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Association between heart rate variability and apolipoprotein B / apolipoprotein A1 ratio in patients with diabetic kidney disease stratified by estimated glomerular filtration rate

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Abstract: Objective To investigate the stratified correlation between heart rate variability (HRV) and the apolipoprotein B/apolipoprotein A1 (ApoB/ApoA1) ratio in patients with diabetic kidney disease (DKD) across different levels of estimated glomerular filtration rate (eGFR), aiming to provide a reference for the precise assessment of cardiovascular risk in this population. **Methods** A cross-sectional study was conducted, selecting 258 patients with DKD admitted to Jiangsu Province Official Hospital from January 2022 to June 2024. Based on eGFR levels, patients were divided into the ≥60 group [eGFR≥60 mL/(min·1.73 m^2), n=95], the 30–<60 group[eGFR 30–<60 mL/(min·1.73 m^2), n=118], and the <30 group[eGFR<30 mL/(min·1.73 m^2), n=45]. 24–hour ambulatory electrocardiography was performed in all groups to analyze HRV parameters, and the ApoB/ApoA1 ratio was concurrently collected. Spearman correlation analysis and multiple linear regression analysis were used to explore the relationship between HRV and the ApoB/ApoA1 ratio. **Results** Statistically significant differences were observed among the three groups in age, duration of diabetes, serum creatinine, and urinary protein/creatinine ratio (P<0.05). As eGFR declined, the standard deviation of normal–to–normal intervals (SDNN) decreased (P<0.01), with SDNN decreasing by 10.8 ms for every 10 mL/ (min·1.73 m^2) reduction in eGFR (P<0.01); the root mean square of successive differences (RMSSD) also showed a downward trend (P=0.003). The ApoB/ApoA1 ratio significantly increased with declining eGFR (P<0.01). Correlation analysis revealed a significant negative correlation between SDNN and the ApoB/ApoA1 ratio (r=–0.381, P<0.01), and this correlation was also statistically significant in the 30–<60 group (r=–0.356, P=0.001) and the <30 group (r=–0.487, P=0.003). Multiple linear regression analysis showed that eGFR (β=5.670, P<0.01) and the ApoB/ApoA1 ratio (β=–12.730, P=0.034) were independent influencing factors for SDNN. **Conclusion** In patients with DKD, the negative correlation between HRV and the ApoB/ApoA1 ratio strengthens significantly as renal function deteriorates, demonstrating a clear eGFR stratification effect. Monitoring the ApoB/ApoA1 ratio may be helpful for the stratified management of cardiovascular autonomic nerve risk in patients with renal insufficiency.

Keywords: Diabetic kidney disease; Heart rate variability; Apolipoprotein; Estimated glomerular filtration rate; Stratified correlation; Renal function

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Diabetic kidney disease (DKD) is the most severe and most common chronic complication of diabetes mellitus, and it constitutes the leading cause of end-stage kidney disease [1]. Moreover, compared with diabetic patients without kidney involvement, patients with DKD have a significantly higher risk of cardiovascular disease, with cardiovascular-related mortality accounting for 50%–80% of deaths, far exceeding the mortality attributable to renal failure itself [2]. Therefore, it is of paramount importance to identify early assessment tools and intervention targets for cardiovascular risk in patients with DKD. Cardiac autonomic neuropathy is another common complication of diabetes, among which heart rate variability (HRV), as a non-invasive and quantitative indicator for evaluating cardiac autonomic function, has been shown to be markedly reduced in patients with DKD [3]. Previous studies have demonstrated that HRV is significantly impaired in patients with long-standing type 1 diabetes mellitus presenting with proteinuria or overt nephropathy, and that such abnormalities possess predictive value for subsequent progressive deterioration of renal function [4].

Apolipoproteins (Apo), as key regulators of lipid metabolism, play an important role in the development and progression of DKD [5]. The ApoB/ApoA1 ratio has been widely recognized as a strong predictor for assessing cardiovascular risk [6]. Research has found that the ApoB/ApoA1 ratio is associated with an increased risk of macrovascular and microvascular events in patients with type 2 diabetes mellitus (T2DM) [7]. In the context of kidney disease, one previous study has shown that abnormalities in the ApoB/ApoA1 ratio are correlated with the progression of renal disease, and that high ApoB/ApoA1 ratio is significantly associated with an increased risk of developing end-stage kidney disease. Besides that, apolipoprotein metabolic derangements, as a common feature of chronic kidney disease, play an important role in the progression of various types of kidney disease [8].

Estimated glomerular filtration rate (eGFR) is the gold standard for assessing renal function, staging kidney disease, and determining prognosis [9]. Although reduced nocturnal blood pressure dipping and decreased HRV in diabetic patients have been confirmed to be associated with cardiovascular morbidity, studies on short-term blood pressure variability remain limited [10]. However, in the specific population of DKD, with the gradual deterioration

of renal function, lipid metabolic disturbances may exert differential effects on cardiac autonomic function, and there may exist eGFR-level-dependent stratification characteristics.

Thus, this study was designed to investigate the stratified correlation between HRV and the ApoB/ApoA1 ratio in DKD patients at different eGFR levels, and to provide a novel reference for the precise assessment and stratified management of cardiovascular risk in DKD patients by analyzing changes in this association.

1 Subjects and Methods

1.1 Study Subjects

This study adopted a cross-sectional design and employed a consecutive sampling method. A total of 258 patients with DKD hospitalized in the Department of Endocrinology at Jiangsu Provincial Official Hospital from January 2022 to June 2024 were enrolled as study subjects. This study was approved by the Ethics Committee of Jiangsu Provincial Official Hospital [approval number: (2024) Ethics Review No. 055-2], and all patients provided written informed consent.

(1) ***Inclusion criteria:***

① meeting the diagnostic criteria for T2DM;

② meeting the diagnostic criteria for DKD [11], defined as the presence of persistent proteinuria [urinary protein/creatinine ratio (UPCR) ≥30 mg/g] with or without a reduction in eGFR;

③ aged 18–80 years;

④ diabetes duration ≥1 year.

(2) ***Exclusion criteria:***

① type 1 diabetes mellitus;

② acute kidney injury;

③ non-DKD causes of kidney disease;

④ presence of severe cardiac arrhythmias, atrial fibrillation, or having a pacemaker implanted;

⑤ complicated by acute infection or malignant tumors;

⑥ severe hepatic insufficiency;

⑦ pregnant or lactating women;

⑧ inability to obtain or verify the complete medication history.

1.2 Data Collection and Laboratory Measurements

General data of the patients was recorded, including age, gender, height, body weight, body mass index (BMI), duration of diabetes, and medication history. Blood pressure was measured under resting conditions; three consecutive measurements were taken and the average value was used as the final blood pressure reading. On the morning of the second day after admission, 5–8 mL of fasting antecubital venous blood was collected from all patients. Blood samples were centrifuged to separate serum, which was then stored at -80 °C for subsequent analysis. Fasting plasma glucose, glycosylated hemoglobin (HbA1c), serum creatinine (SCr), blood urea nitrogen, and other biochemical parameters were measured using a fully automated biochemical analyzer (Beckman Coulter AU5800, USA). Apolipoprotein A1 and ApoB levels were determined by immunoturbidimetry using corresponding kits purchased from Roche Diagnostics (Switzerland), and the ApoB/ApoA1 ratio was calculated accordingly. Lipid parameters included total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula to evaluate renal function: $eGFR=141\times\min(SCr/\kappa,1)^{\alpha}\times\max(SCr/\kappa,1)^{-1.209}\times 0.993^{\wedge age}\times 1.018$ (if female). SCr is expressed in mg/dL (1 mg/dL≈88.4 μmol/L); for females, κ=0.7, α=–0.329; for males, κ=0.9, α=–0.411. The UPCR was also calculated.

