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ORIGINAL RESEARCH

Investigation of Uric Acid/HDL-Cholesterol Ratio as an Independent Risk Factor for Diabetic Nephropathy: A Cross-Sectional Study

Zekeriya KESKİN[1], Onur BÜYÜKTEKELİ[2], Muhammed Faruk AŞKIN[2]

[1] Sivas Cumhuriyet University, Department of Internal Medicine, Sivas, Türkiye.
[2] Sivas Cumhuriyet University, Department of Nephrology, Sivas, Türkiye.

ABSTRACT

Diabetic nephropathy (DN) is a major microvascular complication requiring early markers for risk stratification. We investigated the clinical utility of the uric acid (UA) to high density lipoprotein cholesterol (HDL-C) ratio (UHR) as a practical proinflammatory-prooxidative marker for DN. In this retrospective cross-sectional study, records of 934 patients with diabetes mellitus (DM) were analyzed. UHR was calculated as [UA/HDL] x 100. DN was defined based on the albumin-to-creatinine ratio (ACR) and/or estimated glomerular filtration rate (eGFR) criteria. Patients were evaluated according to the presence of nephropathy, stage of nephropathy, and albuminuria categories. ROC analysis was performed for UHR, UA and HDL-C. Factors associated with DN were evaluated using logistic regression analysis. UHR was significantly higher in patients with DN compared to those without DN ($p<0.001$). UHR showed a significant increase across nephropathy stages and albuminuria categories ($p<0.001$). In the ROC analysis, UA demonstrated the highest performance in distinguishing DN (AUC=0.763; 95% CI: 0.733–0.794; $p<0.001$). The AUC value for UHR was 0.740 (95% CI: 0.709–0.771; $p<0.001$), and for HDL-C, it was 0.591 (95% CI:0.555–0.627; $p<0.001$). The optimal cutoff value for UHR was determined to be 13.07. In the multivariate logistic regression analysis, UHR was found to be independently associated with DN after adjusting for age, sex, systolic blood pressure, HbA1c, and triglycerides (OR=1.221; 95% CI: 1.179–1.265; $p<0.001$). In the component-based model, UA showed a strong positive association with DN (OR=1.971; 95% CI: 1.766–2.200; $p<0.001$), while HDL-C showed a significant inverse association (OR=0.983; 95% CI: 0.969–0.997; $p=0.018$). UHR was found to be significantly associated with the presence of DN, stage of nephropathy, and albuminuria categories. However, the fact that UA demonstrates slightly higher discriminatory performance compared to UHR suggests that UHR should be interpreted as an easily calculable complementary biomarker rather than a superior standalone marker in the assessment of DN. These findings require validation in prospective studies.

Keywords: Diabetic nephropathy. Uric acid to HDL-C ratio. UHR. Diabetes mellitus. Chronic kidney disease.

Diyabetik Nefropati için Bağımsız Bir Risk Faktörü Olarak Ürik Asit/HDL Kolesterol Oranının İncelenmesi: Kesitsel Bir Çalışma

ÖZET

Diyabetik nefropati (DN), risk sınıflandırması için erken belirteçlere ihtiyaç duyulan önemli bir mikrovasküler komplikasyondur. Bu çalışmada, DN için pratik bir proinflamatuar-prooksidatif belirteç olarak ürik asit/HDL kolesterol oranının (UHR) klinik yararını araştırdık. Bu retrospektif kesitsel çalışmada, 934 diyabetik (DM) hastanın kayıtları analiz edilmiştir. UHR, [UA/HDL] x 100 olarak hesaplanmıştır. DN, albümin-kreatinin oranı (ACR) ve/veya tahmini glomerüler filtrasyon hızı (eGFR) kriterlerine göre tanımlanmıştır. Hastalar nefropati varlığı, nefropati evresi ve albüminüri kategorilerine göre değerlendirildi. UHR, UA ve HDL-C için ROC analizi yapıldı. DN ile ilişkili faktörler lojistik regresyon analizi kullanılarak değerlendirildi. UHR, DN'si olmayan hastalara kıyasla DN'si olan hastalarda anlamlı olarak daha yüksekti ($p<0,001$). UHR, nefropati evreleri ve albüminüri kategorileri boyunca anlamlı bir artış gösterdi ($p<0,001$). ROC analizinde, UA, DN'yi ayırt etmede en yüksek performansı gösterdi (AUC=0,763; %95 CI: 0,733–0,794; $p<0,001$). UHR için AUC değeri 0,740 (95% CI: 0,709–0,771; $p<0,001$), HDL-C için ise 0,591 (95% CI: 0,555–0,627; $p<0,001$) idi. UHR için optimal kesme değeri 13,07 olarak belirlendi. Çok değişkenli lojistik regresyon analizinde, yaş, cinsiyet, sistolik kan basıncı, HbA1c ve trigliseridler için düzeltme yapıldıktan sonra UHR'nin DN ile bağımsız olarak ilişkili olduğu bulunmuştur (OR = 1,221; %95 CI: 1,179–1,265; $p<0,001$). Bileşen tabanlı modelde, UA, DN ile güçlü bir pozitif ilişki gösterirken (OR=1,971; %95 CI: 1,766–2,200; $p<0,001$), HDL-C ise anlamlı bir ters ilişki gösterdi (OR=0,983; %95 CI: 0,969–0,997; $p=0,018$). UHR'nin DN varlığı, nefropati evresi ve albüminüri kategorileriyle anlamlı bir ilişkisi olduğu bulunmuştur. Ancak, UA'nın UHR'ye kıyasla biraz daha yüksek ayırt edici performans sergilemesi, UHR'nin DN değerlendirmesinde üstün bir tek başına belirteçten ziyade, kolayca hesaplanabilir tamamlayıcı bir biyobelirteç olarak yorumlanması gerektiğini düşündürmektedir. Bu bulguların prospektif çalışmalarda doğrulanması gerekmektedir.

Anahtar Kelimeler: Diyabetik nefropati. Ürik asit/HDL-K oranı. UHR. Diabetes mellitus. Kronik böbrek hastalığı.

