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Correlation between serum adenosine deaminase levels and the risk of diabetic kidney disease in patients with type 2 diabetes mellitus

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Abstract: Objective To compare the serum adenosine deaminase (ADA) levels in patients with and without diabetic kidney disease (DKD) in type 2 diabetes mellitus (T2DM), and explore the correlation between ADA levels and the risk of DKD. **Methods** A cross-sectional retrospective study was conducted, including 5 485 T2DM patients hospitalized at the First Hospital Affiliated to Army Medical University from January 2019 to September 2023. Patients were grouped based on the presence or absence of DKD (1 659 cases in DKD group and 3 826 cases in non-DKD group). Clinical data and laboratory indices of both groups were collected from the medical record system and compared. Multivariate logistic regression analysis was used to examine the relationship between ADA levels and DKD risk, with subgroup analysis performed. **Results** Among 5 485 T2DM patients, the incidence of DKD was 30.24%, with ADA levels ranging from 0.2 to 53.9 u/L. ADA levels were significantly higher in the DKD group compared to the non-DKD group[14.0 (11.1, 22.2) u/L *vs* 12.0 (9.6, 15.4) u/L, Z=20.287, P<0.01]. After dividing into quartiles based on ADA levels, the proportion of DKD showed an upward trend (Q1 group 21.30%, Q2 group 25.51%, Q3 group 32.56%, Q4 group 42.86%) . Multivariate logistic regression showed that, after adjusting for relevant risk factors, each 1 u/L increase in ADA was associated with a 4% increased risk of DKD (*OR*=1.040, 95% *CI*:1.011-1.064, P<0.01),and the Q4 group had a 1.45-fold higher risk of DKD than the Q1 group (*OR*=1.450, 95%*CI*:1.112-1.893, P=0.007). Subgroup analysis showed that when β2-microglobulin ⩾ 3 mg/L, elevated ADA significantly increased the risk of DKD (*OR*=1.033, 95%*CI*: 1.002-1.066, P=0.039); when eGFR <60 mL/ (min·1.73m^2), the effect of ADA was amplified [*vs* eGFR 30 to <60 mL/ (min·1.73m^2) group, *OR*=1.102; *vs* eGFR< 30 mL/ (min·1.73m^2) group, *OR*=1.150]. **Conclusion** Elevated serum ADA levels in T2DM patients are significantly associated with the incidence of DKD, especially in stages G3 and beyond of chronic kidney disease. Dynamic monitoring of ADA levels may aid in early risk stratification and individualized interventions.

Keywords: Type 2 diabetes mellitus; Diabetic kidney disease; Adenosine deaminase; Estimated glomerular filtration rate; Microgloblin; Urine albumin-to-creatinine ratio; Glycated hemoglobin

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Diabetic kidney disease (DKD) is one of the common complications of diabetes mellitus, and its pathogenesis is complex, mainly involving the interaction of multiple factors such as disorders of glucose metabolism, hemodynamic changes, activation of the polyol pathway, and oxidative stress [1]. Among these, the inflammatory response plays a crucial role in the progression of DKD. Currently, the diagnosis of DKD mainly relies on the urine albumin-to-creatinine ratio (UACR) and/or progressive decline in estimated glomerular filtration rate (eGFR) [2]. However, accumulating evidence indicates that these indicators have insufficient sensitivity in the early stage of DKD. When significant abnormalities in UACR and estimated GFR (eGFR) occur in diabetic patients, renal injury has already progressed to a certain extent [3-4]. There is an urgent need to identify new diagnostic markers for earlier diagnosis of DKD.

Adenosine deaminase (ADA) is a lymphocyte proliferation and differentiation-dependent enzyme that is widely expressed in human tissues. It irreversibly deaminates adenosine to inosine and is crucial for regulating adenosine concentration [5]. Recent studies have found that serum ADA levels are significantly elevated in patients with type 2 diabetes mellitus (T2DM) and is also positively correlated with insulin resistance and also highly correlated with glycated hemoglobin (HbA_{1C}) [6], suggesting a close association between ADA levels and poor glycemic control [7]. ADA has gradually gained attention in research on the early diagnosis, treatment, and mechanisms of immune disorders in diabetes, and the clinical value of dynamic detection of ADA levels is being in-depth evaluated [8]. ADA may play an important role in the pathogenesis of T2DM complications. Therefore, this study aims to evaluate the correlation between serum ADA levels and the presence of DKD in T2DM patients through a cross-sectional design.

1 Materials and methods

1.1 Study subjects

A cross-sectional study was conducted, and data of hospitalized patients with (T2DM in the Department of Endocrinology, the First Hospital Affiliated to Army Medical University from January 2019 to September 2023 were retrospectively collected. The diagnostic criteria for T2DM were in accordance with the Interpretation of the China Guidelines for the Prevention and Treatment of Diabetes (2024 Edition) [9].

Exclusion criteria: (1) Age < 18 years; (2) Other types of diabetes mellitus, with or without acute complications; (3) Complicated with diseases such as heart failure, chronic hepatitis, malignant tumors, and severe infections; (4) Renal damage caused by other reasons, such as drugs, nephritis, nephrotic syndrome, etc.; (5) Incomplete clinical data.

Diagnostic criteria for DKD were as follows [10]. With a definite history of T2DM, and after excluding chronic kidney disease caused by other reasons, DKD was diagnosed if one of the following conditions was met: (1) Reaching the criteria in 2 out of 3 repeated tests within 3–6 months, UACR ⩾ 30 mg/g or urinary albumin excretion rate (UAER) ⩾30 mg/24 h (after excluding other interfering factors such as infection), and/or eGFR <60 mL/(min·1.73 m²) persisting for more than 3 months; (2) Renal biopsy consistent with the pathological changes of DKD [1]. Finally, a total of 5,485 T2DM patients were included, among whom 1,659 had DKD and 3,826 did not have DKD **[Figure 1]**. This study was approved by the Ethics Committee of First Affiliated Hospital of Army Medical University (Ethics No.: KY2024007).

