric Acid-to-albumin Ratio and Oxidative Stress in Type 2 Diabetes With and Without Nephropathy

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ABSTRACT

Background: This study evaluated the uric acid-to-albumin ratio (UAR) and its association with oxidative stress markers and clinical parameters in patients with type 2 diabetes mellitus (T2DM) with and without diabetic nephropathy (DN).

Materials and Methods: In this comparative cross-sectional study, diabetic patients were divided into two groups: T2DM with DN and T2DM without DN. Clinical, biochemical, oxidative stress, and inflammatory markers were assessed. UAR was calculated and compared between the groups. Correlations between UAR and metabolic, oxidative, inflammatory, and lipid parameters were analyzed. Receiver operating characteristic (ROC) analysis was performed to evaluate the diagnostic performance of UAR for DN.

Results: Patients with DN had significantly lower serum albumin levels and higher UAR values compared with uncomplicated diabetic patients (1.15±0.33 vs 1.09±0.26, P=0.047). Serum creatinine levels were significantly higher, whereas HDL (high-density lipoprotein) and LDL (low-density lipoprotein) cholesterol levels were lower in the DN group. UAR demonstrated a significant inverse correlation with reduced glutathione (GSH) (r=−0.364, P=0.013) and HDL cholesterol (r=−0.250, P=0.034), as well as a positive correlation with the neutrophil-to-lymphocyte ratio (NLR) (r=0.254, P=0.031). No significant associations were observed between UAR and total antioxidant capacity (TAC) or most lipid and glycemic parameters. ROC analysis demonstrated poor discriminatory ability of UAR for DN (AUC=0.551, P=0.426).

Conclusion: UAR is modestly elevated in patients with DN and is associated with selected oxidative stress and inflammatory markers; however, its limited diagnostic performance restricts its utility as a standalone biomarker.

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Research in Molecular Medicine

Introduction

Diabetes mellitus (DM) is one of the most prevalent metabolic disorders worldwide and is associated with a wide range of systemic microvascular and macrovascular complications. Among these, DN is recognized as one of the leading causes of end-stage renal disease (ESRD) and remains a major public health concern [1]. Given the substantial clinical and economic burden of diabetic nephropathy (DN), the identification of reliable and accessible biomarkers for early detection and disease monitoring is of critical importance. The pathophysiology of diabetic nephropathy is multifactorial; however, accumulating evidence highlights oxidative stress as a central mechanism in the initiation and progression of renal injury in diabetic patients. Oxidative stress arises from an imbalance between the production of reactive oxygen species (ROS) and the capacity of antioxidant defense systems [2]. Chronic hyperglycemia promotes excessive ROS generation through multiple metabolic pathways, leading to oxidative damage to DNA, proteins, and lipids [3]. The kidney is particularly vulnerable to such damage due to its high metabolic activity and rich vascularization, ultimately resulting in glomerular dysfunction, proteinuria, and a decline in glomerular filtration rate (GFR) [4]. Uric acid, the final product of purine metabolism, has a dual role in the pathophysiology of renal and metabolic diseases. At physiological levels, uric acid may act as an antioxidant; however, in hyperuricemic states, it exerts pro-oxidant effects by promoting oxidative stress, inflammation, and endothelial dysfunction, thereby contributing to renal tissue injury [5].

Epidemiological studies have also linked elevated serum uric acid levels to an increased risk of developing and progressing DN [6]. On the other hand, serum albumin is a key circulating protein with important antioxidant and anti-inflammatory properties. Reduced serum albumin levels not only reflect nutritional or inflammatory status but also indicate diminished antioxidant capacity, thereby exacerbating oxidative stress. In diabetic nephropathy, increased urinary albumin excretion (albuminuria) is one of the earliest markers of glomerular damage. The albumin-to-creatinine ratio (ACR) is widely used as a standard clinical indicator for diagnosis and monitoring of DN [7]. Even microalbuminuria has been associated with worse clinical outcomes and increased cardiovascular risk in diabetic patients [8].

Given the independent and sometimes opposing roles of uric acid and albumin in oxidative and inflammatory processes, increasing attention has been directed toward composite biochemical indices. Ratios, such as blood urea nitrogen-to-creatinine or various inflammatory indices have been shown to provide more comprehensive insights into disease pathophysiology than single markers alone [9]. In this context, the uric acid-to-albumin ratio (UAR) has emerged as a novel composite biomarker that simultaneously reflects pro-oxidant burden (uric acid) and antioxidant capacity (albumin), thereby potentially providing a more integrated assessment of oxidative stress status. Recent studies have suggested that UAR may serve as a prognostic indicator in various clinical settings, including the prediction of acute kidney injury (AKI) after cardiac surgery, where higher UAR values have been associated with an increased risk of renal complications and an underlying inflammatory and oxidative state [10]. However, evidence regarding its clinical utility in patients with type 2 diabetes mellitus (T2DM), particularly for the assessment of DN, remains scarce.