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Dr. Zekeriya KESKİN
Sivas Cumhuriyet University, Faculty of Medicine,
Department of Internal Medicine, 58140 Sivas, Türkiye
E-mail: zekeriyakeskinsh@gmail.com

AUTHORS' ORCID INFORMATION
Zekeriya KESKİN: 0000-0003-3623-9892
Onur BÜYÜKTEKELİ: 0000-0003-2321-7651
Muhammed Faruk AŞKIN: 0000-0003-0115-1567

Diabetic nephropathy (DN) is one of the microvascular complications of diabetes mellitus (DM) and has adverse effects on chronic kidney disease (CKD), cardiovascular diseases (CVD), and mortality. Since DN is often asymptomatic, early diagnosis and taking necessary precautions are very important. Therefore, it is recommended that DM patients undergo DN screening, classification, and follow-up using albuminuria and/or estimated glomerular filtration rate (eGFR)[1].

Uric acid (UA) levels are associated with DN formation and progression. Elevated UA levels have been shown to be associated with the risk of progression[2,3]. Oxidative stress, endothelial dysfunction, inflammation, and renal fibrosis have been used to explain the pathophysiology of UA's role in DN[2].

High-density lipoprotein (HDL) is associated with cardiometabolic risk, particularly due to its antioxidant, anti-inflammatory, and reverse cholesterol transport effects. In DM, dyslipidemia, inflammation, and impaired HDL function increase susceptibility to microvascular complications. Given these characteristics, attention has been drawn in recent years to the uric acid/HDL ratio (UHR) as an easily calculable indicator of proinflammatory and prooxidative balance[4,5].

Recent literature has increasingly focused on the relationship between UHR and microvascular complications of diabetes, particularly DN[4,6]. However, more evidence and studies are needed to address issues such as how UHR changes according to the stages of nephropathy, whether UHR is an independent marker independent of classic risk markers such as blood pressure and glycemic control, what threshold value may be clinically meaningful, and whether these may vary across populations.

The aim of our study is to evaluate the relationship between UHR and DN in patients with DM, its status according to nephropathy stages, its ability to distinguish nephropathy, and whether it is an independent predictor.

Materials and Methods

Our study was conducted retrospectively, and the records of DM patients who visited our hospital's internal medicine and nephrology outpatient clinics between June 2023 and June 2025 were screened using the hospital information management system (HIMS). Our study was approved by the Ethics Committee of Health Sciences Research at Sivas Cumhuriyet University on July 10, 2025, with decision number 2025-07/32. Due to the retrospective nature of the study, informed consent forms were not obtained with the knowledge of the ethics committee. Our study was conducted in accordance with the principles of the Declaration of Helsinki.

Inclusion criteria for the study were: ≥18 years of age, diagnosis of type 2 DM, serum UA, HDL measurement, and creatinine, albumin/creatinine ratio (ACR), and eGFR measurement for nephropathy assessment. The exclusion criteria were defined as follows: type 1 DM, gestational diabetes, pregnancy, active infection, active malignancy and/or inflammatory disease, acute kidney injury (AKI) that developed within the last 3 months, renal replacement therapy (RRT), patients currently receiving allopurinol and febuxostat therapy, and patients with missing laboratory and/or clinical data. In addition, stage 5 chronic kidney disease patients not receiving renal replacement therapy were excluded from the study. A total of 1,324 patients were screened, and after applying the exclusion criteria, a study group of 934 patients was formed.

UHR was calculated by dividing the UA (mg/dl) value by the HDL (mg/dl) value and multiplying the result by 100. Diabetic nephropathy was defined as ACR ≥ 30 mg/g in at least 2 of 3 measurements over a period of more than 3 months and/or eGFR < 60 mL/min/1.73 m² (1). eGFR was calculated using serum creatinine levels with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula and expressed in mL/min/1.73 m². Participants were first divided into two groups: presence or absence of nephropathy. Subsequently, nephropathy was classified into four stages based on eGFR: Stage 1 (≥90), Stage 2 (60–89), Stage 3 (30–59) and Stage 4 (15–29). For ease of analysis, stages G3a and G3b were combined into a single 'Stage 3 (30–59)' group. Additionally according to ACR values, patients were classified into three albuminuria categories: A1/normoalbuminuria, defined as ACR <30 mg/g; A2/microalbuminuria, defined as ACR 30–300 mg/g; and A3/macroalbuminuria, defined as ACR >300 mg/g[7].

Demographic data such as age and gender, laboratory parameters such as systolic blood pressure (SBP), diastolic blood pressure (DBP), HbA1c, fasting blood glucose (FBG), creatinine, lipid profile, UA, ACR, and protein/creatinine ratio (PCR) were screened and recorded.

Statistical analyses were performed using IBM SPSS Statistics v.23. Continuous variables are presented as mean ± standard deviation, and categorical variables as n (%). The independent samples t-test was used for comparisons between two groups of continuous variables, and the chi-square test was used for categorical variables. Comparisons across nephropathy stages and albuminuria categories were performed using one-way ANOVA. Tukey or Games-Howell post-hoc tests were used according to the homogeneity of variances. The discriminatory

performance of UHR, UA, and HDL-C for DN was evaluated using ROC curve analysis, and the discriminatory power was reported using AUC. The optimal cut-off value was determined based on the Youden index (J = sensitivity + specificity − 1). Since lower HDL-C levels were associated with DN, HDL-C was evaluated in the inverse direction in ROC analysis. Pearson correlation analysis was used to examine the relationship between nephropathy stages and UHR and other variables. Binary logistic regression analysis was applied to identify independent variables associated with DN. First, univariate logistic regression analyses were performed for candidate variables. The covariates included in the multivariate logistic regression models were selected based on their clinical significance and their availability in the retrospective dataset. Age and sex were included in the model as basic demographic variables. SBP and HbA1c were added to the model due to their known roles in the development of DN; triglycerides (TG) were included to reflect the lipid-metabolic status associated with UHR. UHR was considered the primary variable of the study. Since UHR is calculated from UA and HDL-C values, UHR and its components were not included together in the same multivariate model to avoid multicollinearity. Therefore, two separate models were created: Model A included UHR, while Model B evaluated UA and HDL-C instead of UHR. Results were reported as odds ratios (OR) and 95% confidence intervals (CI). All statistical tests were considered significant at $p<0.05$.