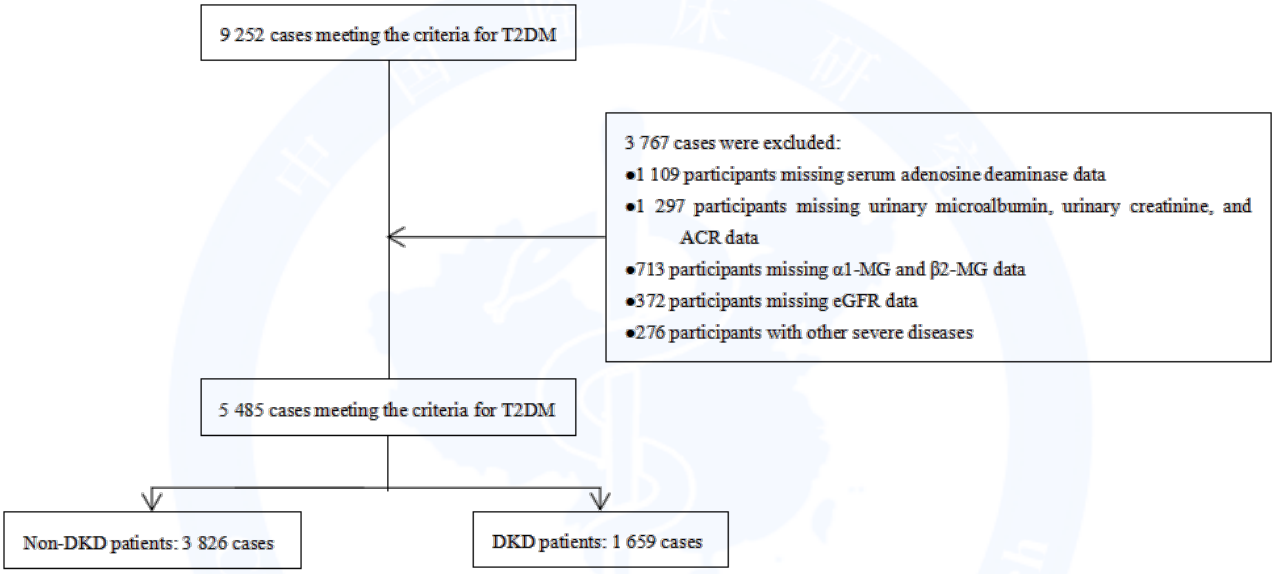

Fig. 1 Flowchart for participant screening

1.2 Collection of clinical data and detection of serological indicators

General data of patients were collected, including gender, age, body mass index (BMI), smoking history, drinking history, etc. After fasting for 8 hours, patients underwent venipuncture to collect early morning fasting venous blood the next day. An automatic biochemical analyzer (Cobas 8000, Roche) was used to determine glycated hemoglobin (HbA_{1C}), fasting blood glucose (FBG), alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transferase (GGT), alkaline phosphatase (ALP), total cholesterol (TC), triglycerides (TG), low density lipoprotein cholesterol (LDL-C), α1-macroglobulin (MG), and β2-MG. Serum adenosine deaminase (ADA) levels were detected by colorimetric method (kit purchased from Beijing Leadman Biochemistry). Uric acid, urinary albumin, and urinary creatinine were measured using the Mindray CAL8000 automatic pipeline detection system, and the UACR was calculated. The eGFR was computed according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

1.3 Statistical methods

Statistical analysis was performed using RStudio (version 2025.05.0 + 469) and IBM SPSS 27.0 software. Continuous variables with normal distribution and homogeneous variance were expressed as $\bar{x} \pm s$, and comparisons between groups were performed using *t*-test. Non-normally distributed continuous variables were presented as M (P_{25}, P_{75}), and comparisons between groups were conducted using the Wilcoxon rank-sum test. Categorical variables were expressed as cases (%), and comparisons among multiple groups were analyzed using the χ^2 test. In multivariate logistic regression analysis, potential confounding variables were adjusted, and ADA levels were further analyzed after grouping by quartiles. Subgroup analysis was used to explore the relationship between ADA and DKD, as well as the interaction among different subgroups. In response to non-linear trends identified in subgroup analysis, variance inflation factor (VIF) analysis was performed for all continuous variables

to ensure controllable multicollinearity (VIF<5). A *P* value <0.05 was considered statistically significant.

2 Results

2.1 Baseline Characteristics of Participants

A total of 5 485 patients with T2DM were included. The mean age was (60.21±13.13) years, with 57.76% (3 168/5 485) being male. The proportions of smokers and drinkers were 38.96% (2 137/5 485) and 36.88% (2 023/5 485), respectively. The mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) were (137.27±20.85) mmHg and (85.25±12.89) mmHg, respectively. The mean fasting blood glucose was (8.99±3.52) mmol/L, and the mean HbA_{1C} was 9.42%±2.63%. The prevalence of DKD was 30.24%, and the range of ADA levels in all participants was 0.2–53.9 u/L. Compared with the non-DKD group, the DKD group showed statistically significant differences in age, BMI, SBP, DBP, FBG, HbA_{1C}, uric acid, UACR, α1-MG, and β2-MG (*P*<0.05). Additionally, the DKD group had higher ADA levels and lower eGFR than the non-DKD group (*P*<0.05). **[Table 1]**

2.2 Logistic Regression Analysis of Influencing Factors for DKD

In Model 1 (without adjusting for covariates), each 1 u/L increase in ADA was associated with a 7% increase in the risk of DKD (*OR*=1.07, 95% *CI*: 1.05-1.08, *P*<0.01). After adjusting for all confounding factors (Model 3), each 1 u/L increase in serum ADA level was still associated with a 4% increase in DKD risk (*OR*=1.04, 95%*CI*: 1.01-1.05, *P*<0.01). Furthermore, when ADA was grouped by quartiles, the proportion of DKD patients showed an increasing trend (21.30% in Q1, 25.51% in Q2, 32.56% in Q3, and 42.86% in Q4). Compared with patients in the Q1 group, those in the Q3 (*OR*=1.184, 95%*CI*: 1.030-1.362, *P*=0.020) and Q4 (*OR*=1.450, 95%*CI*: 1.112-1.893, *P*=0.007) groups had significantly higher risks of DKD. The risk of DKD in T2DM patients increased progressively with increasing serum ADA levels (*P* for trend=0.002). **[Table 2]**

Tab.1 Baseline characteristics for participants in DKD group and non-DKD group

Indicator	Non-DKD group (*n*=3,826)	DKD group (*n*=1,659)	*t*/χ^2/*Z* value	*P* value
Male [*n*(%)]	2 083 (54.4)	1 085 (65.4)	56.949	<0.001
Age (years)[a]	59.39 ± 13.50	62.08 ± 12.05	7.165	<0.001
Smoking history [*n*(%)]	1,390 (36.3)	747 (45.0)	36.804	<0.001
Alcohol drinking history [*n*(%)]	1,328 (34.7)	695 (41.9)	25.647	<0.001
BMI (kg/m²)[a]	25.03 ± 3.93	25.67 ± 3.80	5.431	<0.001
SBP (mmHg)[a]	134.95 ± 19.58	143.59 ± 22.63	12.397	<0.001
DBP (mmHg)[a]	84.60 ± 12.45	86.77 ± 14.02	5.068	<0.001
FBG (mmol/L)[a]	8.75 ± 3.45	9.57 ± 3.60	7.548	<0.001
HbA_{1C} (%)[a]	9.20 ± 2.63	9.95 ± 2.54	9.639	<0.001
AST (u/L)[b]	23 (19, 29)	22 (18, 28)	1.220	0.001
ALT (u/L)[a]	29.93 ± 12.49	26.77 ± 11.82	3.517	<0.001
GGT (u/L)[b]	29 (19, 48)	30 (20, 52)	2.000	0.051
ALP (u/L)[b]	86 (72,105)	89 (74, 109)	2.051	<0.001
TC (mmol/L)[b]	4.56 (3.87, 5.30)	4.56 (3.86, 5.39)	1.909	0.605
TG (mmol/L)[b]	1.61 (1.12, 2.43)	1.74 (1.25, 2.58)	2.681	<0.001
LDL-C (mmol/L)[a]	2.87 ± 0.78	2.86 ± 0.83	0.612	0.176
Uric acid (μmol/L)[b]	326 (271, 390)	362 (297, 429)	11.030	<0.001
UACR (mg/g)[b]	5.66 (0.74, 13.32)	149.56 (73.94, 182.76)	75.539	<0.001
eGFR [mL/(min·1.73m²)][a]	88.46 ± 27.38	59.49 ± 27.38	33.036	<0.001
α1-MG (mg/L)[a]	27.47 ± 11.43	39.86 ± 18.20	30.041	<0.001
β2-MG (mg/L)[a]	2.24 ± 1.71	4.83 ± 4.43	30.888	<0.001
ADA (u/L)[b]	12.0 (9.6, 15.4)	14.0 (11.1, 22.2)	20.287	<0.001

Note: [a], the data was represent by $\bar{x} \pm s$.