Moreover, despite the widespread use of conventional biomarkers, such as ACR, eGFR, serum creatinine, and serum uric acid, these markers have important limitations, as each reflects only a single aspect of the complex pathophysiology of DN and may not adequately identify patients at risk of disease progression. Therefore, there is a need for a simple, inexpensive, and readily available biomarker that more comprehensively reflects the underlying pathophysiological mechanisms of DN. Given the central role of oxidative stress in the development and progression of DN, the present study aimed to evaluate the potential clinical utility of the UAR as a novel biomarker by investigating its association with oxidative stress markers and clinical characteristics in patients with type 2 diabetes mellitus (T2DM) with and without DN.

Materials and Methods

Study design and participants

This comparative cross-sectional study was conducted at the Diabetes Center of Imam Hospital, Sari, Iran. A total of 120 patients with T2DM were enrolled and categorized into two groups: 60 patients with DN and 60 diabetic patient without nephropathy (DM group) complications. Participants were recruited from patients attending the Diabetes Center and were selected using simple random sampling among eligible individuals.

The inclusion criteria were age between 50 and 70 years, confirmed diagnosis of T2DM according to the American Diabetes Association (ADA) criteria [11], diabetes duration of at least three years, and willingness to participate in the study. Patients with congestive heart failure, advanced liver disease, acute infection, pregnancy, malignancy, autoimmune disorders, or use of medications known to influence serum uric acid levels (e.g. allopurinol, febuxostat, and thiazide diuretics) were excluded.

Definition of diabetic nephropathy

Diabetic nephropathy (DN) was diagnosed according to clinical records and nephrologist assessment based on established criteria, including persistent albuminuria greater than 300 mg/day or urinary albumin-to-creatinine ratio (UACR) greater than 300 mg/g and/or estimated GFR (eGFR) lower than 60 mL/min/1.73 m^2 [12]. The classification of patients into nephropathy and non-nephropathy groups was confirmed using medical records and laboratory evaluations performed at the Diabetes Center.

Sample size calculation

The sample size was calculated using G*Power software (version 3.1.9.7). Assuming a medium effect size (Cohen's d=0.5), a two-sided significance level (α) of 0.05, and a statistical power of 80%, a minimum of 51 participants per group was required. To compensate for potential missing data and increase statistical power, 60 participants were included in each group, resulting in a total sample size of 120 participants.

Data collection and laboratory measurements

After obtaining written informed consent, demographic and clinical data, including age, sex, duration of diabetes, smoking status, and medication history, were collected through structured questionnaires and medical records.

Following an overnight fast of 10–12 hours, approximately 10 mL of venous blood was collected from each participant under standardized conditions. Five milliliters of blood were transferred into EDTA-containing tubes for glycated hemoglobin (HbA1c) measurement, while the remaining 5 mL were collected into plain tubes for serum separation. Samples were centrifuged at 3000 rpm for 15 minutes at 4 °C, and serum aliquots were stored at −80 °C until analysis.

Serum concentrations of fasting blood glucose (FBG), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), uric acid, creatinine, urea, blood urea nitrogen (BUN), albumin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), calcium, phosphorus, thyroid-stimulating hormone (TSH), and C-reactive protein (CRP) were measured using commercially available enzymatic kits (Pars Azmoon Co., Tehran, Iran) on an automated biochemistry analyzer (BT 3000 Plus, Biotecnica Instruments, Italy). Serum albumin levels were determined using the bromocresol green (BCG) colorimetric method.

Total antioxidant capacity (TAC) and reduced glutathione (GSH) levels, as biomarkers of oxidative stress, were measured using commercially available colorimetric assay kits (Kiazist Life Sciences, Hamedan, Iran) according to the manufacturer's instructions. Absorbance values were measured using a Shimadzu UV–Visible spectrophotometer under standardized laboratory conditions.

HbA1c was determined by high-performance liquid chromatography (HPLC) using a DS5 Glycomat analyzer (Drew Scientific, UK). Two-hour postprandial plasma glucose (2HPP) was measured two hours after a standard meal. Mean plasma glucose (Mean PG) was estimated from HbA1c values using the validated equation (Equation 1) [13]:

1. $\text{Mean PG (mg/dL)} = 28.7 \times \text{HbA1c (\%)} - 46.7$

Complete blood count parameters, including white blood cell count (WBC), red blood cell count (RBC), hemoglobin (HGB), hematocrit (HCT), platelet count, neutrophil count, lymphocyte count, monocyte count, eosinophil count, basophil count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), and mean platelet volume (MPV), were measured using an automated hematology analyzer (Sysmex KX-21N, Sysmex Corporation, Kobe, Japan). All laboratory analyses were performed according to the manufacturers' instructions and under strict internal quality-control procedures.