Results

Our study was conducted with a total of 934 patients. Of these patients, 379 (40.6%) were male and 555 (59.4%) were female. The mean age of the group was 63.44 ± 10.40. The mean UHR was 13.50 ± 6.20. Nephropathy was present in 499 (53.4%) of the study group, and 275 (29.4%) of these were stage 3. Details of the descriptive analyses are provided in Tables I and II.

When comparing groups with and without nephropathy, UHR was significantly higher in the nephropathy group ($p<0.001$). Age and DBP did not show significant differences in either group ($p=0.363$ and $p=0.203$, respectively). Details of the comparative analysis of these two groups are provided in Table III.

When examining subgroups of nephropathy, it was observed that the UHR increased as the stage progressed. While the post hoc analysis revealed no statistically significant difference between stages 2 and 3, the highest UHR value was observed in stage 4, and this difference was found to be statistically significant ($p<0.0033$). No significant increase was detected in the post hoc analysis between the group without nephropathy and stage 1. However, stage 1 had a significantly lower UHR compared to the other stages. No significant difference in age was found between the groups ($P=0.538$). The mean values of the variables and the results of the post hoc analysis according to nephropathy subgroups are presented in Table IV.

Table I. Descriptive analyses of continuous variables

Variables	Mean ± SD	Min–Max
Age (year)	63.44 ± 10.40	32.00–90.00
UHR	13.50 ± 6.20	1.90–49.23
DBP (mmHg)	80.10 ± 12.46	36.00–131.00
SBP (mmHg)	135.57 ± 21.17	81.00–232.00
HbA1c (%)	7.82 ± 1.76	4.46–16.20
FBG (mg/dL)	153.46 ± 74.09	47.00–740.00
TG (mg/dL)	169.25 ± 93.18	38.00–841.00
TC (mg/dL)	178.32 ± 45.30	64.00–386.00
HDL (mg/dL)	45.90 ± 12.16	13.00–109.00
LDL (mg/dL)	109.53 ± 37.12	26.00–263.00
Creatinine (mg/dL)	1.11 ± 0.55	0.36–4.53
CKD-EPI (mL/min/1.73 m²)	68.21 ± 23.79	15.00–130.00
PCR	463.16± 1089.90	15.00-10946.50
ACR	290.93±862.13	0.24-8352.70
UA (mg/dL)	5.73 ± 1.83	1.90–15.80

Abbreviations: UHR, uric acid/HDL; DBP, diastolic blood pressure; SBP, systolic blood pressure; FBG, fasting blood glucose; TG, triglyceride; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; PCR, protein/creatinine ratio; ACR, albumin/creatinine ratio; UA, uric acid

Table II. Frequency analysis of categorical variables

Variable	Category	n	%
Nephropathy stage	No nephropathy	435	46.6
	Stage 1	69	7.4
	Stage 2	84	9.0
	Stage 3	275	29.4
	Stage 4	71	7.6
	Total	**934**	**100.0**
Albuminuria category	A1	535	57.3
	A2	246	26.3
	A3	153	16.4
		934	**100.0**
Baseline nephropathy	No	435	46.6
	Yes	499	53.4
	Total	**934**	**100.0**
Gender	Male	379	40.6
	Female	555	59.4
	Total	**934**	**100.0**

Table III. Comparison of continuous variables between patients with and without baseline nephropathy

Variable	Absent (n=435) Mean ± SD	Presence (n=499) Mean ± SD	*p-value*
Age (year)	63.16 ± 10.69	62.92 ± 11.67	0.363
UHR	10.88 ± 4.41	15.80 ± 6.62	***<0.001****
DBP (mmHg)	79.52 ± 11.73	80.58 ± 13.06	0.203
SBP (mmHg)	132.34 ± 18.92	138.41 ± 22.62	***<0.001****
HbA1c (%)	7.72 ± 1.79	7.90 ± 1.73	***0.048****
FBG (mg/dL)	147.28 ± 65.71	158.92 ± 80.43	***0.015****
TG (mg/dL)	162.10 ± 94.31	175.63 ± 91.86	***0.025****
TC (mg/dL)	181.60 ± 44.24	175.52 ± 46.08	***0.043****
LDL (mg/dL)	112.37 ± 35.64	107.12 ± 38.23	***0.033****
HDL (mg/dL)	47.94 ± 12.51	44.08 ± 11.57	***<0.001****
Creatinine (mg/dL)	0.80 ± 0.17	1.38 ± 0.61	***<0.001****
UA (mg/dL)	4.87 ± 1.39	6.49 ± 1.86	***<0.001****
CKD-EPI	4.87 ± 1.39	53.72 ± 22.58	***<0.001****
PCR	97.73 ± 60.98	783.09 ± 1416.69	***<0.001****
ACR	97.73 ± 60.98	533.47 ± 1125.86	***<0.001****

Abbreviations: UHR, uric acid/HDL; DBP, diastolic blood pressure; SBP, systolic blood pressure; FBG, fasting blood glucose; TG, triglyceride; TC, total cholesterol; HDL, high density lipoprotein; LDL: low density lipoprotein; BUN, blood urea nitrogen; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; PCR, protein/creatinine ratio; ACR, albumin/creatinine ratio, UA, uric acid,
* Indicates statistical significance at $p < 0.05$.