1.3 HRV Measurement and Analysis

HRV analysis was performed in accordance with the guidelines proposed by the European Society of Cardiology (ESC) and the North American Society of Pacing and Electrophysiology (NASPE). A 24-hour ambulatory electrocardiographic monitoring system (DMS 300-4A, DMS Company, USA) was used for HRV detection. Time-domain indices included the standard deviation of normal-to-normal intervals (SDNN), the root mean square of successive differences between adjacent normal-to-normal intervals (RMSSD), and the percentage of adjacent normal-to-normal intervals differing by more than 50 ms (pNN50). Frequency-domain indices included low-frequency power (LF, i.e., power spectral density in the 0.04–0.15 Hz band), high-frequency power (HF, i.e., power spectral density in the >0.15–0.40 Hz band), and the LF/HF ratio. All indices were calculated using a 5-minute time window, and the average values over the 24-hour period were taken as the final analytical values.

1.4 Statistical Methods

Statistical analysis was performed using SPSS 26.0 software. The normality of continuous variables was assessed using the Shapiro-Wilk test. Normally distributed continuous data were expressed as $\bar{x}\pm s$, and comparisons among multiple groups were performed using one-way analysis of variance. Skewed distributed continuous data were expressed as M (Q_1, Q_3), and comparisons between groups were conducted using the Kruskal-Wallis H test. Categorical data were expressed as cases (%) and compared using the chi-square test. Correlation analysis was performed using Spearman's rank correlation, and stratified comparisons were conducted using Fisher's Z transformation. Variables with P<0.10 in univariate analysis were entered into multiple linear regression analysis using the forced entry method to construct regression models, with examination for multicollinearity and residual distribution. Skewed variables were logarithmically transformed prior to regression analysis to approximate a normal distribution. A P-value of <0.05 was considered statistically significant.

2 Results

2.1 Comparison of Clinical Characteristics Among the Three Groups

A total of 258 patients with DKD were enrolled in the present study, including 150 males (58.1%), with a mean age of (62.4±11.2) years. According to eGFR levels, the patients were divided into three groups: the ≥60 group [eGFR ≥60 mL/(min·1.73 m²), n=95], the 30–<60 group [eGFR 30–<60 mL/(min·1.73 m²), n=118], and the <30 group [eGFR <30 mL/(min·1.73 m²), n=45]. The clinical characteristics of the three groups are presented in **Table 1**. Statistically significant differences were observed among the three groups in terms of age, sex distribution, duration of diabetes, SCr, and UPCR (P<0.05).

2.2 Comparison of HRV Indices Among the Three Groups

Among the time-domain indices, SDNN and RMSSD decreased significantly with declining eGFR (P<0.01). Among the frequency-domain indices, LF exhibited a decreasing trend (P=0.042), whereas HF, pNN50, and the LF/HF ratio showed no statistically significant differences among the three groups (P>0.05). See **Table 2**. Linear trend analysis further demonstrated that for every 10 mL/(min·1.73 m²) decrease in eGFR, SDNN decreased by 10.8 ms (β=–1.080, P<0.01), and RMSSD decreased by 6.7 ms (β=–0.670, P=0.003).

2.3 Comparison of Apolipoprotein Indices Among the Three Groups

Statistically significant differences in apolipoprotein indices were observed among the three eGFR groups. With deterioration of renal function, ApoA1 levels decreased significantly (P<0.01), whereas ApoB levels increased significantly (P=0.008), resulting in a marked increase in the ApoB/ApoA1 ratio (P=0.001). In contrast, no statistically significant differences were found in TC, HDL-C, or LDL-C among the three groups (P>0.05). See **Table 3**.

Tab.1 Comparison of clinical data among three groups of patients

Characteristics	≥60 group (n=95)	30–<60 group (n=118)	<30 group (n=45)	$F/\chi^2/H$ value	P value
Basic characteristics					
Age (years, $\bar{x}\pm s$)	58.3±10.1	64.2±11.0[a]	69.1±12.5[ab]	16.403	<0.001
Male [n (%)]	57(60.0)	69(58.5)	24(53.3)	0.568	0.753
BMI (kg/m², $\bar{x}\pm s$)	25.7±3.8	26.3±4.2	26.9±4.6	1.374	0.255
Duration of diabetes [years, $M(Q_1,Q_3)$]	8.0(5.0,13.0)	12.0(8.0,18.0)[a]	16.0(11.0,22.0)[ab]	12.850	0.003
HbA1c [%, $M(Q_1,Q_3)$]	7.6(6.5,8.8)	8.0(6.9,9.1)	8.4(7.2,9.8)	4.920	0.087
Renal function parameters					
SCr (μmol/L, $\bar{x}\pm s$)	98.6±22.4	158.7±31.2[a]	293.8±78.1[ab]	345.574	<0.001
UPCR [mg/g, $M(Q_1,Q_3)$]	680.0 (380.0, 1 120.0)	1 050.0 (520.0, 1 680.0)[a]	1 860.0 (1 120.0, 2 850.0)[ab]	18.470	0.002
Cardiovascular parameters					
SBP (mmHg, $\bar{x}\pm s$)	135.1±17.2	140.3±19.1	141.8±20.6	2.810	0.062
Resting heart rate (beats/min, $\bar{x}\pm s$)	76.8±13.4	79.2±14.6	81.3±15.1	1.664	0.191

Note: Compared with ≥60 group, [a]P<0.05; Compared with 30–<60 group, [b]P<0.05.

Tab.2 Comparison of HRV indicators among three groups ($\bar{x}\pm s$)

Group	Case	SDNN (ms, $\bar{x}\pm s$)[a]	RMSSD (ms, $\bar{x}\pm s$)[a]	pNN50 [%, $M(Q_1,Q_3)$]	LF [ms², $M(Q_1,Q_3)$]	HF [ms², $M(Q_1,Q_3)$]	LF/HF ($\bar{x}\pm s$)
≥60 group	95	135.6±36.2	29.8±13.1	6.8(4.2,12.5)	956(742,1 387)	687(521,946)	1.44±0.39
30–<60 group	118	102.4±29.7[a]	22.1±10.8[a]	5.1(2.8,9.6)[a]	731(568,1 089)[a]	578(442,748)	1.51±0.44
<30 group	45	86.3±24.8[a]	17.2±8.6[ab]	3.2(1.4,6.8)[a]	596(423,842)[a]	456(312,621)	1.62±0.58
***F*/*H* value**		47.036	22.005	8.950	12.380	7.820	2.461
***P* value**		<0.001	<0.001	0.011	0.002	0.020	0.087

Note: Compared with ≥60 group, [a]P<0.05; Compared with 30–<60 group, [b]P<0.05.

Tab.3 Comparison of APO indicators among three groups($\bar{x}\pm s$)

Group	Case	ApoA1 (g/L)	ApoB (g/L)	ApoB/ApoA1	TC (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)
≥60 group	95	1.3±0.2	0.9±0.3	0.7±0.2	4.8±1.1	1.2±0.3	2.9±0.8
30–<60 group	118	1.2±0.2[a]	1.0±0.3[a]	0.9±0.3[a]	5.1±1.2	1.1±0.3	3.1±0.9
<30 group	45	1.1±0.2[ab]	1.2±0.4[ab]	1.1±0.4[ab]	5.3±1.4	1.0±0.3	3.2±1.0
***F* value**		11.078	10.925	24.542	3.071	7.239	2.202
***P* value**		<0.001	<0.001	<0.001	0.048	0.001	0.113

Note: Compared with ≥60 group, [a]P<0.05; Compared with 30–<60 group, [b]P<0.05.