Calculation of biochemical and inflammatory indices

The UAR, the primary variable of interest, was calculated by dividing serum uric acid concentration (mg/dL) by serum albumin concentration (g/dL).

Additional renal indices included ACR and UCR.

Lipid-related indices included the total cholesterol-to-HDL cholesterol ratio (TC/HDL), triglyceride-to-HDL cholesterol ratio (TG/HDL), LDL cholesterol-to-HDL cholesterol ratio (LDL/HDL), non-HDL cholesterol, and cholesterol-to-albumin ratio (ChAR). Non-HDL cholesterol was calculated by subtracting HDL cholesterol from total cholesterol.

Inflammatory indices were calculated from routine hematological measurements. The monocyte-to-HDL cholesterol ratio (MHR) was calculated as the ratio of monocyte count to the HDL cholesterol concentration. The neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio (PLR), and HDL-to-platelet ratio (HPR) were calculated using standard formulas.

Insulin resistance was estimated using the triglyceride-glucose (TyG) index, calculated as the natural logarithm of the product of fasting triglycerides and fasting blood glucose divided by two. The TyG index was calculated according to the Equation 2 [14]:

2. TyG index=ln [TG (mg/dL)×FBG (mg/dL)/2]

Statistical analysis

Statistical analyses were performed using SPSS software, version 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as the Mean±SD, and categorical variables as frequencies and percentages. Data normality was assessed using the Kolmogorov–Smirnov test. Between-group comparisons were conducted using the independent-samples t-test or Mann–Whitney U test, as appropriate. Pearson correlation analysis was used to evaluate associations between UAR and oxidative stress, inflammatory, lipid, and glycemic parameters. Receiver operating characteristic (ROC) curve analysis was performed to assess the discriminative ability of UAR for DN. A two-tailed $P<0.05$ was considered statistically significant.

Ethical considerations

The study protocol was approved by the Ethics Committee of Mazandaran University of Medical Sciences. Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

Results

A total of 120 individuals were enrolled in this study, including 60 patients with DN and 60 patients with DM without DN. The baseline demographic and clinical characteristics of the participants are presented in Table 1. No significant differences were observed between the two groups regarding age, sex distribution, or duration of diabetes (all $P>0.05$). Body mass index (BMI) data were unavailable and were therefore not included in the baseline comparisons (Table 1).

Comparative biochemical and clinical parameters between the diabetes mellitus and diabetic nephropathy groups

As shown in Tables 2, 3, 4, and 5, patients in the DN group exhibited significantly lower serum albumin levels and significantly higher UAR values than those in the DM group ($P=0.002$ and $P=0.047$, respectively). In addition, serum creatinine was significantly higher, whereas ACR and UCR values were significantly lower in the DN group ($P=0.023$, $P=0.003$, and $P=0.019$, respectively).

Regarding lipid profile parameters, HDL and LDL cholesterol levels were significantly lower in the DN group ($P=0.012$ and $P=0.046$, respectively), whereas the TG/HDL ratio showed borderline statistical significance ($P=0.051$).

No statistically significant differences were observed between the two groups in glycemic indices, oxidative stress markers, hepatic enzymes, inflammatory markers, hematological parameters, mineral profile, or the remaining derived indices (all $P>0.05$).

Correlations of uric acid-to-albumin ratio with oxidative stress, inflammatory markers, lipid profile, and glycemic parameters

As expected from its mathematical construction, UAR demonstrated a strong positive correlation with serum uric acid ($r=0.933$, $P<0.001$) and a moderate negative correlation with serum albumin levels ($r=-0.436$, $P<0.001$). Regarding oxidative stress parameters, UAR showed a significant inverse correlation with GSH ($r=-0.364$,

Table 1. Baseline demographic and clinical characteristics of the study participants

Variables	Mean±SD/No. (%)		P
	DM Group	DN Group	
Age (y)	62.4±8.1	64.1±7.6	0.18
Male	33(54.2)	35(58.3)	0.42
Female	27(45.8)	25(41.7)	0.42

Abbreviations: DN: Diabetic nephropathy; DM: Diabetes mellitus; SD: Standard deviation.

P=0.013), whereas its correlation with TAC was not statistically significant (r=0.112, P=0.421). In terms of inflammatory markers, UAR was positively correlated with NLR (r=0.254, P=0.031). However, no significant correlations were observed with CRP, ESR, WBC, PLR, MLR, MHR, or HPR (all P>0.05). With respect to lipid profile parameters, UAR exhibited a significant inverse correlation with HDL (r=−0.250, P=0.034), while no significant associations were found with total cholesterol, triglycerides, LDL, Chol/HDL, TG/HDL, LDL/HDL, non-HDL-C, or the TyG index. Finally, regarding glycemic parameters, UAR showed weak but statistically significant negative correlations with HbA1c (r=−0.231, P=0.041) and mean plasma glucose (r=−0.229, P=0.048), whereas no significant correlations were observed with FBG or 2HPP (Figure 1).