Table IV. Comparison of continuous variables across nephropathy stages

Variable	No nephropathy (n=435)	Stage 1 (n=69)	Stage 2 (n=84)	Stage 3 (n=275)	Stage 4 (n=71)	p value
UHR	10.88 ± 4.41^{a}	12.04 ± 4.18^{a}	14.37 ± 6.03^{b}	16.04 ± 6.21^{b}	20.17 ± 8.06^{c}	***<0.001****
UA (mg/dL)	4.87 ± 1.39^{a}	5.12 ± 1.44^{a}	5.97 ± 1.67^{b}	6.71 ± 1.59^{c}	7.59 ± 2.41^{d}	***<0.001****
HDL-C (mg/dL)	47.94 ± 12.51^{c}	44.72 ± 12.04^{abc}	43.83 ± 9.01^{ab}	45.29 ± 11.97^{b}	39.32 ± 11.25^{a}	***<0.001****
CKD-EPI (mL/min/1.73 m²)	4.87 ± 1.39^{d}	93.39 ± 8.62^{e}	71.96 ± 8.87^{c}	46.42 ± 8.69^{b}	22.35 ± 4.40^{a}	***<0.001****
Creatinine (mg/dL)	0.80 ± 0.17^{b}	0.71 ± 0.13^{a}	0.97 ± 0.17^{c}	1.38 ± 0.29^{d}	2.50 ± 0.62^{e}	***<0.001****
PCR	97.73 ± 60.98^{a}	690.43 ± 778.75^{b}	1019.89 ± 1654.48^{b}	622.21 ± 1267.86^{b}	1206.51 ± 1941.72^{b}	***<0.001****
ACR	97.73 ± 60.98^{a}	449.71 ± 547.53^{b}	759.12 ± 1409.19^{b}	415.67 ± 1004.25^{b}	808.44 ± 1486.04^{b}	***<0.001****
TG (mg/dL)	162.10 ± 94.31^{a}	201.23 ± 106.82^{b}	187.45 ± 100.50^{ab}	167.29 ± 84.77^{ab}	168.01 ± 87.49^{ab}	***0.007****
FBG (mg/dL)	147.28 ± 65.71^{a}	188.51 ± 83.53^{c}	186.45 ± 117.81^{bc}	146.31 ± 64.99^{a}	145.87 ± 60.16^{ab}	***<0.001****
HbA1c (%)	7.72 ± 1.79^{a}	8.53 ± 2.00^{c}	8.44 ± 2.17^{bc}	7.64 ± 1.49^{a}	7.68 ± 1.40^{ab}	***<0.001****
SBP (mmHg)	132.34 ± 18.92^{a}	138.54 ± 22.46^{ab}	141.63 ± 22.31^{b}	137.66 ± 21.60^{b}	137.28 ± 26.63^{ab}	***<0.001****
DBP (mmHg)	79.52 ± 11.73^{ab}	83.57 ± 12.96^{bc}	84.08 ± 14.11^{c}	80.00 ± 12.34^{abc}	75.90 ± 13.03^{a}	***<0.001****
TC (mg/dL)	181.60 ± 44.24^{ab}	187.80 ± 44.14^{b}	178.23 ± 48.74^{ab}	173.73 ± 46.48^{ab}	166.93 ± 40.92^{a}	***0.013****
LDL-C (mg/dL)	112.37 ± 35.64^{ab}	118.55 ± 37.91^{b}	108.93 ± 41.76^{ab}	105.45 ± 37.64^{ab}	99.85 ± 34.44^{a}	***0.005****
Age (years)	63.16 ± 10.69^{a}	62.86 ± 10.20^{a}	62.46 ± 10.20^{a}	64.01 ± 9.95^{a}	64.68 ± 10.80^{a}	0.538

Abbreviations: UHR, uric acid/HDL; DBP, diastolic blood pressure; SBP, systolic blood pressure; FBG, fasting blood glucose; TG, triglyceride; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BUN, blood urea nitrogen; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; PCR, protein/creatinine ratio; ACR, albumin/creatinine ratio; UA, uric acid
* Indicates statistical significance at $p < 0.05$.

Table V. Comparison of clinical and laboratory parameters according to albuminuria categories

Variable	A1 / Normoalbuminuria n=535	A2 / Microalbuminuria n=246	A3 / Macroalbuminuria n=153	p-value
UHR	12.16 ± 5.34^{a}	15.01 ± 6.89^{b}	15.79 ± 6.63^{b}	<0.001*
UA mg/dL	5.40 ± 1.69^{a}	6.00 ± 1.96^{b}	6.50 ± 1.91^{c}	<0.001*
HDL-C, mg/dL	47.88 ± 12.67^{a}	42.68 ± 10.83^{b}	44.12 ± 11.01^{b}	<0.001*
CKD-EPI, mL/min/1.73 m²	74.65 ± 19.70^{a}	61.57 ± 26.10^{b}	56.37 ± 25.57^{b}	<0.001*
Creatinine, mg/dL	0.94 ± 0.33^{a}	1.26 ± 0.62^{b}	1.44 ± 0.76^{c}	<0.001*
PCR	95.48 ± 59.17^{a}	268.20 ± 278.40^{b}	2062.29 ± 2010.68^{c}	<0.001*
ACR	10.28 ± 7.41^{a}	97.95 ± 69.42^{b}	1582.57 ± 1592.96^{c}	<0.001*
TG, mg/dL	159.19 ± 89.41^{a}	173.69 ± 88.33^{ab}	197.29 ± 107.01^{b}	<0.001*
HbA1c, %	7.60 ± 1.68^{a}	8.03 ± 1.76^{b}	8.23 ± 1.92^{b}	<0.001*
FBG, mg/dL	144.05 ± 60.93^{a}	160.07 ± 74.04^{b}	175.70 ± 104.59^{b}	<0.001*
SBP, mmHg	132.17 ± 18.77^{a}	137.48 ± 23.60^{b}	144.41 ± 22.15^{c}	<0.001*
DBP, mmHg	79.08 ± 11.85^{a}	81.03 ± 13.33^{ab}	82.16 ± 12.82^{b}	0.010*
TC, mg/dL	178.76 ± 43.21^{ab}	171.63 ± 46.83^{a}	187.56 ± 48.38^{b}	0.003*
LDL-C, mg/dL	109.92 ± 34.96^{ab}	104.60 ± 38.27^{a}	116.10 ± 41.47^{b}	0.010*
Age, years	63.23 ± 10.55^{a}	63.50 ± 9.95^{a}	64.08 ± 10.64^{a}	0.670

Abbreviations: UHR, uric acid/HDL; DBP, diastolic blood pressure; SBP, systolic blood pressure; FBG, fasting blood glucose; TG, triglyceride; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BUN, blood urea nitrogen; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; PCR, protein/creatinine ratio; ACR, albumin/creatinine ratio; UA, uric acid
* Indicates statistical significance at $p < 0.05$.