2.4 Correlation Analysis

2.4.1 Overall Correlation Analysis

Correlation analysis revealed that time-domain HRV indices were all significantly negatively correlated with the ApoB/ApoA1 ratio, among which SDNN showed the strongest correlation (r_s=–0.381, P<0.01), followed by RMSSD (r_s=–0.252, P=0.008). The correlations between frequency-domain indices and the ApoB/ApoA1 ratio were relatively weak, with only LF showing a marginally significant negative correlation (r_s=–0.174, P=0.062), while the remaining indices were not statistically significant. HRV indices were all positively correlated with eGFR, with time-domain indices showing stronger correlations. SDNN exhibited the strongest correlation with eGFR (r=0.486, P<0.01), followed by RMSSD (r=0.341, P<0.01). Among frequency-domain indices, only LF was significantly positively correlated with eGFR (r_s=0.198, P=0.028). Regarding apolipoprotein indices, ApoA1 was significantly positively correlated with eGFR (r_s=0.398, P<0.01), ApoB was significantly negatively correlated with eGFR (r_s=–0.287, P<0.01), and the ApoB/ApoA1 ratio was significantly negatively correlated with eGFR (r_s=–0.389, P<0.01). See **Table 4**.

2.4.2 Stratified Correlation Analysis

Stratified analysis according to eGFR levels revealed a clear stratification effect in the correlation between SDNN and the ApoB/ApoA1 ratio. In the ⩾60 group, the correlation was not statistically significant (r=–0.198, P=0.067); in the 30–<60 group, SDNN was negatively correlated with the ApoB/ApoA1 ratio (r=–0.356, P=0.001); and in the <30 group, SDNN was also negatively correlated with the ApoB/ApoA1 (r=–0.487, P=0.003). According to Fisher's Z transformation test, this stratification effect was statistically significant (Z=2.340, P=0.019).

2.5 Multivariate Regression Analysis

Univariate analysis showed that eGFR, ApoB/ApoA1 ratio, age, duration of diabetes, HbA1c, and SBP were significantly associated with SDNN (P<0.10). These variables were then all entered into the multiple linear regression model. The final model was statistically significant (F=24.573, P<0.01, R^2=0.378). The results demonstrated that after adjustment for other confounding factors, only eGFR and the ApoB/ApoA1 ratio were independent influencing factors of SDNN (P<0.05). For every 10 mL/(min·1.73 m²) increase in eGFR, SDNN increased by 5.67 ms; for every 0.1 increase in the ApoB/ApoA1 ratio, SDNN decreased by 1.27 ms. Age, duration of diabetes, and HbA1c were not statistically significant after adjustment for other factors (P>0.05). See **Table 5**.

Tab.4 Results of overall correlation analysis

Variable	ApoB/ApoA1		eGFR	
	r value	*P* value	*r* value	P value
HRV Indicators				
SDNN	−0.381	<0.001	0.486	<0.001
RMSSD	−0.252	0.008	0.341	<0.001
pNN50	−0.128	0.156	0.164	0.089
LF	−0.174	0.062	0.198	0.028
HF	−0.142	0.124	0.151	0.106
Apo Indicators				
ApoA1	−0.612	<0.001	0.398	<0.001
ApoB	0.543	<0.001	−0.287	0.002
ApoB/ApoA1	1.000	–	−0.389	<0.001

Tab.5 Univariate and multivariate linear regression analysis of factors affecting SDNN

Variable	Univariate regression analysis				Multivariate analysis			
	β	*SE*	*P* value	95%*CI*	*β*	*SE*	*P* value	95%*CI*
Independent variable								
eGFR	7.23	0.92	<0.001	5.42 – 9.04	5.67	1.21	<0.001	3.28 – 8.06
ApoB/ApoA1	-18.45	4.74	0.001	-27.82 – -9.08	-12.73	5.98	0.034	-24.48 – -0.98
Control variable								
Age	-0.89	0.30	0.003	-1.47 – -0.31	-0.54	0.31	0.082	-1.15 – 0.07
Duration of diabetes	-0.67	0.30	0.028	-1.27 – -0.07	-0.23	0.28	0.412	-0.78 – 0.32
HbA1c	-4.12	1.68	0.015	-7.43 – -0.81	-2.16	1.94	0.267	-5.98 – 1.66
SBP	-0.24	0.13	0.067	-0.50 – 0.02	–	–	–	–

Note: The eGFR variable represents an increase of 10 mL/(min·1.73m²).

3 Discussion

Through a systematic analysis of patients with DKD at different eGFR levels, this study revealed a significant eGFR-stratified correlation between HRV and the ApoB/ApoA1 ratio. The results demonstrated that with the deterioration of renal function, the negative impact of the ApoB/ApoA1 ratio on cardiac autonomic function became progressively stronger. This study showed that HRV indices, specifically SDNN and RMSSD, exhibited a significant decreasing trend with declining eGFR levels in DKD patients. This finding is consistent with the report by Mylonopoulou *er al*. [16] in patients with end-stage kidney disease, who suggested that the accumulation of uremic toxins and the chronic inflammatory state are important contributors to impaired autonomic function. Previous studies have also indicated a direct pathophysiological link between renal function deterioration and cardiac autonomic dysfunction [13]. Of particular note, the present study found that the ApoB/ApoA1 ratio changed significantly with worsening renal function, whereas conventional lipid parameters (TC, HDL-C, and LDL-C) showed no statistically significant differences among the three groups, which may reflect the unique sensitivity of the ApoB/ApoA1 ratio as an indicator of lipid metabolic derangement.

The reduction in HRV reflects impairment of cardiac autonomic nervous system function, particularly

diminished vagal tone [14]. During the progression of DKD, metabolic acidosis, electrolyte disturbances, uremic toxin accumulation, and chronic microinflammatory states may all directly or indirectly affect the normal function of the autonomic nervous system [15]. In addition, diabetic microvascular pathology itself may also involve the autonomic nerve fibers innervating the heart, thereby exacerbating cardiac autonomic dysfunction [16].

This study found that as eGFR declined, ApoA1 levels decreased while ApoB levels increased, resulting in a progressive elevation of the ApoB/ApoA1 ratio. This trend is consistent with the findings of the large-scale cohort study conducted by the Chronic Kidney Disease Prognosis Consortium [17], further confirming the close association between lipoprotein metabolic disturbances and the degree of renal impairment. It is noteworthy that conventional lipid parameters such as TC, HDL-C, and LDL-C did not differ significantly among the three eGFR groups, whereas apolipoprotein indices exhibited clear intergroup differences; this phenomenon may reflect the unique advantage of the ApoB/ApoA1 ratio as a marker of lipid metabolic abnormalities [8]. The ApoB/ApoA1 ratio integrates information on both atherogenic and anti-atherogenic lipoproteins, thus it can more accurately reflect the overall status of lipid metabolism [18]. The potential mechanisms by which renal function deterioration leads to apolipoprotein metabolic abnormalities include: (1) decreased renal clearance of lipoproteins; (2) uremic toxin-induced alterations in hepatic lipoprotein synthesis; (3) chronic inflammation-related changes in the activity of lipoprotein metabolic enzymes; and (4) insulin resistance-exacerbated lipid metabolic derangements [19].

This study identified a significant negative correlation between SDNN and the ApoB/ApoA1 ratio, and this correlation exhibited a stratification effect across different eGFR levels. In the ⩾60 group, the correlation was not statistically significant; in the 30–<60 group, the correlation reached statistical significance; and in the <30 group, the correlation was further strengthened. This stratification effect suggests that as renal function deteriorates, the impact of lipid metabolic abnormalities on cardiac autonomic function gradually intensifies [20]. First, apolipoprotein metabolic abnormalities may affect the blood supply to the autonomic nerves innervating the heart by promoting the progression of atherosclerosis, leading to neural dysfunction [21]. Second, ApoB-rich lipoprotein particles are prone to oxidative modification, and the resulting oxidized low-density lipoproteins can directly damage neurons and impair neural conduction [22]. Third, lipid metabolic disturbances may exacerbate chronic inflammatory responses, and inflammatory mediators such as tumor necrosis factor-α and interleukin-6 have been shown to directly suppress cardiac vagal activity [23]. The strongest correlation observed in the <30 group in the present study may be mechanistically attributed to the synergistic effects in patients with severely impaired renal function, which render the impact of the ApoB/ApoA1 ratio on HRV more pronounced [24].

