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Dose-response relationship between glycated albumin/glycated hemoglobin ratio and renal lesion progression in patients with type 2 diabetes mellitus

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Abstract: Objective To analyze the dose-response relationship between the glycated albumin (GA)/glycated hemoglobin (HbA1c) ratio and renal lesion progression in patients with type 2 diabetes mellitus (T2DM) using a restricted cubic spline (RCS) model, and to provide a reference for predicting renal lesion progression. **Methods** A total of 90 T2DM patients admitted to Anqing First People's Hospital Affiliated to Anhui Medical University from August 2021 to May 2024 were enrolled, and followed up until May 2025 (the endpoint event was renal lesion progression). The patients were divided into the progression group ($n=19$) and non-progression group ($n=71$) according to whether renal lesion progression occurred. The GA/HbA1c ratio and other clinical data were compared between the two groups. Multivariate logistic regression analysis was used to identify the risk factors for renal lesion progression in T2DM patients. The RCS model was applied to analyze the dose-response relationship between the GA/HbA1c ratio and renal lesion progression in T2DM patients, and a receiver operating characteristic (ROC) curve was plotted to evaluate the predictive value of the GA/HbA1c ratio for renal lesion progression in T2DM patients.

Results The proportion of hypertension, as well as the levels of serum creatinine, blood urea nitrogen, serum uric acid, cystatin C, and GA/HbA1c ratio in the progression group were higher than those in the non-progression group ($P<0.05$). Logistic regression analysis showed that hypertension, elevated blood urea nitrogen, cystatin C, and GA/HbA1c ratio were risk factors for renal lesion progression in T2DM patients ($P<0.05$). The RCS model revealed a non-linear dose-response relationship between the GA/HbA1c ratio and renal lesion progression in T2DM patients ($P=0.034$, P for nonlinear=0.040), and the risk of renal lesion progression events in T2DM patients gradually increased with the increase of the GA/HbA1c ratio. The ROC curve showed that the area under the curve of the GA/HbA1c ratio for predicting renal lesion progression in T2DM patients was 0.869 (95%CI: 0.820-0.912), with an optimal cut-off value of 2.025, a sensitivity of 85.00%, and a specificity of 75.00%. **Conclusion** There is a nonlinear dose-response relationship between the GA/HbA1c ratio and renal lesion progression in T2DM patients. An elevated GA/HbA1c ratio is associated with an increased risk of renal progression events in T2DM patients, and has good predictive value for the occurrence of renal lesion progression events in T2DM patients.

Keywords: Type 2 diabetes mellitus; Diabetic kidney disease; Glycated albumin; Glycated hemoglobin; Restricted cubic spline

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Type 2 diabetes mellitus (T2DM), a common chronic disease, has been increasing in incidence globally year by year [1]. Diabetic kidney disease (DKD) is one of the most important microvascular complications of T2DM. It not only seriously affects the quality of life of patients but also is an important cause of end-stage renal disease, imposing a heavy economic burden on society and families [2]. As the disease progresses, once obvious renal lesions occur in T2DM patients, treatment is often challenging. Therefore, early identification and intervention of risk factors for renal progression are crucial. Poor glycemic control is one of the key factors for the development of renal lesions in T2DM patients [3]. Currently, glycated hemoglobin (HbA1c) is commonly used in clinical practice to evaluate long-term glycemic control in patients, reflecting the average blood glucose level over the past 2-3 months. However, HbA1c has certain limitations in reflecting short-term blood glucose

fluctuations [4]. Glycated albumin (GA) mainly reflects glycemic control over the past 2-4 weeks. Compared with HbA1c, GA can reflect recent blood glucose changes more timely [5]. In recent years, the GA/HbA1c ratio has gradually attracted attention. Studies have shown that an increase in this ratio may be closely associated with an increased risk of diabetic chronic complications [6], but its relationship with the progression of renal lesions in T2DM patients remains unclear. The restricted cubic spline (RCS) model is a flexible nonparametric regression method that can effectively explore complex nonlinear relationships between continuous variables, avoiding the limitation of preassuming variable relationships [7]. This study aims to analyze the dose-response relationship between the GA/HbA1c ratio and the progression of renal lesions in T2DM patients based on the RCS model, providing new ideas and theoretical basis for clinical early intervention and prevention of DKD.