Tab.2 Multivariate logistic regression analysis of the relationship between ADA and DKD

Serum ADA	Model 1		Model 2		Model 3	
	OR (95%*CI*)	*P* value	*OR* (95%*CI*)	*P* value	*OR* (95%*CI*)	*P* value
Continuous variable	1.07 (1.05–1.08)	<0.001	1.06 (1.04–1.07)	<0.001	1.04 (1.01–1.06)	<0.001
Quartile						
Q1	Reference		Reference		Reference	
Q2	1.15 (0.94–1.40)	0.020	1.10 (0.89–1.36)	0.400	1.07 (0.97–1.14)	0.400
Q3	1.73 (1.43–2.10)	<0.001	1.76 (1.42–2.17)	<0.001	1.18 (1.03–1.36)	0.020
Q4	2.35 (1.94–2.58)	<0.001	2.58 (2.08–3.20)	<0.001	1.45 (1.11–1.89)	0.007
P for trend	<0.001		<0.001		0.002	

Note: Model 1: Unadjusted; Model 2: Adjusted for demographic and basic health indicators (age, gender, smoking history, alcohol drinking history, SBP, DBP, BMI); Model 3: Further adjusted for renal function indicators (uric acid, eGFR, UACR, α1-MG, β2-MG) and metabolic and liver function indicators (HbA_{1c}, FBG, TG, AST, ALT, ALP) on the basis of Model 2. VIF test showed that all variables had VIF<5 (maximum VIF=3.5), excluding multicollinearity interference.

2.3 Subgroup Analysis of the Relationship between ADA and DKD Risk

Subgroup analyses stratified by age, gender, BMI, HbA_{1c}, etc., and interaction tests showed that after adjusting for age, gender, smoking, alcohol consumption, SBP, DBP, BMI, FBG, TG, uric acid, AST, ALT, eGFR, HbA_{1c}, α1-MG, β2-MG, and UACR, the relationship between ADA level and DKD risk exhibited interactions with β2-MG and eGFR. The relationship between serum ADA and DKD risk was not linear, and its direction of effect was highly dependent on baseline renal function status. When β2-MG < 3 mg/L, an increase in ADA was associated with a reduced risk of DKD (*OR*=0.938). When β2-MG was elevated (≥ 3 mg/L), an increase in ADA instead increased the risk of DKD (*OR*=1.033, 95%*CI*: 1.002-1.066, *P*=0.039). With the decline in renal function and increase in ADA, the risk of DKD significantly increased (*P*<0.05). **[Table 3]**

Tab.3 Subgroup analysis of the correlation between ADA and the risk of DKD

Variables	DKD group	Non-DKD group	*OR* (95%*CI*)	*P* value	$P_{interaction}$ value
Age					0.066
< 60 years	699	1,798	0.970(0.927,1.016)	0.201	
⩾ 60 years	960	2,028	1.024(0.992,1.058)	0.147	
Gender					0.281
Male	1,085	2 083	1.003(0.970,1.037)	0.846	
Female	574	1,743	1.005(0.961,1.051)	0.826	
BMI					0.337
< 25 kg/m^2	717	1,945	1.010(0.972,1.050)	0.597	
⩾ 25 kg/m^2	942	1,881	0.998(0.962,1.036)	0.921	
HbA_{1C}					0.597
< 6.5%	128	701	1.126(1.000,1.267)	0.051	
⩾ 6.5%	1,531	3,125	0.999(0.972,1.026)	0.923	
α1-MG					0.818
< 30 mg/L	559	2,766	0.912(0.864,0.962)	<0.001	
⩾ 30 mg/L	1,100	1,060	1.041(1.008,1.075)	0.014	
β2-MG					0.012
< 3 mg/L	766	3,273	0.938(0.896,0.981)	0.006	
⩾ 3 mg/L	893	553	1.033(1.002,1.066)	0.039	
eGFR mL/(min·1.73 m²)					<0.001
≥ 120	63	319	1.001(0.952,1.166)	0.983	
90 - < 120	295	1,734	0.724(0.638,0.823)	<0.001	
60-<90	403	1,268	0.989(0.898,1.089)	0.818	
30- <60	535	371	1.102(1.013,1.198)	0.023	
< 30	363	134	1.150(1.047,1.264)	0.003	

3 Discussion

DKD is a common microvascular complication of diabetes and the most common cause of end-stage renal disease (ESRD) [11]. Early intervention can effectively delay renal failure and improve patient prognosis [12]. However, once patients develop massive proteinuria, they often miss the optimal treatment opportunity [13]. Therefore, finding more effective diagnostic indicators is crucial. This study evaluated the relationship between serum ADA levels and DKD in patients with T2DM. The results showed that elevated serum ADA was significantly correlated with the risk of DKD in T2DM patients, and ADA may reflect tubulointerstitial injury and decreased glomerular filtration function.

Lu *et al.* [14], through a study of 400 T2DM patients, found that serum ADA was closely related to DKD and partially reflected the risk of DKD in T2DM patients, which is generally consistent with the results of this study. Gondouin *et al.* [15] also found that ADA was significantly elevated in DKD patients, which increased the risk of cardiovascular events. In addition, elevated ADA is also associated with an increased risk of diabetic retinopathy [16], peripheral neuropathy [17], and diabetic cardiomyopathy [18].

This study found that ADA further increased with poor glycemic control and progression of DKD. When eGFR < 60 mL/(min·1.73m²), the risk effect of ADA on DKD was significantly enhanced, which may be attributed to the following: (1) In the early stage of DKD, ADA is slightly elevated, and its substrate adenosine can still regulate renin release and glomerular filtration rate [19], activate adenosine 2b receptors, inhibit the release of inflammatory factors [tumor necrosis factor (TNF)-α, interleukin (IL)-1β], and alleviate renal tissue damage [20]; (2) With the persistent decline of eGFR, excessive elevation of ADA accelerates adenosine degradation, losing its protective anti-inflammatory effect and aggravating renal damage; (3) High ADA activates CD4+ T lymphocytes, releasing a large number of inflammatory factors such as interferon-γ and IL-2, which accelerates the progression of DKD [21-22]; (4) High ADA inhibits cellular glucose uptake by degrading adenosine, exacerbating insulin resistance [7] and indirectly damaging the kidneys. Multiple factors collectively lead to a significant increase in the risk effect of ADA as eGFR decreases.