Multivariate linear regression analysis revealed that after adjustment for multiple traditional risk factors, eGFR and the ApoB/ApoA1 ratio remained independent influencing factors of SDNN. The regression coefficient of the ApoB/ApoA1 ratio on SDNN changed notably in the multivariate model, attenuating from β=–18.450 in univariate analysis to β=–12.730, suggesting that eGFR may play a partial mediating role in the pathway through which the ApoB/ApoA1 ratio affects HRV. Furthermore, the ApoB/ApoA1 ratio may serve as a novel biomarker for the assessment of cardiovascular risk in DKD patients; moreover, targeted improvement of lipid metabolic abnormalities may contribute to the preservation of cardiac autonomic function. Previous studies have indicated that statins not only lower cholesterol levels but also improve the apolipoprotein profile, providing a novel therapeutic strategy for cardiovascular protection in DKD patients [25].

This study has certain limitations. First, the cross-sectional design precludes inferences regarding causality. Second, although multiple confounding factors were controlled, the possibility of residual confounding remains. Third, the sample size was relatively limited, particularly in the <30 group, which may have affected statistical power. Nevertheless, the findings of the present study still hold important clinical applicability. Apolipoprotein testing is relatively simple and cost-effective, and the ApoB/ApoA1 ratio has the potential to become a practical tool for cardiovascular risk stratification in DKD patients. Combined with HRV assessment, it may enable a more comprehensive evaluation of patients' cardiovascular status and provide a reference for the formulation of individualized treatment strategies. Future studies should adopt prospective cohort designs to further validate the predictive value of the ApoB/ApoA1 ratio for cardiovascular events and to explore the efficacy of targeted interventions.

In conclusion, this study demonstrates that in patients with DKD, the negative correlation between HRV and the ApoB/ApoA1 ratio is significantly strengthened with declining renal function. For patients with eGFR <60 mL / (min·1.73 m²), regular monitoring of the ApoB/ApoA1 ratio may facilitate more precise assessment of cardiovascular autonomic risk and guide the management of lipid metabolism.

Conflict of Interest None

References

[1] Xing Jingru, Sun Wei. Based on data mining analysis, professor Sun Wei's prescription law for diabetic nephropathy[J]. Chin J Integr Tradit West Nephrol, 2024, 25(7): 614-618. **[In Chinese]**

[2] Xu Yanchao, Zheng Shuqin. Comparative study on syndrome of diabetes nephropathy in micro proteinuria stage and clinical proteinuria stage based on data mining technology[J]. J Tianjin Univ Tradit Chin Med, 2024, 43(11): 1017-1020. **[In Chinese]**

[3] Zhou Ting, Qu Kai, Chen Zhiyong, et al. Analysis of syndrome and medication regularity of diabetic kidney disease based on data mining[J]. J Shandong Univ Tradit Chin Med, 2023, 47(4): 439-445. **[In Chinese]**

[4] Zhang Xiaoyu, Xiao Huijie, Fu Shaojie, et al. Investigate the genetic mechanisms of diabetic kidney disease complicated with inflammatory bowel disease through data mining and bioinformatic analysis[J]. Front Endocrinol, 2022, 13: 1081747.

[5] CHEN Zhanke, CHEN Kaili, LIU Haolin, et al. Medication rules and mechanism of TCM in TCM prevention and treatment of diabetic kidney disease with spleen and kidney qi deficiency syndrome based on data mining and network pharmacology[J]. Acta Chin Med, 2024, 39(10): 2217-2226. **[In Chinese]**
[6] China Association of Chinese Medicine, Dongzhimen Hospital of Beijing University of Chinese Medicine, Beijing University of Chinese Medicine. Diagnosis and treatment guideline of integrated traditional Chinese and western medicine for diabetic kidney disease[J]. J Beijing Univ Tradit Chin Med, 2024, 47(4): 580-592. **[In Chinese]**
[7] Chinese Diabetes Society. Guidelines for prevention and treatment of type 2 diabetes in China (2013 edition)[J]. Chin J Diabetes, 2014, 22(8): I0002-I0042. **[In Chinese]**
[8] The State Bureau of Quality and Technical Supervision. Terminology of clinical diagnosis and treatment of traditional Chinese medicine-Disease part[M]. Beijing: Standards Press of China, 1997. **[In Chinese]**
[9] Gao Xuemin. Chinese materia Medica[M]. 2nd ed. Beijing: China Press of Traditional Chinese Medicine, 2007. **[In Chinese]**
[10] Chinese Pharmacopoeia Commission. Pharmacopoeia of People's Republic of China (PRC)-part I-2020 edition[M]. Beijing: China Medical Science Press, 2020. **[In Chinese]**
[11] Nanjing University of Chinese Medicine. Dictionary of traditional Chinese Medicine[M]. 2nd ed. Shanghai: Shanghai Scientific & Technical Publishers, 2014. **[In Chinese]**
[12] Elendu C, John Okah M, Fiemotongha K D J, et al. Comprehensive advancements in the prevention and treatment of diabetic nephropathy: a narrative review[J]. Medicine, 2023, 102(40): e35397.
[13] Dwivedi S, Sikarwar M S. Diabetic nephropathy: pathogenesis, mechanisms, and therapeutic strategies[J]. Horm Metab Res, 2025, 57(1): 7-17.
[14] Sun Donglin, Wei Shuqi, Wang Dandan, et al. Integrative analysis of potential diagnostic markers and therapeutic targets for Glomerulus-associated diabetic nephropathy based on cellular senescence[J]. Front Immunol, 2023, 14: 1328757.
[15] Li Mengyu, Shang Haitao, Zhang Shiwen, et al. Exploration on the medication law of Zhang binghou in treating diabetic kidney disease based on data mining[J]. Chin J Inf Tradit Chin Med, 2024, 31(9): 58-65. **[In Chinese]**
[16] Qian Qi, An Xiaofei. Research progress on traditional Chinese medicine syndrome differentiation and classification of diabetic nephropathy[J]. Shandong J Tradit Chin Med, 2024, 43(1): 93-98, 107. **[In Chinese]**
[17] Yu Yunfeng, Hu Gang, Yang Xinyu, et al. A strategic study of acupuncture for diabetic kidney disease based on meta-analysis and data mining[J]. Front Endocrinol, 2024, 15: 1273265.
[18] Shen Zilong, Du Yonglin, Zhao Wenjing. Study on the law of syndrome differentiation and treatment about TCM for the treatment of type 2 diabetic kidney disease stage Ⅳ based on literature study[J]. Int J Tradit Chin Med, 2023, 45(8): 1044-1048. **[In Chinese]**
[19] Duan Hangyu, Liu Jing, Luo Chengxin, et al. Clinical medication mechanism of traditional Chinese medicine in treatment of diabetic nephropathy with qi and Yin deficiency and blood stasis based on medication network, target network, and molecular docking technology[J]. Mod Chin Med, 2024, 26(7): 1197-1207. **[In Chinese]**
[20] Chen Yimeng, Jiang De. Study on diabetic nephropathy evidence elements and medication pattern based on the analysis of modern Chinese medical case literature[J]. J Sichuan Tradit Chin Med, 2024, 42(2): 211-218. **[In Chinese]**
[21] Liu Yang, Guo Luxuan, Zhao Pengbo, et al. Mechanism and clinical research progress of Radix salviae and its active ingredients in treatment of DN[J]. Acta Chin Med Pharmacol, 2023, 51(6): 93-98. **[In Chinese]**
[22] Wang Wei, Gan Xiaoyang, Xu Huiqin, et al. The protective effect and mechanism of cornuside on diabetic nephropathy model mice[J]. China Pharm, 2024, 35(4): 395-400. **[In Chinese]**