1 Materials and Methods

1.1 General Information

A total of 90 patients with T2DM who received treatment at the Anqing First People's Hospital Affiliated to Anhui Medical University from August 2021 to May 2024 were retrospectively enrolled, including 54 males and 36 females, aged 45 to 75 (60 ± 15) years.

Inclusion criteria:

- (1) Definite diagnosis of T2DM;
- (2) Aged ≥ 18 years;
- (3) Complete clinical data available;
- (4) Voluntarily signed informed consent form.

Exclusion criteria:

- (1) Type 1 diabetes mellitus or other special types of diabetes mellitus;
- (2) Complicated with severe diseases of liver, heart, brain or other vital organs;
- (3) Pregnant or lactating women;
- (4) History of severe infection, trauma or major surgery within the recent 3 months;
- (5) Currently taking special medications that may affect blood glucose levels or renal function.

This study was approved by the Medical Ethics Committee of the Anqing First People's Hospital (Ethics Approval No. AQYY-YXLL-LWLL-69).

1.2 Methods

1.2.1 Calculation of GA/HbA1c Ratio

On the morning after admission, 3 mL of fasting venous blood was collected from each patient. GA levels were measured using an enzymatic method, and HbA1c levels were detected by high-performance liquid chromatography. The GA/HbA1c ratio was then calculated. The detection system and matching reagents were all products from Roche, and all experimental operations strictly followed the standard operating procedures provided by the manufacturer.

1.2.2 Data Collection

Clinical data of patients within 24 hours after admission were collected, including gender, age, body mass index (BMI), smoking history, drinking history, family history of diabetes, duration of diabetes, comorbidities (hypertension, coronary heart disease), white blood cell count, platelet count, cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), serum creatinine, blood urea nitrogen, serum uric acid, cystatin C, fasting blood glucose, and GA/HbA1c ratio.

1.2.3 Follow-up and Grouping

Regular outpatient follow-up combined with telephone follow-up was adopted, with the follow-up deadline set as May 31, 2025. The primary endpoint was the progression of kidney disease, which was defined as meeting any of the following criteria: doubling of serum creatinine level, a decrease in estimated glomerular filtration rate (eGFR) by more than 25%, urinary albumin-to-creatinine ratio (UACR) > 300 mg/g, requirement for renal replacement therapy, or occurrence of all-cause death [8]. According to the follow-up results, patients were divided into the progression group (19 cases) and the non-progression group (71 cases).

1.3 Statistical Methods

Data analysis was performed using SPSS 28.0 software. Count data were expressed as n (%), and analyzed using the χ^2 test or corrected χ^2 test. Measurement data conforming to a normal distribution were expressed as $\bar{x} \pm s$, and analyzed using the t test. A logistic regression model was used to analyze the influencing factors of renal lesion progression in T2DM patients. A RCS model was applied to analyze the dose-response relationship between the GA/HbA1c ratio and renal lesion progression in T2DM patients. A receiver operating characteristic (ROC) curve was used to evaluate the predictive value of the GA/HbA1c ratio for renal lesion progression in T2DM patients. A P value < 0.05 was considered statistically significant.

2 Results

2.1 Comparison of Clinical Data between Progression Group and Non-progression Group

The proportion of hypertension, levels of serum creatinine, blood urea nitrogen, serum uric acid, cystatin C, and GA/HbA1c ratio in the progression group were significantly higher than those in the non-progression group ($P < 0.05$). No statistically significant differences were observed between the two groups in terms of gender, age, BMI, smoking history, drinking history, family history of diabetes, duration of diabetes, proportion of coronary heart disease, as well as levels of white blood cell count, platelet count, cholesterol, triglycerides, HDL-C, LDL-C, and fasting blood glucose ($P > 0.05$). See **Table 1**.