Pearson correlation analysis revealed that serum uric acid levels were significantly negatively correlated with GSH (r=−0.34, P=0.021), HDL (r=−0.232, P=0.046), HbA1c (r=−0.249, P=0.025), and mean plasma glucose (r=−0.251, P=0.028) levels, while showing significant positive correlations with WBC counts (r=0.296, P=0.010) and the TG/HDL ratio (r=0.258, P=0.025). No significant correlations were observed between serum uric acid and albumin (r=0.199, P=0.068), TAC (r=0.193, P=0.221), CRP (r=0.029, P=0.890), ESR (r=0.082, P=0.636), NLR (r=0.224, P=0.053), PLR (r=−0.006, P=0.958), MLR (r=0.054, P=0.645), MHR (r=0.183, P=0.116), HPR (r=−0.214, P=0.065), total cholesterol (r=0.105, P=0.349), triglycerides (r=0.114, P=0.312), LDL (r=−0.015, P=0.899), Chol/HDL (r=0.197, P=0.092), LDL/HDL (r=0.161, P=0.172), non-HDL-C (r=0.118, P=0.318), the TyG index (r=0.031, P=0.784), FBG (r=−0.142, P=0.191), or 2HPP (r=−0.117, P=0.316) (Figure 2).

Table 2. Primary study variables (uric acid, albumin, UAR, TAC, GSH) and glycemic control parameters

Parameter	Mean±SD		P
	DM Group	DN Group	
Uric acid	4.80±1.22	4.81±1.26	0.958
Albumin	4.42±0.35	4.18±0.37	0.002
UAR (uric acid/albumin)	1.09±0.26	1.15±0.33	0.047
TAC	1.71±0.24	1.67±0.43	0.488
GSH	0.53±0.14	0.55±0.27	0.743
FBG	164.18±62.29	151.49±85.89	0.235
2hpp	263.71±96.03	259.77±99.74	0.778
HbA1C	8.17±1.86	7.91±1.98	0.339
Mean PG	187.19±54.07	179.02±56.88	0.295
TyG	9.45±0.61	9.40±0.86	0.637

Abbreviations: UAR: Uric acid-to-albumin ratio; TAC: Total antioxidant capacity; GSH: Reduced glutathione; FBG: Fasting blood glucose; 2HPP: 2-hour postprandial plasma glucose; HbA1c: Glycated hemoglobin; Mean PG: Mean plasma glucose; TyG: Triglyceride-glucose index; SD: Standard deviation.

Table 3. Renal function and nephropathy-related parameters

Parameter	Mean±SD		P
	DM Group	DN Group	
Urea	36.66±13.13	42.63±21.38	0.127
Creatinine	1.09±0.23	1.24±0.39	0.023
ACR (Albumin/Creatinine)	4.32±0.96	3.62±0.98	0.003
UCR (uric acid/creatinine)	4.64±1.27	4.06±1.18	0.019

Abbreviations: DN: Diabetic nephropathy; ACR: Albumin-to-creatinine ratio; UCR: Uric acid-to-creatinine ratio; SD: Standard deviation.

Pearson correlation analysis revealed that serum albumin levels were significantly negatively correlated with MLR (r=−0.334, P=0.004) and positively correlated with the TyG index (r=0.234, P=0.037). No significant correlations were observed between serum albumin levels and serum uric acid (r=0.199, P=0.068), TAC (r=0.202, P=0.199), GSH (r=0.161, P=0.285), CRP (r=0.184, P=0.401), ESR (r=−0.234, P=0.190), WBC (r=0.205, P=0.083), NLR (r=−0.097, P=0.419), PLR (r=−0.22, P=0.063), MHR (r=−0.082, P=0.491), HPR (r=−0.079, P=0.508), total cholesterol (r=0.177, P=0.119), triglycerides (r=0.191, P=0.095), HDL (r=0.104, P=0.385), LDL (r=0.105, P=0.381), Chol/HDL (r=0.087, P=0.471), TG/HDL (r=0.215, P=0.070), LDL/HDL (r=0.027, P=0.823), non-HDL-C (r=0.159, P=0.186), FBG (r=0.006, P=0.954), 2HPP (r=−0.074, P=0.531), HbA1c (r=−0.107, P=0.346), or mean plasma glucose (r=−0.121, P=0.303) (Figure 2).