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·论　著·

基于估算肾小球滤过率分层的糖尿病肾病患者心率变异性与载脂蛋白B/载脂蛋白A1比值相关性研究

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摘要：目的　探讨糖尿病肾病（DKD）患者心率变异性（HRV）与载脂蛋白B/载脂蛋白A1比值（ApoB/ApoA1比值）在不同估算肾小球滤过率（eGFR）水平下的分层相关性，以期为该人群的心血管风险精准评估提供参考。**方法**　采用横断面研究，选取2022年1月至2024年6月江苏省省级机关医院收治的258例DKD患者作为研究对象。根据eGFR水平分为≥60组［eGFR≥60 mL/（min·1.73 m^2），n=95］，30~<60组［eGFR 30~<60 mL/（min·1.73 m^2），n=118例］和<30组［eGFR<30 mL/（min·1.73 m^2），n=45］。各组患者行24小时动态心电图检查以分析HRV指标，同时收集ApoB/ApoA1比值。采用Spearman相关分析和多元线性回归分析探讨HRV与ApoB/ApoA1比值的关系。**结果**　三组患者在年龄、糖尿病病程、血清肌酐及尿蛋白/肌酐比值上差异均有统计学意义（P<0.05）。随着eGFR下降，正常窦性心搏间期标准差（SDNN）降低（P<0.01），eGFR每下降10 mL/（min·1.73 m^2），SDNN减少10.8 ms（P<0.01）；相邻正常窦性心搏间期差值的均方根（RMSSD）同样呈下降趋势（P=0.003）。ApoB/ApoA1比值随eGFR下降而显著升高（P<0.01）。相关性分析显示，SDNN与ApoB/ApoA1比值呈显著负相关（r=−0.381，P<0.01），且该相关性在30~<60组（r=−0.356，P=0.001）和<30组（r=−0.487，P=0.003）亦有统计学意义。多元线性回归分析显示，eGFR（β=5.670，P<0.01）和ApoB/ApoA1比值（β=−12.730，P=0.034）是SDNN的独立影响因素。**结论**　在DKD患者中，HRV与ApoB/ApoA1比值的负相关性随肾功能减退而显著增强，呈现明确的eGFR分层效应。监测ApoB/ApoA1比值或有助于对肾功能不全患者的心血管自主神经风险进行分层管理。

关键词：糖尿病肾病；心率变异性；载脂蛋白；估算肾小球滤过率；分层相关性；肾功能
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Association between heart rate variability and apolipoprotein B / apolipoprotein A1 ratio in patients with diabetic kidney disease stratified by estimated glomerular filtration rate

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Abstract: Objective　To investigate the stratified correlation between heart rate variability (HRV) and the apolipoprotein B/apolipoprotein A1 (ApoB/ApoA1) ratio in patients with diabetic kidney disease (DKD) across different levels of estimated glomerular filtration rate (eGFR), aiming to provide a reference for the precise assessment of cardiovascular risk in this population. **Methods**　A cross-sectional study was conducted, selecting 258 patients with DKD admitted to Jiangsu Province Official Hospital from January 2022 to June 2024. Based on eGFR levels, patients were divided into the ≥60 group [eGFR≥60 mL/(min·1.73 m^2), n=95], the 30-<60 group [eGFR 30-<60 mL/(min·1.73 m^2), n=118], and the <30 group [eGFR<30 mL/(min·1.73 m^2), n=45]. 24-hour ambulatory electrocardiography was performed in all groups to analyze HRV parameters, and the ApoB/ApoA1 ratio was concurrently collected. Spearman correlation analysis and

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multiple linear regression analysis were used to explore the relationship between HRV and the ApoB/ApoA1 ratio. **Results** Statistically significant differences were observed among the three groups in age, duration of diabetes, serum creatinine, and urinary protein/creatinine ratio (P<0.05). As eGFR declined, the standard deviation of normal-to-normal intervals (SDNN) decreased (P<0.01), with SDNN decreasing by 10.8 ms for every 10 mL/(min·1.73 m^2) reduction in eGFR (P<0.01); the root mean square of successive differences (RMSSD) also showed a downward trend (P=0.003). The ApoB/ApoA1 ratio significantly increased with declining eGFR (P<0.01). Correlation analysis revealed a significant negative correlation between SDNN and the ApoB/ApoA1 ratio (r=−0.381, P<0.01), and this correlation was also statistically significant in the 30−<60 group (r=−0.356, P=0.001) and the <30 group (r=−0.487, P=0.003). Multiple linear regression analysis showed that eGFR(β=5.670, P<0.01) and the ApoB/ApoA1 ratio(β=−12.730, P=0.034) were independent influencing factors for SDNN. **Conclusion** In patients with DKD, the negative correlation between HRV and the ApoB/ApoA1 ratio strengthens significantly as renal function deteriorates, demonstrating a clear eGFR stratification effect. Monitoring the ApoB/ApoA1 ratio may be helpful for the stratified management of cardiovascular autonomic nerve risk in patients with renal insufficiency.

Keywords: Diabetic kidney disease; Heart rate variability; Apolipoprotein; Estimated glomerular filtration rate; Stratified correlation; Renal function

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糖尿病肾病(diabetic kidney disease, DKD)是糖尿病最严重和常见的慢性并发症,是终末期肾病的主要病因[1]。此外,DKD患者合并心血管疾病的风险较单纯糖尿病患者显著增加,心血管事件相关死亡率可为50%~80%,远超肾衰竭本身所致的死亡[2]。因此,探寻DKD患者心血管风险的早期评估与干预靶点至关重要。心脏自主神经病变是糖尿病的另一常见并发症,其中心率变异性(heart rate variability, HRV)作为评估心脏自主神经功能的无创、定量指标,在DKD患者中表现为显著降低[3]。既往研究表明,HRV在伴有蛋白尿或明显肾病的长期1型糖尿病患者中显著受损,且这种异常对肾功能随后的进行性恶化具有预测价值[4]。

载脂蛋白(apolipoprotein, Apo)作为脂质代谢的关键调节因子,在DKD的发生发展中发挥重要作用[5]。ApoB/ApoA1比值被广泛认为是评估心血管风险的强预测指标[6]。研究发现ApoB/ApoA1比值与2型糖尿病患者大血管和微血管事件风险增加相关[7]。在肾脏疾病方面,已有研究显示ApoB/ApoA1比值异常与肾脏疾病进展相关,ApoB/ApoA1比值增高与终末期肾病发展风险显著增加相关,且Apo代谢异常作为慢性肾脏病的共同特征,在不同类型肾脏疾病的进展中发挥重要作用[8]。

估算肾小球滤过率(estimated glomerular filtration rate, eGFR)是评估肾功能和分期、判断预后的金标准[9]。虽然糖尿病患者夜间血压下降减少和HRV降低已被证实与心血管发病率相关,但关于短期血压变异性的研究有限[10]。但关于在DKD这一特定人群中,随着肾功能的逐渐恶化,脂质代谢紊乱可能对心脏自主神经功能产生不同程度的影响,可能存在eGFR水平依赖性的分层特征。

基于此,本研究旨在探讨不同eGFR水平DKD患者HRV与ApoB/ApoA1比值的分层相关性,通过分析其关联强度变化,为DKD患者心血管风险的精准评估和分层管理提供新的参考依据。

1 对象与方法

1.1 *研究对象* 本研究为横断面设计,采用连续抽样方法,选取2022年1月至2024年6月在江苏省省级机关医院内分泌科住院治疗的DKD患者258例为研究对象。(1) 纳入标准:①符合2型糖尿病诊断标准;②符合DKD诊断标准[11],即存在持续性蛋白尿[尿蛋白/肌酐比值(urinary protein/creatinine ratio, UPCR)≥30 mg/g]伴或不伴eGFR下降;③年龄18~80岁;④糖尿病病程≥1年。(2) 排除标准:①1型糖尿病;②急性肾损伤;③非DKD;④存在严重心律失常、心房颤动或安装起搏器者;⑤合并急性感染、恶性肿瘤;⑥严重肝功能不全;⑦处于妊娠期或哺乳期的妇女;⑧无法获取或核实其完整用药史信息。本研究经江苏省省级机关医院伦理委员会批准[批准号:〔2024〕伦审第(055-2)号],所有患者均签署知情同意书。