When patients were classified according to albuminuria categories, UHR showed a significant difference across the albuminuria categories (p<0.001). The mean UHR value was lowest in group A1 and was significantly higher in groups A2 and A3: 12.16±5.34, 15.01±6.89, and 15.79±6.63, respectively. In the post-hoc analysis, the A1 group was found to be significantly different from the A2 and A3 groups, but there was no significant difference between A2 and A3.

Similarly, UA levels increased as albuminuria categories increased; HDL-C levels, however, were lower in the albuminuric groups compared to the normoalbuminuric group. Details of this analysis are provided in Table V.

When examining the correlation of UHR with other variables, a moderately significant correlation was found with creatinine r=0.485, p<0.001). Based on the relationship with creatinine, a significant negative correlation was found between CKD-EPI and UHR (r=-0.476, p<0.001). No significant correlation was found between UHR and SBP, HbA1c, or FBG. Details of the correlation analysis are provided in Table VI.

Table VI. Correlation between UHR and clinical/laboratory parameters

Variable	r	p-value
SBP (mmHg)	−0.047	0.155
DBP (mmHg)	−0.113	***0.001****
HbA1c (%)	0.002	0.958
FBG (mg/dL)	−0.013	0.693
TG (mg/dL)	0.180	***<0.001****
TC (mg/dL)	−0.231	***<0.001****
HDL (mg/dL)	−0.632	***<0.001****
LDL (mg/dL)	−0.188	***<0.001****
Creatinine (mg/dL)	0.485	***<0.001****
CKD-EPI (mL/min/1.73 m²)	−0.476	***<0.001****
UA (mg/dL)	0.813	***<0.001****
PCR	0.111	***0.001****
ACR	0.105	***0.001****
Age (year)	0.036	0.278

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure; FBG, fasting blood glucose; TG, triglyceride; TC, total cholesterol; HDL, high density lipoprotein; LDL: low density lipoprotein; blood urea nitrogen; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; PCR, protein/creatinine ratio; ACR, albumin/creatinine ratio, UA, uric acid

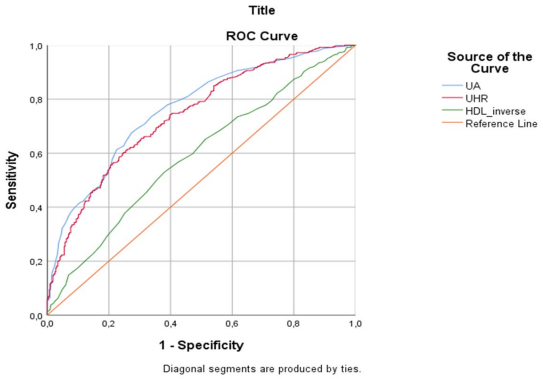
* Indicates statistical significance at $p < 0.05$.

In the ROC analysis, the highest performance in distinguishing DN was observed with UA. The AUC was 0.763 for UA, 0.740 for UHR, and 0.591 for HDL-C. Optimal cutoff values were determined as ≥5.55 mg/dL for uric acid, ≥13.07 for UHR, and ≤43.5 mg/dL for HDL-C. Details of this analysis are provided in Table VII and Figure 1.

Table VII. ROC analysis of UHR, uric acid and HDL-C for discriminating diabetic nephropathy

Marker	AUC	95% CI	p-value	Optimal cut-off	Sensitivity	Specificity
UA, mg/dL	0.763	0.733–0.794	<0.001	≥5.55	67.5%	72.6%
UHR	0.740	0.709–0.771	<0.001	≥13.07	61.1%	74.5%
HDL-C, mg/dL	0.591	0.555–0.627	<0.001	≤43.50	52.9%	62.1%

ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval; UHR, uric acid/HDL cholesterol ratio; HDL-C, high-density lipoprotein cholesterol; UA, uric acid.



Abbreviations: UHR, uric acid/HDL cholesterol ratio; UA, uric acid; HDL-C, high-density lipoprotein cholesterol; ROC, receiver operating characteristic. Diabetic nephropathy was defined as the positive state. HDL-C was analyzed in the inverse direction because lower HDL-C values indicated higher nephropathy risk.

Figure 1.
ROC curves of UHR, UA, and HDL-C for discriminating DN

In univariate logistic regression analysis, a significant association was found between the presence of DN and UHR (OR=1.196, p<0.001). Similarly, SBP (OR=1.014, p<0.001) and TG (OR=1.002, p=0.030) were found to be associated with the presence of DN. The details of this analysis are presented in Table VIII.

Table VIII. Univariate Logistic Regression Analysis According to the Presence of Nephropathy

Predictor	OR (Exp(B))	%95 CI	p
UHR	1.196	1.159–1.234	***<0.001****
Age (years)	1.005	0.993–1.017	0.436
SBP (mmHg)	1.014	1.008–1.020	***<0.001****
HbA1c (%)	1.063	0.987–1.145	0.106
TG (mg/dL)	1.002	1.000–1.003	***0.030****
Male sex (vs female)	1.229	0.945–1.598	0.124
UA (mg/dL)	1.915	1.726–2.124	***<0.001****
HDL-C (mg/dL)	0.974	0.963–0.985	***<0.001****

Abbreviations: OR, odds ratio; CI, confidence interval; UHR, uric acid/HDL cholesterol ratio; HDL-C, high-density lipoprotein cholesterol; glycated hemoglobin.

* Indicates statistical significance at $p < 0.05$.