This study found that when the renal tubular injury marker β2-MG ⩾ 3 mg/L, elevated ADA increased the risk of DKD; when β 2-MG was normal, ADA instead reduced the risk. This bidirectional effect may be explained as follows: (1) In the early stage with normal renal function, slightly elevated ADA catalyzes adenosine deamination, which prevents adenosine from activating adenosine A1 receptors, thereby avoiding renal vasoconstriction, decreased filtration rate, and podocyte apoptosis induction [20], exerting a protective effect; (2) After renal tubular injury (β2-MG ⩾ 3 mg/L), damage-associated molecular patterns (DAMPs) are released, activating macrophages and upregulating ADA, leading to adenosine depletion and forming an inflammation-injury positive feedback loop [27]; (3) High concentrations of ADA catalyze inosine metabolism to uric acid, and uric acid crystal deposition can activate the NOD-like receptor protein 3 (NLRP3) inflammasome, leading to IL-1β release and reactive oxygen species (ROS) burst, which directly damages tubular epithelial cells [24]. These results support that elevated serum ADA may serve as a potential biomarker reflecting tubulointerstitial injury and decreased glomerular filtration function.

In conclusion, this study found that elevated serum ADA in T2DM patients was associated with the risk of DKD, and the impact of ADA on DKD risk varied with changes in β2-MG levels. However, the study has limitations: the cross-sectional design cannot infer a causal relationship between ADA and DKD; the failure to detect inflammatory factors and adenosine metabolites limits mechanistic interpretation; and the single-center sample may have selection bias. Future prospective cohort studies are needed to validate the early warning value of ADA. Given the wide distribution of ADA and its association with multiple diabetic complications, it is necessary to further explore the relationship between ADA and other diabetic microvascular complications.

In summary, this study indicates that elevated serum ADA significantly increases the risk of DKD as renal function declines. The correlation between ADA and β2-MG may reflect renal tubular injury in T2DM patients. Serum ADA levels are of great significance for the progression of DKD and are expected to become an important detection indicator for early DKD lesions, providing a theoretical basis for subsequent studies on serum ADA and diabetic complications.

Author contributions

Zhang Pengrui: study conception, data statistics and analysis, manuscript writing; Peng Guiliang, Zhang Yuling: data collection, collation, and analysis; Zhang Xinyu, Sun Lijuan: data collection and proofreading; Long Min: study design, manuscript guidance, and revision.

Reference

[1] Młynarska E, Buławska D, Czarnik W, et al. Novel insights into diabetic kidney disease[J]. Int J Mol Sci, 2024, 25(18): 10222.

[2] China guidelines for clinical diagnosis and treatment of diabetic nephropathy[J]. Chin J Nephrol, 2021, 37(3): 255-304.

[3] Wang Y, Jin MY, Cheng CK, et al. Tubular injury in diabetic kidney disease: molecular mechanisms and potential therapeutic perspectives[J]. Front Endocrinol (Lausanne), 2023, 14: 1238927.

[3] Wang Y, Jin MY, Cheng CK, et al. Tubular injury in diabetic kidney disease: molecular mechanisms and potential therapeutic perspectives[J]. Front Endocrinol, 2023, 14: 1238927. [PubMed]

[4] Tuttle KR, Agarwal R, Alpers CE, et al. Molecular mechanisms and therapeutic targets for diabetic kidney disease[J]. Kidney Int, 2022, 102(2): 248-260.

[5] Gao X. Significance of combined detection of serum cystatin C and adenosine deaminase in early diagnosis of diabetic nephropathy[J]. Guide China Med, 2018, 16(5): 145-146.

[6] Kurtul N, Pence S, Akarsu E, et al. Adenosine deaminase activity in the serum of type 2 diabetic patients[J]. Acta Medica (Hradec Kralove), 2004, 47(1): 33-35.

[7] Sapkota LB, Thapa S, Subedi N. Correlation study of adenosine deaminase and its isoenzymes in type 2 diabetes mellitus[J]. BMJ Open Diabetes Res Care, 2017, 5(1): e000357.

[8] Alfaqih MA, Ababneh E, Mhedat K, et al. Vitamin D reduces the activity of adenosine deaminase and oxidative stress in patients with type two diabetes mellitus[J]. Mol Nutr Food Res, 2024, 68(12): e2300870.

[9] Guidelines for prevention and treatment of diabetes in China (2024 edition)[J]. Chin J Diabetes Mellit, 2025, 17(1): 16-139.

[10] Clinical guideline for the prevention and treatment of diabetic kidney disease in China (2021 edition) [J]. Chin J Diabetes Mellit, 2021, 13(8): 762-784.

[11] Li HX, Lu WH, Wang AN, et al. Changing epidemiology of chronic kidney disease as a result of type 2 diabetes mellitus from 1990 to 2017: Estimates from Global Burden of Disease 2017[J]. J Diabetes Investig, 2021, 12(3): 346-356.

[12] Guedes M, Pecoits-Filho R. Can we cure diabetic kidney disease? Present and future perspectives from a nephrologist's point of view[J]. J Intern Med, 2022, 291(2): 165-180.

[13] Goycheva P, Petkova-Parlapanska K, Georgieva E, et al. Biomarkers of oxidative stress in diabetes mellitus with diabetic nephropathy complications[J]. Int J Mol Sci, 2023, 24(17): 13541.

[14] Lu CF, Liu WS, Ge XQ, et al. Serum adenosine deaminase levels are associated with diabetic kidney disease in type 2 diabetic patients[J]. Endocr Connect, 2021, 10(9): 973-979.

[15] Gondouin B, Jourde-Chiche N, Sallee M, et al. Plasma xanthine oxidase activity is predictive of cardiovascular disease in patients with chronic kidney disease, independently of uric acid levels[J]. Nephron, 2015, 131(3): 167-174.

[16] Zeiner J, Loukovaara S, Losenkova K, et al. Soluble and membrane-bound adenylate kinase and nucleotidases augment ATP-mediated inflammation in diabetic retinopathy eyes with vitreous hemorrhage[J]. J Mol Med (Berl), 2019, 97(3): 341-354.

[17] Yu C, Zhuang L, Xu F, et al. Increased levels of serum adenosine deaminase and increased risk of diabetic peripheral neuropathy in type 2 diabetes[J]. Front Endocrinol (Lausanne), 2022, 13: 997672.

[18] Reichert KP, Castro MFV, Assmann CE, et al. Diabetes and hypertension: Pivotal involvement of purinergic signaling[J]. Biomed Pharmacother, 2021, 137: 111273.

[19] Yap SC, Lee HT. Adenosine and protection from acute kidney injury[J]. Curr Opin Nephrol Hypertens, 2012, 21(1): 24-32.

[20] Heruye SH, Myslinski J, Zeng C, et al. Inflammation primes the murine kidney for recovery by activating AZIN1 adenosine-to-inosine editing[J]. J Clin Invest, 2024, 134(17): e180117.

[21] Rayego-Mateos S, Rodrigues-Diez RR, Fernandez-Fernandez B, et al. Targeting inflammation to treat diabetic kidney disease: the road to 2030[J]. Kidney Int, 2023, 103(2): 282-296.

[22] Gao X, Wei WJ, Yang XB, et al. Effect of yishen Huayu decoction on renal function and expression of peripheral dlood adenosine deaminase in the treatment of diabetic kidney disease[J]. Prog Mod Biomed, 2023, 23(2): 239-243.

[23] Elwakiel A, Mathew A, Isermann B. The role of endoplasmic reticulum-mitochondria-associated membranes in diabetic kidney disease[J]. Cardiovasc Res, 2024, 119(18): 2875-2883.

[24] Chen YJ, Yang HM, Wang ZY. A dynamic study on serum biomarkers and kidney injury in a gosling model of hyperuricemia[J]. Poult Sci, 2025, 104(6): 105144.