1.2　资料收集及实验室检测　记录患者的基本信息，包括年龄、性别、身高、体质量、身体质量指数（body mass index，BMI）、糖尿病病程及用药史等。测量静息状态下血压，连续测量3次，取平均值作为其血压值。所有患者于入院次日清晨空腹采集肘正中静脉血5~8 mL。血液样本经离心处理后分离血清，并置于-80 ℃冰箱保存待测。使用全自动生化分析仪（Beckman Coulter AU5800，美国）检测空腹血糖、糖化血红蛋白（glycosylated hemoglobin，HbA_{1C}）、血清肌酐（serum creatinine，SCr）及血尿素氮等生化指标。采用免疫比浊法测定ApoA1和ApoB水平，相应试剂盒购自罗氏诊断公司（瑞士），并据此计算ApoB/ApoA1比值。血脂指标：总胆固醇（total cholesterol，TC）、高密度脂蛋白胆固醇（high-density lipoprotein cholesterol，HDL-C）及低密度脂蛋白胆固醇（low-density lipoprotein cholesterol，LDL-C）。采用慢性肾脏病流行病学合作研究组（Chronic Kidney Disease Epidemiology，CKD-EPI）公式计算eGFR评估肾功能：$eGFR = 141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{年龄} \times 1.018$（女性）。其中SCr单位为mg/dL（1 mg/dL≈88.4 μmol/L）；女性κ=0.7，α=-0.329；男性κ=0.9，α=-0.411。计算UPCR。

1.3　HRV检测与分析　按照欧洲心脏病学会（European Society of Cardiology，ESC）与北美起搏和电生理学会（North American Society of Pacing and Electrophysiology，NASPE）提出的指南进行HRV分析，采用24小时动态心电图监测系统（DMS 300-4A，美国DM公司）进行HRV检测。时域指标包括正常窦性心搏间期标准差（standard deviation of normal-to-normal intervals，SDNN）、相邻正常窦性心搏间期差值的均方根（root mean square of successive differences，RMSSD）、相邻正常窦性RR间期差值超过50 ms的百分比（percentage of adjacent normal-to-normal intervals differing by more than 50 ms，pNN50）。频域指标包括低频功率（low frequency，LF，即0.04~0.15 Hz频段的功率谱密度）、高频功率（high frequency，HF，即>0.15~0.40 Hz频段的功率谱密度）及LF/HF比值。所有指标均采用5 min时间窗口进行计算，并取24小时内的平均值作为最终分析值。

1.4　统计学方法　采用SPSS 26.0软件进行数据统计分析。连续变量采用Shapiro-Wilk检验验证其正态性，符合正态分布的计量资料以$\bar{x}\pm s$表示，多组间比较采用单因素方差分析。偏态分布的计量资料以$M(Q_1, Q_3)$表示，组间比较采用Kruskal-Wallis H检验。计数资料以例（%）表示，比较采用χ^2检验。相关性分析采用Spearman秩相关进行分析，采用Fisher's Z变换进行分层比较。将单因素分析中P<0.10的变量纳入多元线性回归分析，采用强制进入法构建回归模型，检验多重共线性和残差分布。偏态分布变量在回归分析前进行对数转换以使其接近正态分布。P<0.05为差异有统计学意义。

2　结　果

2.1　三组患者临床资料比较　本研究共纳入258例DKD患者，其中男性150例（58.1%），年龄（62.4±11.2）岁。根据eGFR水平将患者分为三组：≥60组[eGFR≥60 mL/(min·1.73 m²)，n=95]，30~<60组[eGFR 30~<60 mL/(min·1.73 m²)，n=118]和<30组[eGFR<30 mL/(min·1.73 m²)，n=45]。三组患者的临床资料见表1。三组在年龄、性别构成比、糖尿病病程、SCr

表1　三组患者临床资料比较

Tab.1　Comparison of clinical data among three groups of patients

指标	≥60组（n=95）	30~<60组（n=118）	<30组（n=45）	$F/\chi^2/H$值	P值
基本特征					
年龄（岁）[a]	58.3±10.1	64.2±11.0[c]	69.1±12.5[cd]	16.403	<0.001
男性[例（%）]	57（60.0）	69（58.5）	24（53.3）	0.568	0.753
BMI（kg/m²）[a]	25.7±3.8	26.3±4.2	26.9±4.6	1.374	0.255
糖尿病病程（年）[b]	8.0（5.0，13.0）	12.0（8.0，18.0）[c]	16.0（11.0，22.0）[cd]	12.850	0.003
HbA_{1C}（%）[b]	7.6（6.5，8.8）	8.0（6.9，9.1）	8.4（7.2，9.8）	4.920	0.087
肾功能指标					
SCr（μmol/L）[a]	98.6±22.4	158.7±31.2[c]	293.8±78.1[cd]	345.574	<0.001
UPCR（mg/g）[b]	680.0（380.0，1 120.0）	1 050.0（520.0，1 680.0）[c]	1 860.0（1 120.0，2 850.0）[cd]	18.470	0.002
心血管指标					
收缩压（mmHg）[a]	135.1±17.2	140.3±19.1	141.8±20.6	2.810	0.062
静息心率（次/分）[a]	76.8±13.4	79.2±14.6	81.3±15.1	1.664	0.191

注：[a]，数据以$\bar{x}\pm s$表示；[b]，数据以$M(Q_1, Q_3)$表示；与≥60组比较，[c]P<0.05；与30~59组比较，[d]P<0.05。

和UPCR方面差异有统计学意义(P<0.05)。

2.2　HRV 指标的组间比较　在时域指标中,SDNN 与 RMSSD 随 eGFR 下降而显著降低(P<0.01)。在频域指标中,LF 呈下降趋势(P=0.042),而 HF、pNN50 及 LF/HF 比值在三组间差异无统计学意义(P>0.05)。见表 2。线性趋势分析进一步表明,eGFR 每下降 10 mL/(min·1.73 m^2),SDNN 减少 10.8 ms(β=−1.08, P<0.01),RMSSD 减少 6.7 ms(β=−0.670, P=0.003)。

2.3　Apo 指标的组间比较　Apo 指标在不同 eGFR 组间差异有统计学意义。随着肾功能恶化,ApoA1 水平显著下降(P<0.01),而 ApoB 水平显著升高(P=0.008),致使 ApoB/ApoA1 比值显著增加(P=0.001)。相比之下,TC、HDL-C 和 LDL-C 在三组间比较差异均无统计学意义(P>0.05)。见表 3。

2.4　相关性分析

2.4.1　整体相关性分析　相关性分析结果显示,时域 HRV 指标与 ApoB/ApoA1 比值均呈显著负相关,其中 SDNN 相关性最强(r_s=−0.381, P<0.001),RMSSD 次之(r_s=−0.252, P=0.008)。频域指标与 ApoB/ApoA1 比值的相关性较弱,仅 LF 呈边缘显著负相关(r_s=−0.174, P=0.062),其余指标均无统计学意义。HRV 指标与 eGFR 均呈正相关,且时域指标相关性更强。SDNN 与 eGFR 相关性最强(r=0.486, P<0.01),RMSSD 次之(r=0.341, P<0.01)。频域指标中仅 LF 与 eGFR 呈显著正相关(r_s=0.198, P=0.028)。Apo 指标方面,ApoA1 与 eGFR 呈显著正相关(r_s=0.398, P<0.01),ApoB 与 eGFR 呈显著负相关(r_s=−0.287, P<0.01),ApoB/ApoA1 比值与 eGFR 呈显著负相关(r_s=−0.389, P<0.01)。见表 4。