2.2 Analysis of Risk Factors for Renal Progression in T2DM Patients

Taking the occurrence of renal lesion progression in T2DM patients as the dependent variable (yes=1, no=0), and the clinical parameters with $P < 0.05$ in Table 1 [hypertension (yes=1, no=0); serum creatinine, blood urea nitrogen, serum uric acid, cystatin C, and GA/HbA1c ratio as continuous variables with original values] as independent variables, logistic regression analysis was performed. The results showed that complicated hypertension, as well as high levels of blood urea nitrogen, cystatin C, and GA/HbA1c ratio were independent risk factors for renal lesion progression in T2DM patients ($P < 0.05$). See **Table 2**.

2.3 Dose-response Relationship between GA/HbA1c Ratio and Renal Lesion Progression in T2DM Patients

In the RCS model, the GA/HbA1c ratio was set as the abscissa, and the predicted OR as the ordinate, with the shaded area representing the 95% CI. A nonlinear dose-response relationship was found between the GA/HbA1c ratio and renal lesion progression in T2DM patients ($P = 0.034$, P for nonlinearity = 0.040). When the GA/HbA1c ratio was ≤ 2.025 (corresponding to the inflection point of the curve), the risk of renal lesion progression in T2DM patients increased relatively

slowly; when the GA/HbA1c ratio exceeded 2.025, the risk of renal lesion progression rose rapidly with the increase of the ratio. See Figure 1.

2.4 Predictive Value of GA/HbA1c Ratio for Renal Lesion Progression in T2DM Patients

The ROC curve results showed that the area under the curve (AUC) of the GA/HbA1c ratio for predicting renal lesion progression in T2DM patients was 0.869 (95%CI: 0.820-0.912), with an optimal cut-off value of 2.025, corresponding to a sensitivity of 85.00% and a specificity of 75.00%. See Figure 2.

Tab.1 Comparison of clinical data between the progression group and the non-progression group

Item	Progression group (n=19)	Non-progression group (n=71)	χ^2/t value	P value
Gender [n (%)]			0.100	0.752
Male	12 (63.16)	42 (59.15)		
Female	7 (36.84)	29 (40.85)		
Age [n (%)]			2.802	0.094
< 60 years	8 (42.11)	45 (63.38)		
≥ 60 years	11 (57.89)	26 (36.62)		
BMI (kg/m ² , $\bar{x}\pm s$)	25.77 ± 4.96	25.02 ± 5.26	0.558	0.578
Smoking history [n (%)]	12 (63.16)	32 (45.07)	1.962	0.161
Alcohol consumption history [n (%)]	8 (42.11)	26 (36.62)	0.192	0.661
Family history of diabetes [n (%)]	5 (26.32)	10 (14.08)	0.854	0.355
Duration of diabetes (years, $\bar{x}\pm s$)	11.94 ± 3.26	11.52 ± 4.47	0.383	0.703
Comorbidities [n (%)]				
Hypertension	12 (63.16)	12 (16.90)	16.400	< 0.001
Coronary heart disease	8 (42.11)	25 (35.21)	0.307	0.580
White blood cell count (×10 ⁹ /L, $\bar{x}\pm s$)	6.88 ± 2.12	7.84 ± 2.71	1.429	0.156
Platelet count (×10 ⁹ /L, $\bar{x}\pm s$)	198.49 ± 48.64	207.61 ± 44.56	0.780	0.438
Cholesterol (mmol/L, $\bar{x}\pm s$)	3.75 ± 1.41	3.94 ± 1.25	0.599	0.551
Triglycerides (mmol/L, $\bar{x}\pm s$)	1.73 ± 0.55	1.74 ± 0.63	0.063	0.950
HDL-C (mmol/L, $\bar{x}\pm s$)	1.21 ± 0.30	1.27 ± 0.43	0.571	0.569
LDL-C (mmol/L, $\bar{x}\pm s$)	2.30 ± 0.72	2.13 ± 0.53	1.147	0.255
Serum creatinine (μmol/L, $\bar{x}\pm s$)	62.35 ± 8.07	55.12 ± 8.47	3.336	0.001
Blood urea nitrogen (mmol/L, $\bar{x}\pm s$)	8.56 ± 2.96	5.89 ± 1.52	5.426	< 0.001
Serum uric acid (μmol/L, $\bar{x}\pm s$)	365.21 ± 47.06	331.92 ± 32.66	3.573	0.001
Cystatin C (mmol/L, $\bar{x}\pm s$)	1.51 ± 0.45	0.98 ± 0.52	4.378	< 0.001
Fasting blood glucose (mmol/L, $\bar{x}\pm s$)	12.99 ± 2.75	11.87 ± 2.44	1.730	0.087
GA/HbA1c ratio ($\bar{x}\pm s$)	1.97 ± 0.36	1.74 ± 0.22	3.492	< 0.001