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·论 著·

2型糖尿病患者血清腺苷脱氨酶水平与糖尿病肾病风险的相关性研究

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摘要：目的 比较有无糖尿病肾病（DKD）的2型糖尿病（T2DM）患者血清腺苷脱氨酶（ADA）水平，探讨ADA水平与DKD发生风险的相关性。**方法** 研究采用横断面回顾性研究设计，纳入2019年1月至2023年9月于陆军军医大学第一附属医院住院的T2DM患者5 485例，根据是否患有DKD进行分组（DKD组1 659例，非DKD组3 826例）。通过病历系统收集两组患者的临床数据及实验室指标并进行比较。采用多因素logistic回归分析ADA与DKD风险的关系并进行亚组分析。**结果** 5 485例T2DM患者中，DKD者占30.24%，ADA水平范围为0.2~53.9 u/L。DKD组ADA水平显著高于非DKD组[14.0（11.1，22.2）u/L *vs* 12.0（9.6，15.4）u/L，*Z*=20.287，*P*<0.01]。按ADA水平四分位分组后，DKD占比呈上升趋势（Q1组21.30%，Q2组25.51%，Q3组32.56%，Q4组42.86%）。多因素logistic回归显示，在校正相关危险因素后，血清ADA每升高1 u/L，DKD风险增加4%（*OR*=1.040，95%*CI*：1.011~1.064，*P*<0.01），Q4组的DKD风险较Q1组升高45%（*OR* = 1.450，95%*CI*：1.112~1.893，*P*=0.007）。亚组分析显示当β2-微球蛋白≥ 3 mg/L时，ADA升高显著增加DKD风险（*OR*=1.033，95%*CI*：1.002~1.066，*P*=0.039）；eGFR < 60 mL/(min·1.73 m²)时，ADA效应放大[eGFR 30~<60 mL/(min·1.73 m²)组，*OR*=1.102；eGFR< 30 mL/(min·1.73 m²)组，*OR*=1.150]。**结论** T2DM患者中，血清ADA水平升高与DKD患病显著相关，尤其在慢性肾脏病G3期及以后阶段作用显著，其水平动态监测或有助于早期风险分层及个体化干预。

关键词： 2型糖尿病；糖尿病肾病；腺苷脱氨酶；估算肾小球滤过率；微球蛋白；白蛋白/尿肌酐比值
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Correlation between serum adenosine deaminase levels and the risk of diabetic kidney disease in patients with type 2 diabetes mellitus

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Abstract: Objective To compare the serum adenosine deaminase (ADA) levels in patients with and without diabetic kidney disease (DKD) in type 2 diabetes mellitus (T2DM), and explore the correlation between ADA levels and the risk of DKD. **Methods** A cross-sectional retrospective study was conducted, including 5 485 T2DM patients hospitalized at the First Hospital Affiliated to Army Medical University from January 2019 to September 2023. Patients were grouped based on the presence or absence of DKD (1 659 cases in DKD group and 3 826 cases in non-DKD group). Clinical data and laboratory indices of both groups were collected from the medical record system and compared. Multivariate logistic regression analysis was used to examine the relationship between ADA levels and DKD risk, with subgroup analysis performed. **Results** Among 5 485 T2DM patients, the proportion of DKD was 30.24%, with ADA levels ranging from 0.2 to 53.9 u/L. ADA levels were significantly higher in the DKD group compared to the non-DKD group [14.0 (11.1, 22.2) u/L *vs* 12.0 (9.6, 15.4) u/L, *Z*=20.287, *P*<0.01]. After dividing into quartiles based on ADA levels, the proportion of DKD showed an upward trend (Q1 group 21.30%, Q2 group 25.51%, Q3 group 32.56%, Q4

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group 42.86%). Multivariate logistic regression showed that, after adjusting for relevant risk factors, each 1 u/L increase in ADA was associated with a 4% increased risk of DKD (*OR*= 1.040, 95%*CI*: 1.011-1.064, *P*<0.01), and the Q4 group had a 1.45-fold higher risk of DKD than the Q1 group (*OR* = 1.450, 95%*CI*: 1.112-1.893, *P*=0.007). Subgroup analysis showed that when β2-microglobulin ≥ 3 mg/L, elevated ADA significantly increased the risk of DKD (*OR*=1.033, 95%*CI*: 1.002-1.066, *P*=0.039); when eGFR < 60 mL/(min·1.73 m^2), the effect of ADA was amplified [*vs* eGFR 30 to <60 mL/(min·1.73 m^2) group, *OR*=1.102; *vs* eGFR< 30 mL/(min·1.73 m^2) group, *OR*=1.150]. **Conclusion** Elevated serum ADA levels in T2DM patients are significantly associated with the incidence of DKD, especially in stages G3 and beyond of chronic kidney disease. Dynamic monitoring of ADA levels may aid in early risk stratification and individualized interventions.

Keywords: Type 2 diabetes mellitus; Diabetic kidney disease; Adenosine deaminase; Estimated glomerular filtration rate; Microglobulin; Urine albumin-to-creatinine ratio

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糖尿病肾脏病（diabetic kidney disease，DKD）是常见的糖尿病并发症之一，其发病机制错综复杂，主要包括糖代谢紊乱、血流动力学改变、多元醇通路激活、氧化应激等多因素相互作用[1]，其中炎症反应在DKD的进展中发挥着关键作用。目前，DKD诊断主要依赖尿白蛋白/尿肌酐比值（urine albumin-to-creatinine ratio，UACR）和（或）估算肾小球滤过率（estimated glomerular filtration rate，eGFR）进行性下降[2]。然而，这些指标在DKD早期阶段的敏感性不足。当糖尿病患者UACR和eGFR出现明显异常时，肾脏损伤已发展到一定程度[3-4]。目前迫切需要寻找新的诊断标志以更早期诊断DKD。

腺苷脱氨酶（adenosine deaminase，ADA）是一种淋巴细胞增殖和分化的依赖性酶，不可逆地将腺苷脱氨为肌苷，对调节腺苷水平至关重要[5]。近年研究发现，2型糖尿病（type 2 diabetes mellitus，T2DM）患者血清ADA水平显著升高，升高的ADA与胰岛素抵抗呈正相关，同样与糖化血红蛋白（glycated hemoglobin，HbA_{1C}）有高度相关性[6]，提示ADA水平与血糖控制不佳存在密切联系[7]。动态检测ADA水平的临床价值正被深入评估[8]。ADA也可能在T2DM并发症的发病机制中发挥重要作用。因此，本研究通过横断面设计评估血清ADA水平与T2DM患者合并DKD的相关性。

1　对象与方法

1.1　*研究对象*　采用横断面研究，回顾性采集2019年1月至2023年9月于陆军军医大学第一附属医院内分泌科住院的T2DM患者。T2DM患者的诊断标准符合《中国糖尿病防治指南（2024版）》标准[9]。排除标准：（1）年龄小于18周岁；（2）其他类型糖尿病，伴或不伴急性并发症；（3）合并心力衰竭、慢性肝炎、恶性肿瘤和严重感染等疾病；（4）其他原因引起的肾脏损害，例如药物、肾炎、肾病综合征等；（5）临床资料不完整。DKD诊断标准[10]如下。有明确的T2DM病史，并排除其他原因引起的慢性肾脏病，符合以下情况之一可诊断为DKD：（1）在3~6个月内重复检查3次中有2次达到UACR ≥30 mg/g或尿白蛋白排泄率（urinary albumin excretion rate，UAER）≥30 mg/24 h并排除感染等其他干扰因素和（或）eGFR<60 mL/(min·1.73 m^2)持续3个月以上；（2）肾活检符合DKD病理改变[1]。最终纳入T2DM患者5 485例，其中伴有DKD者1 659例，不伴DKD者3 826例（图1）。本研究已获得陆军军医大学第一附属医院伦理委员会批准（伦理号：KY2024007）。