2.4.2　分层相关性分析　按 eGFR 水平分层分析发现,SDNN 与 ApoB/ApoA1 比值的相关性存在明显的分层效应。在≥60 组,两者相关性无统计学意义(r=−0.198, P=0.067);在 30~<60 组 SDNN 与 ApoB/ApoA1 比值呈负相关(r=−0.356, P=0.001);在<30 组亦 SDNN 与 ApoB/ApoA1 比值呈负相关(r=−0.487, P=0.003)。经 Fisher's Z 变换检验,此分层效应具有统计学意义(Z=2.340, P=0.019)。

2.5　多因素回归分析　单因素分析显示,eGFR、ApoB/ApoA1 比值、年龄、糖尿病病程、HbA_{1C} 和收缩压与 SDNN 显著相关(P<0.10)。随后将上述变量全部纳入多元线性回归模型。最终模型具有统计学意义(F=24.573, P<0.01, R^2=0.378)。结果显示,在调整了其他混杂因素后,仅 eGFR 和 ApoB/ApoA1 比值是 SDNN 的独立影响因素(P<0.05)。eGFR 每增加 10 mL/(min·1.73 m^2),SDNN 增加 5.67 ms;ApoB/ApoA1 比值每增加 0.1,SDNN 减少 1.27 ms。而年龄、糖尿病病程和 HbA_{1C} 在调整其他因素后均无统计学意义(P>0.05)。见表 5。

表 2　三组 HRV 指标比较

Tab.2　Comparison of HRV indicators among three groups

项目	≥60组(n=95)	30~<60组(n=118)	<30组(n=45)	F/H值	P值
SDNN (ms)[a]	135.6±36.2	102.4±29.7[c]	86.3±24.8[c]	47.036	<0.001
RMSSD (ms)[a]	29.8±13.1	22.1±10.8[c]	17.2±8.6[cd]	22.005	<0.001
pNN50 (%)[b]	6.8(4.2,12.5)	5.1(2.8,9.6)[c]	3.2(1.4,6.8)[c]	8.950	0.011
LF (ms^2)[b]	956(742,1 387)	731(568,1 089)[c]	596(423,842)[c]	12.380	0.002
HF (ms^2)[b]	687(521,946)	578(442,748)	456(312,621)	7.820	0.020
LF/HF[a]	1.44±0.39	1.51±0.44	1.62±0.58	2.461	0.087

注:[a],数据以 $\bar{x}\pm s$ 表示;[b],数据以 $M(Q_1,Q_3)$ 表示;与≥60组比较,[c]P<0.05;与30~<60组比较,[d]P<0.05。

表 3　三组 Apo 指标比较　($\bar{x}\pm s$)

Tab.3　Comparison of APO indicators among three groups ($\bar{x}\pm s$)

项目	≥60组(n=95)	30~<60组(n=118)	<30组(n=45)	F值	P值
ApoA1(g/L)	1.3±0.2	1.2±0.2[a]	1.1±0.2[ab]	11.078	<0.001
ApoB(g/L)	0.9±0.3	1.0±0.3[a]	1.2±0.4[ab]	10.925	<0.001
ApoB/ApoA1 比值	0.7±0.2	0.9±0.3[a]	1.1±0.4[ab]	24.542	<0.001
TC(mmol/L)	4.8±1.1	5.1±1.2	5.3±1.4	3.071	0.048
HDL-C(mmol/L)	1.2±0.3	1.1±0.3	1.0±0.3	7.239	0.001
LDL-C(mmol/L)	2.9±0.8	3.1±0.9	3.2±1.0	2.202	0.113

注:与≥60组比较,[a]P<0.05;与30~<60组比较,[b]P<0.05。

表 4　整体相关性分析结果

Tab.4　Results of overall correlation analysis

变量	ApoB/ApoA1 比值		eGFR	
	r_s值	P值	r_s值	P值
HRV 指标				
SDNN	−0.381	<0.001	0.486	<0.001
RMSSD	−0.252	0.008	0.341	<0.001
pNN50	−0.128	0.156	0.164	0.089
LF	−0.174	0.062	0.198	0.028
HF	−0.142	0.124	0.151	0.106
Apo 指标				
ApoA1	−0.612	<0.001	0.398	<0.001
ApoB	0.543	<0.001	−0.287	0.002
ApoB/ApoA1 比值	1.000	—	−0.389	<0.001

表 5　SDNN 影响因素的单因素和多因素线性回归分析

Tab.5　Univariate and multivariate linear regression analysis of factors affecting SDNN

变量	单因素分析				多因素分析			
	β	*SE*	*P* 值	95%*CI*	*β*	*SE*	*P* 值	95%*CI*
主要变量								
eGFR	7.23	0.92	<0.001	5.42~9.04	5.67	1.21	<0.001	3.28~8.06
ApoB/ApoA1 比值	−18.45	4.74	0.001	−27.82~−9.08	−12.73	5.98	0.034	−24.48~−0.98
协变量								
年龄	−0.89	0.30	0.003	−1.47~−0.31	−0.54	0.31	0.082	−1.15~0.07
糖尿病病程	−0.67	0.30	0.028	−1.27~−0.07	−0.23	0.28	0.412	−0.78~0.32
HbA_{1c}	−4.12	1.68	0.015	−7.43~−0.81	−2.16	1.94	0.267	−5.98~1.66
收缩压	−0.24	0.13	0.067	−0.50~0.02	—	—	—	—

注：eGFR 变量为每上升 10 mL/(min·1.73 m^2)。

3　讨　论

本研究通过系统分析不同 eGFR 水平的 DKD 患者，揭示了 HRV 与 ApoB/ApoA1 比值之间存在显著的 eGFR 分层相关性。结果发现，随着肾功能恶化，ApoB/ApoA1 比值对心脏自主神经功能的负性影响逐渐增强。本研究显示，随着 eGFR 水平下降，DKD 患者的 HRV 指标 SDNN 和 RMSSD 呈显著递减趋势。这一发现与 Mylonopoulou 等[16]在终末期肾病患者中的报道一致，该作者认为尿毒症毒素的蓄积和慢性炎症状态是导致自主神经功能受损的重要原因。有研究提示肾功能恶化与心脏自主神经功能损害之间存在直接的病理生理联系[13]。值得关注的是，本研究发现 ApoB/ApoA1 比值随肾功能恶化显著变化，而传统血脂指标（TC、HDL-C、LDL-C）在三组间差异无统计学意义，可能反映了 ApoB/ApoA1 比值作为脂质代谢紊乱评估指标的独特敏感性。HRV 的降低反映了心脏自主神经系统功能的受损，特别是迷走神经张力的减弱[14]。在 DKD 进展过程中，代谢性酸中毒、电解质紊乱、尿毒症毒素蓄积以及慢性微炎症状态均可直接或间接影响自主神经系统的正常功能[15]。此外，糖尿病本身引起的微血管病变也可能累及支配心脏的自主神经纤维，加重心脏自主神经功能障碍[16]。

本研究发现，随着 eGFR 下降，ApoA1 水平降低而 ApoB 水平升高，导致 ApoB/ApoA1 比值进行性增加。这一趋势与 Chronic KIDNEY Disease Prognosis Consortium 的大型队列研究结果相符[17]，进一步证实了脂蛋白代谢紊乱与肾功能损害程度的密切关联。值得注意的是，传统血脂指标如 TC、HDL-C 和 LDL-C 在不同 eGFR 组间差异无统计学意义，而 Apo 指标表现出明显的组间差异，这一现象可能反映了 ApoB/ApoA1 比值作为脂质代谢异常标志物的独特优势[8]。ApoB/ApoA1 比值整合了致动脉粥样硬化脂蛋白和抗动脉粥样硬化脂蛋白的信息，能够更准确地反映脂质代谢的整体状况[18]。肾功能恶化导致 Apo 代谢异常的机制可能包括：（1）肾脏清除脂蛋白能力下降；（2）尿毒症毒素影响肝脏脂蛋白合成；（3）慢性炎症状态改变脂蛋白代谢酶活性；（4）胰岛素抵抗加重脂质代谢紊乱[19]。