Table 4. Lipid profile and related indices

Parameter	Mean±SD		P
	DM Group	DN Group	
Chol	156.69±48.2	143.32±40.72	0.101
TG	180.04±94.65	207.5±134.88	0.125
VLDL	34.15±13.61	34.33±17.44	0.931
HDL	40.93±8.75	36.64±10.25	0.012
LDL	89.34±40.29	77.15±27.58	0.046
Chol/HDL	3.98±1.42	4.27±1.68	0.231
TC/HDL	3.92±1.41	4.23±1.71	0.191
LDL/HDL	2.25±1.11	2.28±1.11	0.868
TG/HDL	4.73±3.11	6.64±5.41	0.051
Non-HDL-C	114.66±48.39	107.57±41.56	0.290
ChAR (Chol/albumin)	35.96±11.22	35.92±9.63	0.983

Abbreviations: Chol: Total cholesterol; TG: Triglycerides; VLDL: Very-low-density lipoprotein; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; TC/HDL: Total cholesterol-to-HDL cholesterol ratio; LDL/HDL: LDL cholesterol-to-HDL cholesterol ratio; TG/HDL: Triglyceride-to-HDL cholesterol ratio; non-HDL-C: Non-high-density lipoprotein cholesterol; ChAR: Cholesterol-to-albumin ratio; SD: Standard deviation.

Table 5. Hepatic, inflammatory, and hematological parameters, minerals, and other derived ratios

Parameter	Mean±SD		P
	Without DN	With DN	
SGOT	24.45±4.49	26.85±7.34	0.152
SGPT	24.4±8.3	25.35±9.45	0.696
CRP	4.46±2.79	5.92±3.77	0.259
ESR	20.56±18.73	23.05±24.05	0.691
TSH	2.84±1.37	3.56±2.44	0.231
Calcium	9.58±0.46	9.59±0.36	0.891
Phosphorus	3.79±0.48	3.64±0.47	0.237
WBC	7.29±1.49	7.64±1.93	0.272
RBC	4.64±0.66	4.51±0.65	0.208
HGB	12.43±1.27	12.21±2.34	0.394
HCT	38.15±3.44	38.47±4.95	0.730
MCV	83.3±9.27	83.97±13.80	0.674
MCH	27.2±3.53	27.52±3.73	0.633
MCHC	32.59±1.32	32.7±1.08	0.688
RDW	13.64±1.71	13.42±0.97	0.286
MPV	9.37±1.62	9.35±0.91	0.882
Platelets	257.26±79.49	255.65±58.85	0.873
Absolute neutrophils	3.85±1.17	4±1.49	0.425
Absolute lymphocytes	2.74±0.76	2.8±0.88	0.600
Absolute monocytes	0.46±0.14	0.48±0.16	0.342
Absolute eosinophils	0.24±0.14	0.3±0.26	0.200
Absolute basophils	0.007±0.013	0.007±0.009	0.891
NLR	1.51±0.62	1.49±0.58	0.797
MLR	0.18±0.07	0.18±0.07	0.716
LMR	6.39±2.31	6.12±1.93	0.401
PLR	99.34±37.44	99.46±39.37	0.989
MHR	0.038±0.013	0.046±0.045	0.259
HPR	0.053±0.018	0.051±0.019	0.486

Abbreviations: DN: Diabetic nephropathy; SGOT: Serum glutamic-oxaloacetic transaminase; SGPT: Serum glutamic-pyruvic transaminase; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; TSH: Thyroid-stimulating hormone; WBC: White blood cell count; RBC: Red blood cell count; HGB: Hemoglobin; HCT: Hematocrit; MCV: Mean Corpuscular volume; MCH: Mean Corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; RDW: Red cell distribution width; MPV: Mean platelet volume; NLR: Neutrophil-to-lymphocyte ratio; MLR: Monocyte-to-lymphocyte ratio; LMR: Lymphocyte-to-monocyte ratio; PLR: Platelet-to-lymphocyte ratio; MHR: Monocyte-to-HDL cholesterol ratio; HPR: HDL-to-platelet ratio; SD: Standard deviation.