1.2　*临床资料及血清学指标检测*　收集患者一般情况包括性别、年龄、身体质量指数（body mass index，BMI）、吸烟史、饮酒史等。患者在禁食8 h后，于次日抽取清晨空腹静脉血，使用全自动生化分析仪（Cobas 8000，罗氏）测定HbA_{1C}、空腹血糖（fasting blood glucose，FBG）、丙氨酸转氨酶（alanine aminotransferase，ALT）、天冬氨酸转氨酶（aspartate aminotransferase，AST）、γ-谷氨酰转移酶（gamma-glutamyl transferase，GGT）、碱性磷酸酶（alkaline phosphatase，ALP）、总胆固醇（total cholesterol，TC）、三酰甘油（triglycerides，TG）、低密度脂蛋白胆固醇（low density lipoprotein cholesterol，LDL-C）、α1-微球蛋白（macroglobulin，MG）、β2-MG；采用比色法（试剂盒购自北京利德曼生化）检测血清ADA水平。使用迈瑞CAL8000全自动流水线检测系统测定尿酸、尿白蛋白、尿肌酐并计算UACR；根据慢性肾脏病流行病学合作研究（Chronic Kidney Disease Epidemiology Collaboration，CKD-EPI）

公式计算eGFR。

1.3　统计学方法　采用RStudio（version 2025.05.0+469）及IBM SPSS 27.0软件进行数据统计分析。符合正态分布且方差齐的连续变量以$\bar{x}\pm s$表示，组间比较采用t检验。非参数变量用$M(P_{25}, P_{75})$表示，组间比较采用Wilcoxon秩和检验。分类变量以例（%）表示，多组比较采用χ^2检验。在多因素logistic回归分析中对潜在的混杂变量进行调整，并对ADA水平按四分位分组后进行分析。使用亚组分析探究ADA与DKD之间的关系，同时探索各亚组间的相互作用。针对亚组分析发现的非线性趋势，对所有连续变量进行方差膨胀系数（variance inflation factor，VIF）分析，确保多重共线性可控（VIF<5）。P<0.05为差异有统计学意义。

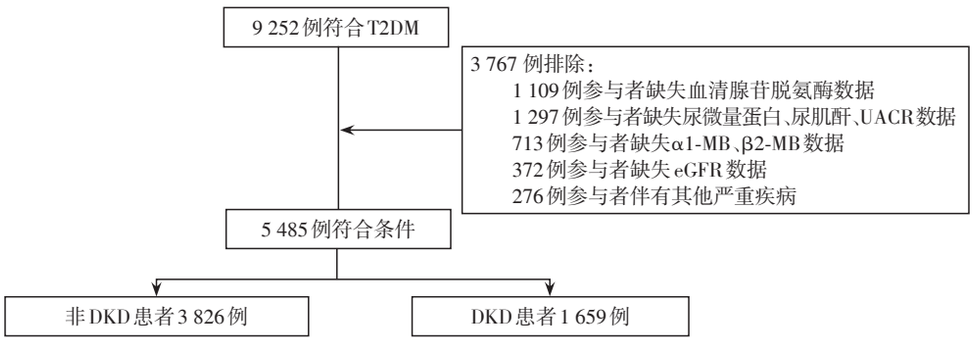

图1　参与者筛选流程图

Fig.1　Flowchart for participant screening

2　结　果

2.1　受试者基线特征　共纳入5 485例T2DM患者，年龄为(60.21±13.13)岁，男性占57.76%(3 168/5 485)，吸烟、饮酒者分别占38.96%(2 137/5 485)、36.88%(2 023/5 485)，收缩压、舒张压分别为(137.27±20.85) mmHg、(85.25±12.89) mmHg，空腹血糖为(8.99±3.52) mmol/L，HbA_{1C}为9.42%±2.63%，DKD的患病率为30.24%，所有参与者的ADA水平范围为0.2~53.9 u/L。相比非DKD组，DKD组中年龄、BMI、收缩压、舒张压、FBG、HbA_{1C}、尿酸、UACR、α1-MG、β2-MG差异有统计学意义（P<0.05）。与非DKD组相比，DKD组中ADA水平更高，而eGFR较低（P<0.05）。见表1。

2.2　DKD影响因素的logistic回归分析　模型1（未调整协变量）：ADA每升高1 u/L，DKD风险增加7%（OR=1.070，95%CI：1.052~1.081，P<0.01），在调整全部混杂因素后（模型3），血清ADA水平每升高1 u/L，DKD风险就增加4%（OR=1.040，95%CI：1.011~1.064，P<0.01）。另外，将ADA按四分位分组后再次分析，DKD患者占比呈上升趋势（Q1组21.30%，Q2组25.51%，Q3组32.56%，Q4组42.86%）。相比Q1组患者，Q3组（OR=1.184，95%CI：1.030~1.362，P=0.020）和Q4组（OR=1.450，95%CI：1.112~1.893，P=0.007）患者DKD风险显著升高。T2DM患者DKD的风险随血清ADA水平逐级递增（$P_{趋势}$=0.002）。见表2。

表1　DKD组与非DKD组患者基线特征比较

Tab.1　Comparison of baseline characteristics for patients in DKD group and non-DKD group

指标	非DKD组（n=3 826）	DKD组（n=1 659）	$\chi^2/t/Z$值	P值
男性[例(%)]	2 083(54.4)	1 085(65.4)	56.949	<0.001
年龄(岁)[a]	59.39±13.50	62.08±12.05	7.165	<0.001
吸烟史[例(%)]	1 390(36.3)	747(45.0)	36.804	<0.001
饮酒史[例(%)]	1 328(34.7)	695(41.9)	25.647	<0.001
BMI(kg/m²)[a]	25.03±3.93	25.67±3.80	5.431	<0.001
收缩压(mmHg)[a]	134.95±19.58	143.59±22.63	12.397	<0.001
舒张压(mmHg)[a]	84.60±12.45	86.77±14.02	5.068	<0.001
FBG(mmol/L)[a]	8.75±3.45	9.57±3.60	7.548	<0.001
HbA_{1C}(%)[a]	9.20±2.63	9.95±2.54	9.639	<0.001
AST(u/L)[b]	23(19,29)	22(18,28)	1.220	0.001
ALT(u/L)[a]	29.93±12.49	26.77±11.82	3.517	<0.001
GGT(u/L)[b]	29(19,48)	30(20,52)	2.000	0.051
ALP(u/L)[b]	86(72,105)	89(74,109)	2.051	<0.001
TC(mmol/L)[b]	4.56(3.87,5.30)	4.56(3.86,5.39)	1.909	0.605
TG(mmol/L)[b]	1.61(1.12,2.43)	1.74(1.25,2.58)	2.681	<0.001
LDL-C(mmol/L)[a]	2.87±0.78	2.86±0.83	0.612	0.176
尿酸(μmol/L)[b]	326(271,390)	362(297,429)	11.030	<0.001
UACR(mg/g)[b]	5.66（0.74,13.32）	149.56（73.94,182.76）	75.539	<0.001
eGFR[mL/(min·1.73 m²)][a]	88.46±27.38	59.49±27.38	33.036	<0.001
α1-MG(mg/L)[a]	27.47±11.43	39.86±18.20	30.041	<0.001
β2-MG(mg/L)[a]	2.24±1.71	4.83±4.43	30.888	<0.001
ADA(u/L)[b]	12.0(9.6,15.4)	14.0(11.1,22.2)	20.287	<0.001