In the multivariate logistic regression analysis, two separate models were constructed to avoid multicollinearity with the components of UHR. In Model A, which included UHR, UHR was found to be independently associated with DN after adjusting for age, sex, SBP, HbA1c, and TG (OR=1.221, p<0.001). In Model B, which included UA and HDL-C instead of UHR, UA was found to be positively associated, while HDL-C was negatively associated (OR=1.971, p<0.001; OR=0.983, p=0.018, respectively). The explanatory power of Model B was slightly higher than that of Model A. In Model A, the Cox & Snell R^2 value was 0.202, the Nagelkerke R^2 value was 0.270, and the overall classification accuracy was 68.0%. Model B was also generally significant, with a Cox & Snell R^2 of 0.237, a Nagelkerke R^2 of 0.316, and an overall classification accuracy of 69.9%. The details of this analysis are provided in Table IX.

Table IX. Multivariate Logistic Regression Analysis According to the Presence of Nephropathy

Model / Predictor	OR	95% CI	p-value
Model A: male sex,sbp,hba1c,uhr			
Male sex	0.729	0.534–0.994	0.046
SBP (mmHg)	1.018	1.011–1.026	<0.001
HbA1c (%)	1.103	1.014–1.200	0.022
TG (mg/dL)	0.999	0.997–1.000	0.142
UHR	1.221	1.179–1.265	<0.001
Age (years)	1.003	0.990–1.017	0.628
Model B: sbp,hba1c,ua,hdl-c p			
Male sex	0.877	0.637–1.209	0.423
SBP (mmHg)	1.016	1.009–1.024	<0.001
HbA1c (%)	1.167	1.068–1.275	0.001
TG (mg/dL)	1.000	0.998–1.001	0.614
Age (years)	1.005	0.991–1.019	0.518
UA (mg/dL)	1.971	1.766–2.200	<0.001
HDL-C (mg/dL)	0.983	0.969–0.997	0.018

Abbreviations: OR, odds ratio; CI, confidence interval; UHR, uric acid/HDL cholesterol ratio; UA, uric acid; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; HbA1c, glycated hemoglobin.

* Indicates statistical significance at $p < 0.05$.

Discussion and Conclusion

DN is one of the most important microvascular complications of diabetes and is associated with a significant increase in the risk of CKD progression and cardiovascular events. Therefore, early diagnosis, prevention of progression, and implementation of necessary measures and treatments are very important[7]. UHR is a practical ratio that can be calculated from routine tests, developed by considering the proinflammatory / prooxidant effects of UA and the anti-inflammatory/antioxidant effects of HDL. In recent years, its relationship with DN has been studied more extensively, and it is being considered as a potential risk marker[8].

In our study, UHR was initially found to be higher in patients with DN. Subsequently, it was observed to increase as the stage of nephropathy progressed. Additionally, it was found to be significantly higher in albuminuric groups compared to the normoalbuminuric group. In correlation analysis, UHR showed a positive correlation with creatinine and a negative correlation with CKD-EPI; however, since renal function parameters are part of the definition and staging of nephropathy, these findings should be interpreted with caution. In the ROC analysis, UHR demonstrated moderate performance in distinguishing DN. However, the AUC value for UA was slightly higher than that for UHR. In multivariate logistic regression, UHR remained independently associated with DN after adjusting for existing clinical variables. In this analysis, the component-based model showed that UA had a stronger independent association with DN, while HDL-C demonstrated a weaker but significant inverse association. These findings indicate that UHR is associated with DN. However, they suggest that this association may largely stem from the UA component.

Chronic inflammation and endothelial dysfunction play a role in the etiology of DN. It has been previously demonstrated that elevated UA levels are associated with progression of the inflammatory response, endothelial dysfunction, and fibrosis in the kidney, leading to increased renal damage[9,10]. In the context of DM, various studies have shown that the risk of DN increases as UA levels rise[11,12]. However, high HDL levels are a protective factor and decrease in CKD. This can cause microvascular damage and worsen nephropathy. Many studies have shown that HDL is lower in patients with DN[13-15]. Furthermore, based on the results of the ADVANCE study, Morton et al. identified HDL as an independent risk factor for DN[16]. Additionally, Wang et al. noted that, in addition to low HDL, very high HDL levels are also a risk factor for DN[14]. Considering this study and a review published in recent years, HDL dysfunction has been discussed rather than HDL levels[14,17]. Consistent with these findings, our study also showed that UA levels increased in the presence of nephropathy and as the stage of nephropathy progressed, while HDL levels decreased.

Given these findings, UHR has been increasingly studied in recent years for its relationship with DN as an easily calculable and practical biomarker. A study using a very large sample size found a close relationship between UHR and DN and emphasized the potential clinical use of UHR in DN risk assessment[5]. A significant relationship between UHR and microalbuminuria, one of the early indicators of DN, has also been demonstrated[18]. Another study

highlighted the independent relationship between cumulative UHR exposure and CKD progression and incidence[19]. In a study conducted in Türkiye, which is similar to our study in terms of population and important for comparing our findings, UHR was found to be higher in those with DN and was positively correlated with creatinine and ACR. The same study found that a 0.1 point increase in UHR increased the risk of DN by 2.3 times[20]. Other studies have similarly demonstrated this relationship[4,6]. There is no clear consensus regarding the relationship between UHR and other microvascular complications of DM, such as retinopathy and neuropathy[8,21-23]. In our study, our main finding is that UHR is a strong and independent predictor in the presence of DN. Indeed, UHR was found to be higher in the DN group. Furthermore, UHR was observed to increase progressively across stages of nephropathy, and in an analysis by albuminuria categories, it was higher in the microalbuminuria and macroalbuminuria groups compared to the normoalbuminuria group. This finding suggests that UHR may be associated not only with a decline in eGFR but also with the presence of albuminuria. In the ROC analysis, UHR demonstrated moderate performance in distinguishing the presence of DN (AUC=0.740). In the multivariate logistic regression analysis, UHR was found to be independently associated with DN after adjusting for age, sex, SBP, HbA1c, and TG. However, the components of UHR—UA and HDL-C—were evaluated separately. In the ROC analysis, the AUC value for uric acid was found to be slightly higher than that of UHR. Furthermore, in a component-based multivariate model evaluating UA and HDL-C together instead of UHR, uric acid showed a strong and independent association with DN, while HDL-C demonstrated a weaker but significant inverse association. These results support the association between UHR and DN but suggest that this association may be largely attributable to the UA component. Therefore, UHR should be interpreted not as a superior or standalone predictor for DN, but rather as a complementary marker that can be evaluated in conjunction with UA and HDL-C levels.