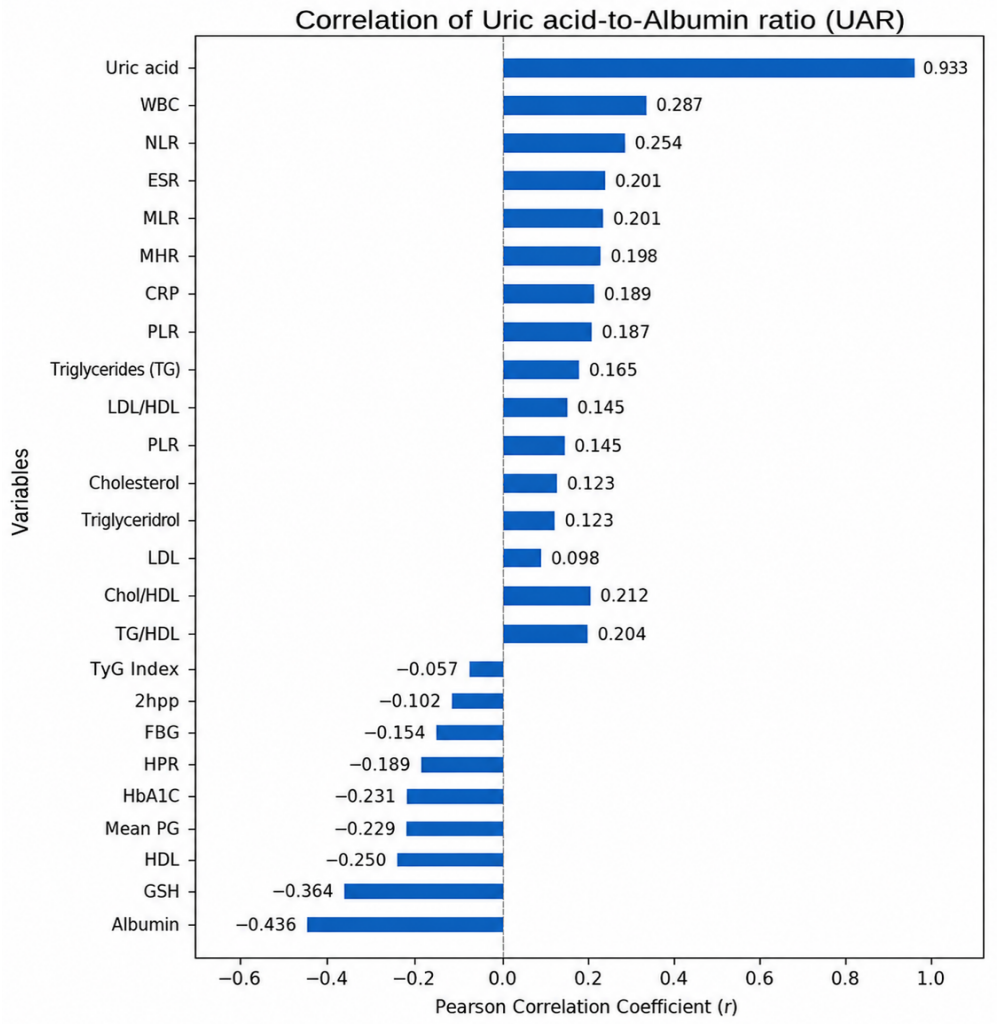


Figure 1. Correlations between the UAR and oxidative stress, inflammatory markers, lipid profile, and glycemic parameters

Abbreviations: UAR: Uric acid-to-albumin ratio; GSH: Reduced glutathione; TAC: Total Antioxidant capacity; NLR: Neutrophil-to-lymphocyte ratio; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; WBC: White blood cell count; PLR: Platelet-to-lymphocyte ratio; MLR: Monocyte-to-lymphocyte ratio; MHR: Monocyte-to-HDL cholesterol ratio; HPR: HDL-to-platelet ratio; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; TG: Triglycerides; FBG: Fasting blood glucose; 2HPP: 2-hour postprandial plasma glucose; HbA1c: Glycated hemoglobin; TyG: Triglyceride-glucose index.

Receiver operating characteristic curve analysis of the uric acid-to-albumin ratio

ROC curve analysis showed that UAR had poor discriminative performance in distinguishing between the study groups, with an AUC of 0.551. The result was not statistically significant (P=0.426), indicating that UAR did not provide meaningful diagnostic accuracy in the present study (Figure 3).

Discussion

The present study investigated the association between UAR and oxidative stress markers in patients with T2DM with and without DN. The principal findings demonstrated that patients with DN exhibited significantly lower serum albumin levels, higher UAR values, elevated serum creatinine concentrations, and reduced HDL cholesterol levels compared with diabetic patients without DN. Furthermore, UAR showed significant correlations with GSH levels, NLR values, HDL cholesterol levels, and glycemic parameters. However, ROC analysis revealed poor diagnostic performance of UAR for discriminating DN.

DN remains one of the most common microvascular complications of diabetes and a leading cause of chronic kidney disease worldwide [1]. Increasing evidence sug-