本研究发现 SDNN 与 ApoB/ApoA1 比值存在显著负相关，且这种相关性在不同 eGFR 水平呈现分层效应。在≥60 组中，两者相关性无统计学意义；在 30~<60 组中，相关性达到统计学意义；在<30 组中，相关性进一步增强。分层效应提示随着肾功能恶化，脂质代谢异常对心脏自主神经功能的影响逐渐加重[20]。第一，Apo 代谢异常可能通过促进动脉粥样硬化进程，影响支配心脏的自主神经血供，导致神经功能受损[21]。第二，ApoB 富含的脂蛋白颗粒容易被氧化修饰，产生的氧化性低密度脂蛋白可直接损伤神经元，影响神经传导功能[22]。第三，脂质代谢紊乱可能加重慢性炎症反应，而炎症介质如肿瘤坏死因子-α、白细胞介素-6 等已被证实能够直接抑制心脏迷走神经活性[23]。本研究中<30 组中观察到最强的相关性，其机制可能是在肾功能严重受损的患者中，协同作用导致 ApoB/ApoA1 比值对 HRV 的影响更加显著[24]。

多元线性回归分析显示，在调整了多种传统危险因素后，eGFR 和 ApoB/ApoA1 比值仍是 SDNN 的独立影响因素，ApoB/ApoA1 比值对 SDNN 的影响在多因素模型中发生了显著变化，其回归系数从单因素分析的 β=−18.450 减弱至 β=−12.730，提示 eGFR 可能在 ApoB/ApoA1 比值影响 HRV 的过程中发挥部分中介作用。此外，ApoB/ApoA1 比值可能成为评估 DKD 患者心血管风险的新的生物标志物；其次，针对性地改善脂质代谢异常可能有助于保护心脏自主神经功能。既往研究表明，他汀类药物不仅能够降低胆固醇水平，还能够改善载脂蛋白谱，为 DKD 患者的心血

管保护提供新的治疗策略[25]。

本研究存在一定局限性。首先，横断面研究无法推断因果关系。其次，尽管已控制多种混杂因素，但残余混杂的可能性依然存在。再者，样本量相对有限，特别是<30组，可能影响统计效力。尽管如此，本研究结果仍具有重要的临床应用价值。Apo检测相对简便且成本较低，ApoB/ApoA1比值有望成为DKD患者心血管风险分层的实用工具。结合HRV检测，可以更全面地评估患者的心血管状态，为个体化治疗策略的制定提供参考依据。未来研究应采用前瞻性队列设计，进一步验证ApoB/ApoA1比值对心血管事件的预测价值，并探索针对性干预措施的效果。

综上所述，本研究表明在DKD患者中，HRV与ApoB/ApoA1比值的负相关性随肾功能减退而显著增强。对于eGFR<60 mL/(min·1.73 m^2)的患者，定期监测ApoB/ApoA1比值，或有助于更精准地评估其心血管自主神经风险并指导脂代谢管理。

利益冲突　无

参考文献

[1] Samsu N. Diabetic nephropathy: challenges in pathogenesis, diagnosis, and treatment[J]. Biomed Res Int, 2021, 2021: 1497449.

[2] 杨烨, 王金洋, 王新玲. 糖尿病肾病致心脏损害机制的研究进展[J]. 山东医药, 2024, 64(25): 108-111.

[3] 罗彦相, 张佳, 蔡青云, 等. 糖尿病心脏自主神经病变的研究进展[J]. 中国心血管杂志, 2025, 30(1): 16-21.

[4] Astrup AS, Tarnow L, Rossing P, et al. Cardiac autonomic neuropathy predicts cardiovascular morbidity and mortality in type 1 diabetic patients with diabetic nephropathy[J]. Diabetes Care, 2006, 29(2): 334-339.

[5] 苗佳盟. TyG指数、LDL/ApoB与2型糖尿病肾病的相关性研究[D]. 保定: 河北大学, 2024.

[6] Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study[J]. Lancet, 2004, 364(9438): 937-952.

[7] Pikkemaat M, Woodward M, Geijerstam PA, et al. Lipids and apolipoproteins and the risk of vascular disease and mortality outcomes in women and men with type 2 diabetes in the ADVANCE study[J]. Diabetes Obes Metab, 2024, 26(12): 5669-5680.

[8] Birn H, Spiegelstein O, Christensen EI, et al. Renal tubular reabsorption of folate mediated by folate binding protein 1[J]. J Am Soc Nephrol, 2005, 16(3): 608-615.

[9] Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate[J]. Ann Intern Med, 2009, 150(9): 604-612.

[10] Spallone V, Ziegler D, Freeman R, et al. Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management[J]. Diabetes Metab Res Rev, 2011, 27(7): 639-653.

[11] 黄秉文. 中美两种2型糖尿病肾病诊断标准中疾病进展及预后因素对比[J]. 医学信息, 2018, 31(22): 68-72.

[12] Mylonopoulou M, Tentolouris N, Antonopoulos S, et al. Heart rate variability in advanced chronic kidney disease with or without diabetes: midterm effects of the initiation of chronic haemodialysis therapy[J]. Nephrol Dial Transplant, 2010, 25(11): 3749-3754.

[13] Chandra P, Sands RL, Gillespie BW, et al. Predictors of heart rate variability and its prognostic significance in chronic kidney disease[J]. Nephrol Dial Transplant, 2012, 27(2): 700-709.

[14] Fukuta H, Hayano J, Ishihara S, et al. Prognostic value of heart rate variability in patients with end-stage renal disease on chronic haemodialysis[J]. Nephrol Dial Transplant, 2003, 18(2): 318-325.

[15] Zoccali C, Mallamaci F, Parlongo S, et al. Plasma norepinephrine predicts survival and incident cardiovascular events in patients with end-stage renal disease[J]. Circulation, 2002, 105(11): 1354-1359.

[16] Vinik AI, Ziegler D. Diabetic cardiovascular autonomic neuropathy[J]. Circulation, 2007, 115(3): 387-397.

[17] Chronic Kidney Disease Prognosis Consortium. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis[J]. Lancet, 2010, 375(9731): 2073-2081.

[18] Sierra-Johnson J, Fisher R M, Romero-Corral A, et al. Concentration of apolipoprotein B is comparable with the apolipoprotein B/apolipoprotein A-I ratio and better than routine clinical lipid measurements in predicting coronary heart disease mortality: findings from a multi-ethnic US population[J]. Eur Heart J, 2009, 30(6): 710-717.

[19] Vaziri ND. Dyslipidemia of chronic renal failure: the nature, mechanisms, and potential consequences[J]. Am J Physiol Renal Physiol, 2006, 290(2): F262-F272.

[20] Shi W, Zhang J, Chen D, et al. Heart rate variability and chronic kidney disease in patients with type 2 diabetes[J]. Appl Bionics Biomech, 2022, 2022: 2475750.

[21] Thayer JF, Yamamoto SS, Brosschot JF. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors[J]. Int J Cardiol, 2010, 141(2): 122-131.

[22] Tsimikas S, Miller YI. Oxidative modification of lipoproteins: mechanisms, role in inflammation and potential clinical applications in cardiovascular disease[J]. Curr Pharm Des, 2011, 17(1): 27-37.

[23] Kelly MJ, Breathnach C, Tracey KJ, et al. Manipulation of the inflammatory reflex as a therapeutic strategy[J]. Cell Rep Med, 2022, 3(7): 100696.

[24] Huang CJ, Webb HE, Zourdos MC, et al. Cardiovascular reactivity, stress, and physical activity[J]. Front Physiol, 2013, 4: 314.

[25] Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines[J]. Circulation, 2014, 129(25 Suppl 2): S1-S45.

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