The relationship between age and DN has been well studied in the literature. A recent meta-analysis has identified age as a factor that increases the risk of developing DN[24]. This relationship can be attributed to chronic inflammation associated with biological aging and microvascular damage following endothelial damage[25]. Although age is an independent risk factor for DN, when evaluated together with UHR, both have been shown to be independent risk factors[26]. In our study, no significant difference was found between age and the presence or absence of nephropathy, nor between stages of nephropathy. We also found that it was not an independent predictor in logistic regression. Furthermore, no correlation was observed between UHR and age. Therefore, age did not emerge as a distinguishing factor for DN in our cohort; the relationship between UHR and DN appeared to be independent of the effect of age.

Blood pressure increases the hemodynamic load in DN, causing progression of kidney disease through glomerular hypertension and albuminuria. Reliable guidelines and studies frequently mention that controlling blood pressure reduces microvascular complications[1,7,27]. In our study, SBP was found to be associated with the presence of nephropathy and was seen to be an independent predictor for DN in logistic regression. In contrast, we did not find a significant relationship between DN and DBP. This suggests that the hemodynamic load in DN may be more related to SBP[28-30].

The adverse effect of chronic hyperglycemia on DN is a well-known fact. The KDIGO guidelines emphasize the importance of correcting hyperglycemia and monitoring HbA1c in individuals with CKD[7]. Similarly, large randomized trials have shown that glycemic control improves renal outcomes and reduces the risk of new nephropathy[31-32]. In our study, the significantly higher HbA1c/FBG levels in the DN group and the independence of HbA1c in regression are consistent with the literature and the pathogenesis of DN.

In terms of lipid profile, dyslipidemia in CKD-DN is not in the form of classic high LDL/TC, but rather high TG and low HDL[33]. This is thought to be related to processes such as decreased clearance of TG-rich lipoproteins and atherogenic particle transformations[34]. In our study, consistent with the literature, elevated TG and lower LDL and TC levels were observed in the DN group.

Among the strengths of our study are the evaluation of a relatively large patient population (n=934), the definition of DN based on ACR and eGFR criteria, and the conduct of additional analyses according to albuminuria categories. Additionally, the evaluation of UHR's discriminatory performance via ROC analysis and the comparison of this performance with uric acid and HDL-C are among the study's advantages. The fact that UHR remained independently associated with DN in multivariate analyses and the establishment of a separate model evaluating uric acid and HDL-C instead of UHR allowed for a more comprehensive interpretation of the study's findings and strengthened our work.

Among the limitations of our study are the inability to draw causal conclusions due to its retrospective and single-center nature; the lack of information on inflammatory markers such as C-reactive protein (CRP), thiazide diuretics used by patients, sodium-glucose cotransporter-2 (SGLT2) inhibitors, statins, and fibrates used by patients, as well as the absence of diabetes duration data in most patients and the

resulting data gaps, which prevented the inclusion of certain clinical variables in the analysis.

In conclusion, UHR was found to be significantly higher in patients with DN and showed a positive association with stages of nephropathy and categories of albuminuria. After adjusting for existing clinical variables, UHR remained independently associated with diabetic nephropathy and demonstrated moderate discriminatory performance in the ROC analysis. However, uric acid demonstrated slightly higher discriminatory performance than UHR, and the component-based regression model suggested that the association between UHR and diabetic nephropathy may largely stem from the uric acid component. Therefore, UHR can be interpreted as an easily calculable complementary marker rather than a standalone diagnostic or predictive tool. However, prospective studies are needed to more comprehensively evaluate other potential confounders that could explain this relationship.