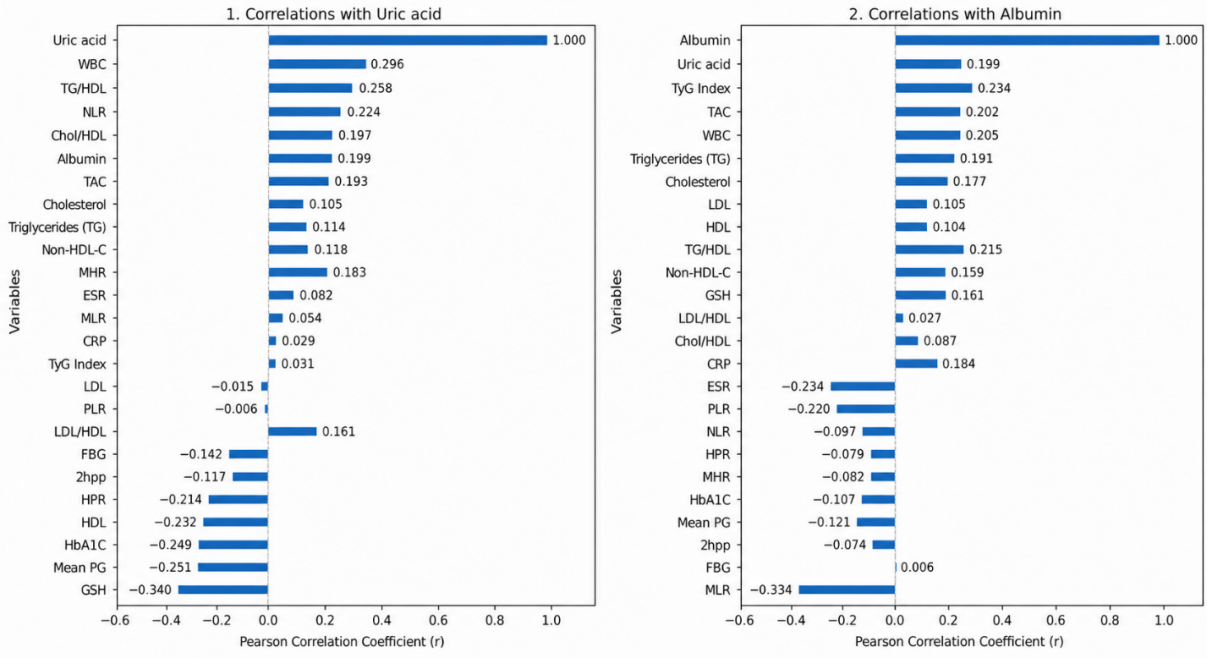


Figure 2. Correlations between uric acid and albumin levels and oxidative stress, inflammatory markers, lipid profile, and glycemic parameters

Abbreviations: GSH: Reduced glutathione; TAC: Total antioxidant capacity; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; WBC: White blood cell count; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; MLR: monocyte-to-lymphocyte ratio; MHR: Monocyte-to-HDL cholesterol ratio; HPR: HDL-to-platelet ratio; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; TG: Triglycerides; FBG: Fasting blood glucose; 2HPP: 2-hour postprandial plasma glucose; HbA1c: Glycated hemoglobin; TyG: Triglyceride-glucose index.

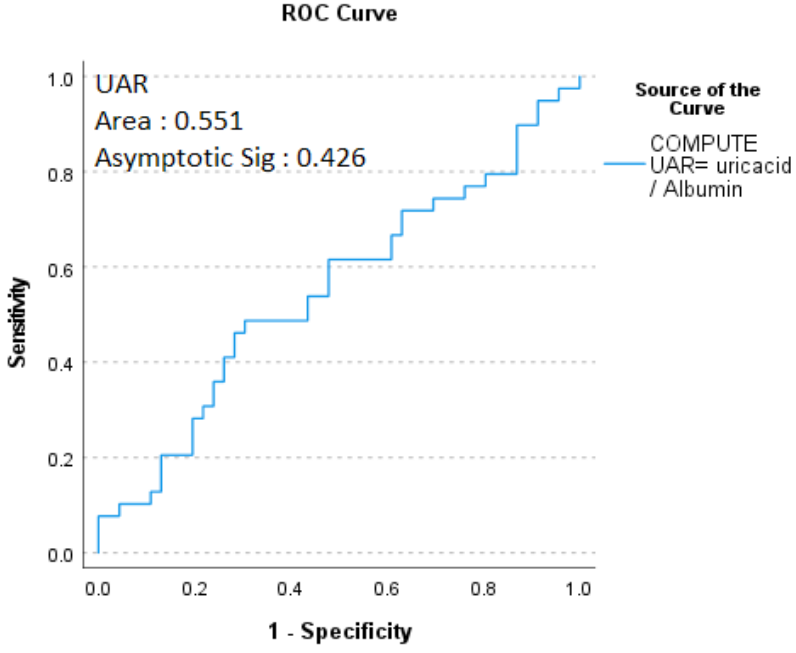


Figure 3. ROC curve analysis of the UAR for discriminating diabetic nephropathy

Abbreviations: UAR: Uric acid-to-albumin ratio; ROC: Receiver operating characteristic; AUC: Area under the curve; DN: Diabetic nephropathy.

gests that oxidative stress, chronic inflammation, and metabolic disturbances contribute significantly to the development and progression of diabetic renal injury [2-4]. In this context, identifying simple and accessible biomarkers that reflect these pathological mechanisms may improve risk stratification and disease monitoring.

One of the major findings of this study was the significantly higher UAR values in patients with DN. Although serum uric acid levels alone did not differ significantly between the groups, lower serum albumin concentrations in nephropathic patients resulted in a significantly elevated UAR. This observation suggests that UAR may provide more comprehensive information than either uric acid or albumin alone. Similar findings have been reported in previous studies, where elevated uric acid-related indices were associated with renal dysfunction and adverse renal outcomes [6, 15]. Hyperuricemia has been implicated in endothelial dysfunction, activation of the renin–angiotensin system, increased oxidative stress, and inflammatory pathways that contribute to renal injury [6].