注：[a]为数据以$\bar{x}\pm s$表示；[b]为数据以$M(P_{25},P_{75})$表示。

2.3　ADA与DKD风险关系的亚组分析　以年龄、性别、BMI、HbA_{1C}水平等进行分层的亚组分析和交互作用检验显示，在校正年龄、性别、吸烟、饮酒、收缩压、舒张压、BMI、FBG、TG、尿酸、AST、ALT、eGFR、HbA_{1C}、

α1-MG、β2-MG、UACR 后，ADA 水平和 DKD 风险关系与β2-MG、eGFR 存在交互作用，血清 ADA 与 DKD 风险的关系并非线性，其作用方向高度依赖基线肾功能状态。当β2-MG < 3 mg/L 时，ADA 升高与 DKD 风险降低相关（*OR*=0.938）当β2-MG 升高（≥ 3 mg/L）时，ADA 升高反而增加 DKD 风险（*OR*=1.033，95%*CI*：1.002~1.066，*P*=0.039）。随着肾功能的下降和 ADA 的升高，DKD 风险显著增加（*P*<0.05）。见表 3。

表 2　ADA 与 DKD 关系的多因素 logistic 回归分析

Tab.2　Multivariate logistic regression analysis of the relationship between ADA and DKD

血清 ADA	模型 1		模型 2		模型 3	
	OR（95%*CI*）	*P* 值	*OR*（95%*CI*）	*P* 值	*OR*（95%*CI*）	*P* 值
连续变量	1.070（1.052~1.081）	<0.001	1.062（1.043~1.072）	<0.001	1.040（1.011~1.064）	<0.001
四分位						
Q1	参照		参照		参照	
Q2	1.152（0.941~1.402）	0.020	1.101（0.894~1.363）	0.400	1.073（0.972~1.144）	0.400
Q3	1.733（1.432~2.101）	<0.001	1.762（1.423~2.171）	<0.001	1.184（1.030~1.362）	0.020
Q4	2.350（1.941~2.580）	<0.001	2.582（2.080~3.201）	<0.001	1.450（1.112~1.893）	0.007
$P_{趋势}$值	<0.001		<0.001		0.002	

注：模型 1 为未校正；模型 2 为校正人口学及基础健康指标（年龄、性别、吸烟史、饮酒史、收缩压、舒张压、BMI）；模型 3 为在模型 2 基础上额外校正肾脏功能指标（尿酸、eGFR、UACR、α1-MG、β2-MG）及代谢与肝功能指标（HbA_{1c}、FBG、TG、AST、ALT、ALP）。经 VIF 检验所有变量 VIF<5（最大 VIF=3.5），排除多重共线性干扰。

表 3　ADA 与 DKD 风险相关性的亚组分析

Tab.3　Subgroup analysis of the correlation between ADA and the risk of DKD

变量	DKD 组	非 DKD 组	*OR*（95%*CI*）	*P* 值	$P_{交互}$值
年龄					
< 60 岁	699	1 798	0.970（0.927，1.016）	0.201	0.066
≥ 60 岁	960	2 028	1.024（0.992，1.058）	0.147	
性别					
男	1 085	2 083	1.003（0.970，1.037）	0.846	0.281
女	574	1 743	1.005（0.961，1.051）	0.826	
BMI					
< 25 kg/m^2	717	1 945	1.010（0.972，1.050）	0.597	0.337
≥ 25 kg/m^2	942	1 881	0.998（0.962，1.036）	0.921	
HbA_{1c}					
< 6.5%	128	701	1.126（1.000，1.267）	0.051	0.597
≥ 6.5%	1 531	3 125	0.999（0.972，1.026）	0.923	
α1-MG					
< 30 mg/L	559	2 766	0.912（0.864，0.962）	<0.001	0.818
≥ 30 mg/L	1 100	1 060	1.041（1.008，1.075）	0.014	
β2-MG					
< 3 mg/L	766	3 273	0.938（0.896，0.981）	0.006	0.012
≥ 3 mg/L	893	553	1.033（1.002，1.066）	0.039	
eGFR					
≥ 120	63	319	1.001（0.952，1.166）	0.983	<0.001
90 ~ < 120	295	1 734	0.724（0.638，0.823）	<0.001	
60~ <90	403	1 268	0.989（0.898，1.089）	0.818	
30~ <60	535	371	1.102（1.013，1.198）	0.023	
< 30	363	134	1.150（1.047，1.264）	0.003	

注：eGFR 的单位为 mL/（min·1.73 m^2）。

3　讨　论

DKD 是糖尿病常见微血管并发症，也是终末期肾病（end-stage renal disease，ESRD）最常见原因[11]。早期干预可有效延缓肾衰竭，改善患者预后[12]，患者一旦出现大量蛋白尿，常错过最佳治疗时机[13]。因此，寻找更有效的诊断指标至关重要。本研究对 T2DM 患者血清 ADA 水平与 DKD 的关系进行了评估。结果表明，血清 ADA 升高与 T2DM 患者 DKD 风险有明显相关性，ADA 可能反映肾小管间质损伤及肾小球滤过功能下降。

Lu 等[14]通过对 400 例 T2DM 患者的研究，发现血清 ADA 与 DKD 密切相关，部分反映了 T2DM 患者 DKD 风险，本研究结果与之大致相同。Gondouin 等[15]也发现 DKD 患者 ADA 明显升高，会增加心血管事件风险。此外，ADA 升高还与糖尿病视网膜病变[16]、周围神经病[17]、糖尿病心肌病[18]风险增加相关。

本研究发现随着血糖控制不佳、DKD 病情进展，ADA 进一步升高。当 eGFR<60 mL（min·1.73 m^2）时，ADA 对 DKD 风险的效应显著增强，可能是：（1）DKD 早期 ADA 轻度升高，其底物腺苷尚可调节肾素的释放和肾小球滤过率[19]，激活腺苷 2b 受体，抑制炎症因子的释放，减轻肾组织损伤[20]；（2）eGFR 持续下降，ADA 过度升高加速腺苷降解，丧失其保护性抗炎作用，加重肾脏的破坏；（3）高 ADA 激活 $CD4^+$T 淋巴细胞，释放大量炎症因子如干扰素-γ和白细胞介素（interleukin，IL）-2 等，加快 DKD 进展[21-22]；（4）高 ADA 通过降解腺苷抑制细胞摄入葡萄糖，加重胰岛素抵抗[7]，间接损伤肾脏。多种因素共同导致 ADA 风险效应随 eGFR 下降明显增大。