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References

1. American Diabetes Association Professional Practice Committee. 11. Chronic Kidney Disease and Risk Management: Standards of Care in Diabetes-2025. Diabetes Care. 2025;48(1 Suppl 1):239-251.
2. Doria A, Galecki AT, Spino C, et al. Serum Urate Lowering with Allopurinol and Kidney Function in Type 1 Diabetes. *N Engl J Med*. 2020;382(26):2493-2503.
3. Zhu L, Wang X, Sun J, Qian Q, Yu J. Hyperuricemia Predicts the Progression of Type 2 Diabetic Kidney Disease in Chinese Patients. Diabetes Ther. 2023;14(3):581-591.
4. Qin C, Li G, Yuan Y, Zou Y. Association between uric acid to high-density lipoprotein cholesterol ratio and diabetic kidney disease in US adults. Sci Rep. 2025;15(1):24353.
5. Che Y, Zhao L, Xu H, et al. Serum uric acid to high-density lipoprotein cholesterol ratio as a novel predictor of diabetic nephropathy: a cross-sectional analysis of NHANES 2011–2018. Clin Exp Med. 2025;25(1):359.
6. Zhao H, Wang Y, Liu Y, Du Z, Tian L. Uric acid to high-density lipoprotein cholesterol ratio is associated with the prevalence of diabetic kidney disease in euthyroid patients with type 1 diabetes mellitus in China: A multicenter cross-sectional study. J Diabetes Investig. 2025;16(9):1683-1691.
7. Stevens PE, Ahmed SB, Carrero JJ, et al. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Vol. 105, Kidney International. 2024;105(4S):117-314.
8. Uzeli U, Doğan AG. The Relationship Between Diabetic Neuropathy and Uric Acid/High-Density Lipoprotein Ratio in Patients With Type-2 Diabetes Mellitus. Cureus. 2023;15(9):e45151.
9. Zhou Y, Fang L, Jiang L, et al. Uric acid induces renal inflammation via activating tubular NF-κB signaling pathway. PLoS One. 2012;7(6):e39738.
10. Zhang Y, He F, Yu X, et al. Hyperuricemia-induced kidney injury: a narrative review of mechanisms and therapeutic advances. BMC Nephrol. 2025;26(1):629.
11. Ji P, Zhu J, Feng J, et al. Serum uric acid levels and diabetic kidney disease in patients with type 2 diabetes mellitus: A dose-response meta-analysis. Prim Care Diabetes. 2022;16(3):457-465.
12. Lai YJ, Chen YY, Ku PW, Chen LJ, Yen YF. Association between uric acid level and incidence of albuminuria in patients with type 2 diabetes mellitus A 4.5-year cohort study. Med (United States). 2021;100(41):e27496.
13. Gao RH, Liu B, Yang Y, et al. Serum Lipoprotein(a) and High-Density Lipoprotein Cholesterol Associate with Diabetic Nephropathy: Evidence from Machine Learning Perspectives. Diabetes, Metab Syndr Obes. 2023;16:1847–1858.
14. Wang H, Wu J, Lin M, et al. High levels of high-density lipoprotein cholesterol may increase the risk of diabetic kidney disease in patients with type 2 diabetes. Sci Rep. 2024;14(1):15362.
15. Nakada K, Tanaka K, Kimura H, et al. High-density lipoprotein cholesterol and kidney disease progression in patients with type 2 diabetes mellitus: The Fukushima Cohort Study. BMJ Open Diabetes Res Care. 2025;13(6):e005581.
16. Morton J, Zoungas S, Li Q, et al. Low HDL cholesterol and the risk of diabetic nephropathy and retinopathy: Results of the advance study. Diabetes Care. 2012;35(11):2201-2206.
17. Liu K, Cooper ME, Chai Z, Liu F. High-Density Lipoprotein in Patients with Diabetic Kidney Disease: Friend or Foe? Int J Mol Sci. 2025;26(4):1683.
18. Qian F, Hong Z, Wei J, et al. Association between the serum uric acid-to-high-density lipoprotein cholesterol ratio and microalbuminuria in individuals with type 2 diabetes mellitus. Eur J Med Res. 2025;30(1):1210.
19. Liu P, Li J, Yang L, et al. Association between cumulative uric acid to high-density lipoprotein cholesterol ratio and the incidence and progression of chronic kidney disease. Front Endocrinol (Lausanne). 2023;14:1269580.
20. Aktas G, Yilmaz S, Kantarci DB, et al. Is serum uric acid-to-HDL cholesterol ratio elevation associated with diabetic kidney injury? Postgrad Med. 2023;135(5):519-523.
21. Xuan Y, Zhang W, Wang Y, et al. Association Between Uric Acid to HDL Cholesterol Ratio and Diabetic Complications in Men and Postmenopausal Women. Diabetes, Metab Syndr Obes. 2023;16:167-177.
22. Wang L, Liu L, Luo H, Wu Y, Zhu L. Correlation Between the Ratio of Uric Acid to High-Density Lipoprotein Cholesterol (UHR) and Diabetic Retinopathy in Patients with Type 2 Diabetes Mellitus:A Cross-Sectional Study. Diabetes, Metab Syndr Obes. 2025;18:173–183.
23. Özkara Yılmaz B, Özenç B, Bayrak D, Yenilmez Yeşildaş P, Altunışık E. Comparison of HbA1c, Uric Acid/HDL-C ratio, and Electroneuromyography (ENMG) results in patients with Type 2 Diabetes Mellitus. Heal Sci Q. 2025; 5(4), 527–534.
24. Xu W, Zhou Y, Jiang Q, Fang Y, Yang Q. Risk prediction models for diabetic nephropathy among type 2 diabetes patients in China: a systematic review and meta-analysis. Front Endocrinol (Lausanne). 2024;15:1407348.

25. Assar M El, Angulo J, Rodríguez-Mañas L. Diabetes and ageing-induced vascular inflammation. J Physiol. 2016;594(8):2125-2146.
26. Chen X, Dong H, Shi F, Qin F, Zhao Y. Association of uric acid to high-density cholesterol ratio (UHR) with biological age acceleration: evidence from NHANES 2009–2018. Sci Rep. 2025;15(1):41847.
27. Turner R, Holman R, Stratton I, et al. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. Br Med J. 1998;317(7160):703-713.
28. George LB, Matthew RW, Shahnaz S, et al. Effects of Blood Pressure Level on Progression of Diabetic Nephropathy. Arch Intern Med. 2003;163(13):1555-1565.
29. Choukem SP, Dzudie A, Dehayem M, et al. Comparison of different blood pressure indices for the prediction of prevalent diabetic nephropathy in a sub-Saharan African population with type 2 diabetes. Pan Afr Med J. 2012;11:67.
30. Anderson RJ, Bahn GD, Emanuele N V., Marks JB, Duckworth WC. Blood pressure and pulse pressure effects on renal outcomes in the Veterans Affairs Diabetes Trial (VADT). Diabetes Care. 2014;37(10):2782-2788.
31. de Boer I, Sun W, Gao X, et al. Effect of intensive diabetes treatment on albuminuria in type 1 diabetes: Long-term follow-up of the diabetes control and complications trial and epidemiology of diabetes interventions and complications study. Lancet Diabetes Endocrinol. 2014;2(10):793-800.
32. Kirkman MS, Mahmud H, Korytkowski MT. Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes Mellitus. Endocrinol Metab Clin North Am. 2018;47(1):81-96.
33. Dušejovská M, Vecka M, Rychlík I, Žák A. Dyslipidemia in patients with chronic kidney disease: Etiology and management. Vnitr Lek. 2020;66(5):275-281.
34. Pontremoli R, Bellizzi V, Bianchi S, et al. Management of dyslipidaemia in patients with chronic kidney disease: a position paper endorsed by the Italian Society of Nephrology. J Nephrol. 2020;33(3):417-430.