Serum albumin was significantly lower in the nephropathy group. Albumin is not only an important nutritional and transport protein but also represents one of the major extracellular antioxidants in circulation [8]. Reduced albumin levels may therefore indicate both impaired nutritional status and diminished antioxidant defense. Previous studies have demonstrated that lower serum albumin levels are associated with poorer renal prognosis and increased cardiovascular risk in diabetic patients [8, 16]. Therefore, the elevated UAR observed in the present study may partly reflect the loss of antioxidant protection associated with declining albumin concentrations.

Oxidative stress is recognized as a central mechanism in the pathogenesis of DN [2-4]. A notable finding of the present study was the significant inverse correlation between UAR and GSH levels. Glutathione is one of the most important endogenous antioxidants, and its depletion indicates increased oxidative burden. Previous investigations have demonstrated that hyperglycemia-induced oxidative stress promotes glomerular and tubular injury through excessive production of ROS [2, 3]. Daenen et al. further highlighted oxidative stress as a major contributor to chronic kidney disease progression [4]. The negative association between UAR and GSH levels observed in our study supports the hypothesis that higher UAR may reflect enhanced oxidative stress in diabetic patients.

In contrast, no significant association was observed between UAR and TAC. TAC represents a composite measure of antioxidant defenses and may be influenced by multiple circulating antioxidants and metabolic factors. Therefore, TAC may be less sensitive than specific oxidative stress biomarkers, such as GSH in detecting subtle alterations in oxidative status among diabetic individuals.

Inflammation is another key mechanism implicated in DN progression. In the present study, UAR demonstrated a significant positive correlation with NLR, a widely recognized marker of systemic inflammation. Elevated NLR has previously been associated with diabetic complications and chronic kidney disease progression. Although significant associations were not observed with CRP or ESR, the correlation with NLR suggests that UAR may partly reflect inflammatory activity. The absence of significant relationships with other inflammatory markers may be attributable to sample size limitations or variability in inflammatory responses among participants.

Regarding lipid metabolism, UAR was inversely associated with HDL cholesterol levels. Patients with DN also exhibited significantly lower HDL concentrations. HDL possesses antioxidant, anti-inflammatory, and endothelial-protective properties; therefore, reduced HDL levels may contribute to increased oxidative stress and vascular dysfunction. Similar observations have been reported in metabolic syndrome populations, where elevated uric acid concentrations were associated with oxidative stress and adverse cardiovascular profiles [17]. UAR showed weak but significant negative correlations with HbA1c and mean plasma glucose. Although poor glycemic control is generally associated with increased oxidative stress, previous studies have suggested that albumin oxidation and alterations in albumin metabolism may occur independently of glycemic indices [18]. Furthermore, glycemic variability rather than average glucose levels may have a greater impact on oxidative stress generation in diabetic patients [3]. Therefore, the observed correlations should be interpreted cautiously and warrant further investigation.

Although UAR differed significantly between the groups, ROC curve analysis demonstrated poor discriminative performance (AUC=0.551), indicating limited diagnostic utility for identifying DN. This finding suggests that UAR should not be considered a standalone diagnostic biomarker for nephropathy. Similar studies have reported greater value for UAR as a prognostic or risk stratification marker rather than a diagnostic indicator [10, 19]. Consequently, UAR may be more useful when interpreted alongside established renal biomarkers and clinical parameters.

The strengths of this study include the simultaneous assessment of UAR, oxidative stress biomarkers, inflammatory indices, and metabolic parameters in patients with and without DN. However, several limitations should be acknowledged. First, the cross-sectional design precludes causal inference. Second, the relatively modest sample size may have limited statistical power. Third, only selected oxidative stress biomarkers were measured. Future prospective studies involving larger cohorts and additional oxidative stress markers are warranted to clarify the clinical significance and prognostic value of UAR in DN.

Conclusion

In conclusion, patients with DN exhibited significantly higher UAR values and lower serum albumin concentrations than diabetic patients without nephropathy. UAR was inversely associated with GSH and HDL cholesterol levels and positively associated with NLR, suggesting a link to oxidative stress and inflammatory pathways. Despite these associations, UAR demonstrated poor diagnostic accuracy for DN. Therefore, UAR may serve as a simple adjunctive biomarker that reflects oxidative stress and inflammation rather than as a standalone diagnostic tool. Further longitudinal studies are required to establish its prognostic value and clinical utility.

Ethical Considerations

Compliance with ethical guidelines

The study protocol was approved by the Ethics Committee of Mazandaran University of Medical Sciences (Code: IR.MAZUMS.REC.1405.097). Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

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Author's contributions

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Conflict of interest

The authors declared no conflict of interest.

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