本研究发现，当肾小管损伤标志物β2-MG ≥ 3 mg/L 时，ADA 升高增加 DKD 风险，当β2-MG 正常时，ADA

反而降低风险，这种双向效应可能是：(1) 早期肾功能正常时，轻度升高的ADA催化腺苷脱氨，可避免其激活腺苷A1受体，继而导致肾血管收缩、滤过率下降，诱导足细胞凋亡[20]，具有保护性。(2) 当肾小管损伤后（β2-MG ≥ 3 mg/L），释放损伤相关分子模式（damage-associated molecular patterns，DAMPs），激活巨噬细胞并上调ADA，使腺苷耗竭，形成炎症-损伤正反馈循环[27]。(3) 高浓度ADA催化肌苷代谢为尿酸，尿酸结晶沉积可激活核苷酸结合寡聚化结构域样受体蛋白3（nucleotide-binding oligomerization domain-like receptor protein 3，NLRP3）炎症小体，导致IL-1β释放，诱导活性氧爆发，直接损伤小管上皮细胞[24]。该结果支持血清ADA升高可能作为反映肾小管间质损伤及肾小球滤过功能下降的潜在生物标志物。

综上，本研究发现T2DM患者血清ADA升高与DKD风险相关，并观察到ADA对DKD风险的影响随β2-MG的水平改变而改变。但研究仍存在局限：横断面设计无法推断ADA与DKD的因果关系；未检测炎症因子及腺苷代谢物，限制了机制解读；单中心样本可能存在选择偏倚，未来需通过前瞻性队列验证ADA的预警价值。鉴于ADA广泛分布且与多种糖尿病并发症相关，有必要进一步探索ADA与其他糖尿病微血管并发症的关系。

总之，本研究表明，随着肾功能下降，血清ADA升高显著增加DKD风险。ADA与β2-MG的相关性可能反映T2DM患者肾小管损伤情况。血清ADA水平对DKD进展具有重要的意义，有望成为DKD早期病变的重要检测指标，为后续血清ADA与糖尿病并发症间的研究提供理论依据。

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参考文献

[1] Młynarska E, Buławska D, Czarnik W, et al. Novel insights into diabetic kidney disease[J]. Int J Mol Sci, 2024, 25(18): 10222.

[2] 中华医学会肾脏病学分会专家组，陈江华，孙林，等. 糖尿病肾脏疾病临床诊疗中国指南[J]. 中华肾脏病杂志，2021，13(3)：255-304.

[3] Wang Y, Jin MY, Cheng CK, et al. Tubular injury in diabetic kidney disease: molecular mechanisms and potential therapeutic perspectives[J]. Front Endocrinol (Lausanne), 2023, 14: 1238927.

[4] Tuttle KR, Agarwal R, Alpers CE, et al. Molecular mechanisms and therapeutic targets for diabetic kidney disease[J]. Kidney Int, 2022, 102(2): 248-260.

[5] 高娴. 血清胱抑素C、腺苷脱氨酶联合检测对糖尿病肾病早期诊断的意义[J]. 中国医药指南，2018，16(5)：145-146.

[6] Kurtul N, Pence S, Akarsu E, et al. Adenosine deaminase activity in the serum of type 2 diabetic patients[J]. Acta Medica (Hradec Kralove), 2004, 47(1): 33-35.

[7] Sapkota LB, Thapa S, Subedi N. Correlation study of adenosine deaminase and its isoenzymes in type 2 diabetes mellitus[J]. BMJ Open Diabetes Res Care, 2017, 5(1): e000357.

[8] Alfaqih MA, Ababneh E, Mhedat K, et al. Vitamin D reduces the activity of adenosine deaminase and oxidative stress in patients with type two diabetes mellitus[J]. Mol Nutr Food Res, 2024, 68(12): e2300870.

[9] 中华医学会糖尿病学分会. 中国糖尿病防治指南(2024版)[J]. 中华糖尿病杂志，2025，17(1)：16-139.

[10] 中华医学会糖尿病学分会微血管并发症学组. 中国糖尿病肾脏病防治指南(2021年版)[J]. 中华糖尿病杂志，2021，13(8)：762-784.

[11] Li HX, Lu WH, Wang AN, et al. Changing epidemiology of chronic kidney disease as a result of type 2 diabetes mellitus from 1990 to 2017: Estimates from Global Burden of Disease 2017[J]. J Diabetes Investig, 2021, 12(3): 346-356.

[12] Guedes M, Pecoits-Filho R. Can we cure diabetic kidney disease? Present and future perspectives from a nephrologist's point of view[J]. J Intern Med, 2022, 291(2): 165-180.

[13] Goycheva P, Petkova-Parlapanska K, Georgieva E, et al. Biomarkers of oxidative stress in diabetes mellitus with diabetic nephropathy complications[J]. Int J Mol Sci, 2023, 24(17): 13541.

[14] Lu CF, Liu WS, Ge XQ, et al. Serum adenosine deaminase levels are associated with diabetic kidney disease in type 2 diabetic patients[J]. Endocr Connect, 2021, 10(9): 973-979.

[15] Gondouin B, Jourde-Chiche N, Sallee M, et al. Plasma xanthine oxidase activity is predictive of cardiovascular disease in patients with chronic kidney disease, independently of uric acid levels[J]. Nephron, 2015, 131(3): 167-174.

[16] Zeiner J, Loukovaara S, Losenkova K, et al. Soluble and membrane-bound adenylate kinase and nucleotidases augment ATP-mediated inflammation in diabetic retinopathy eyes with vitreous hemorrhage[J]. J Mol Med (Berl), 2019, 97(3): 341-354.

[17] Yu C, Zhuang L, Xu F, et al. Increased levels of serum adenosine deaminase and increased risk of diabetic peripheral neuropathy in type 2 diabetes[J]. Front Endocrinol (Lausanne), 2022, 13: 997672.

[18] Reichert KP, Castro MFV, Assmann CE, et al. Diabetes and hypertension: Pivotal involvement of purinergic signaling[J]. Biomed Pharmacother, 2021, 137: 111273.

[19] Yap SC, Lee HT. Adenosine and protection from acute kidney injury[J]. Curr Opin Nephrol Hypertens, 2012, 21(1): 24-32.

[20] Heruye SH, Myslinski J, Zeng C, et al. Inflammation primes the murine kidney for recovery by activating AZIN1 adenosine-to-inosine editing[J]. J Clin Invest, 2024, 134(17): e180117.

[21] Rayego-Mateos S, Rodrigues-Diez RR, Fernandez-Fernandez B, et al. Targeting inflammation to treat diabetic kidney disease: the road to 2030[J]. Kidney Int, 2023, 103(2): 282-296.

[22] 高欣，魏文静，杨薪博，等. 益肾化瘀汤对糖尿病肾病大鼠肾功能及外周血腺苷脱氨酶表达的影响[J]. 现代生物医学进展，2023，23(2)：239-243.

[23] Elwakiel A, Mathew A, Isermann B. The role of endoplasmic reticulum-mitochondria-associated membranes in diabetic kidney disease[J]. Cardiovasc Res, 2024, 119(18): 2875-2883.

[24] Chen YJ, Yang HM, Wang ZY. A dynamic study on serum biomarkers and kidney injury in a gosling model of hyperuricemia[J]. Poult Sci, 2025, 104(6): 105144.

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