Tab.2 Multivariate logistic regression analysis of factors influencing renal lesion progression in patients with T2DM

Items	β	SE	Wald χ^2	P value	OR value	95% CI
Hypertension	2.078	0.917	5.132	0.023	7.987	1.324~48.189
Serum creatinine	0.098	0.054	3.295	0.069	1.103	0.992~1.226
Blood urea nitrogen	0.871	0.321	7.350	0.007	2.389	1.273~4.482
Serum uric acid	0.015	0.012	1.462	0.227	1.015	0.991~1.039
Cystatin C	2.176	0.925	5.534	0.019	8.807	1.437~53.976
GA/HbA1c ratio	3.831	1.582	5.864	0.015	46.103	2.075~1 024.129

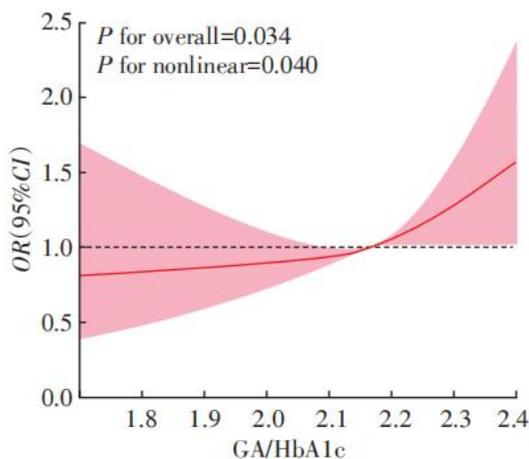


Fig.1 Dose-response relationship between the GA/HbA1c ratio and renal lesion progression in patients with T2DM

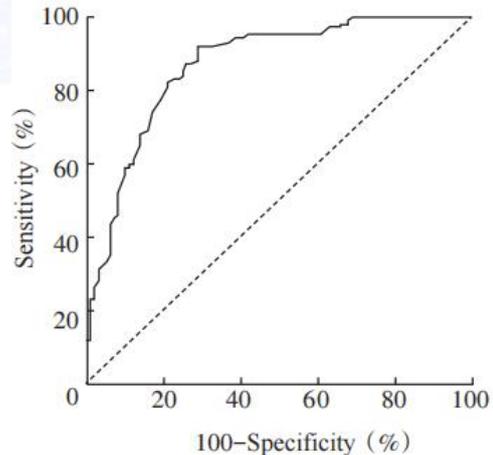


Fig.2 The ROC curve of the GA/HbA1c ratio in predicting renal progression in patients with T2DM

3 Discussion

This study investigated the dose-response relationship between the GA/HbA1c ratio and renal progression in patients with T2DM using a RCS model. The results showed a significant nonlinear positive correlation between the GA/HbA1c ratio and the risk of renal lesion progression, with a clear dose-dependent pattern. This finding differs from previous studies that reported associations of GA or HbA1c alone with DKD [9-10]. The underlying mechanism may be that an elevated GA/HbA1c ratio reflects an imbalance between short-term glycemic fluctuations and long-term glycemic control. This metabolic disorder may accelerate renal injury through multiple pathways: on one hand, glycemic fluctuations exacerbate oxidative stress and inflammatory responses, promoting glomerular basement membrane thickening and mesangial matrix expansion [11-12]. On the other hand, persistent hyperglycemia leads to the accumulation of advanced glycation end products, which aggravate renal fibrosis by activating the receptor for advanced glycation end products [13-14]. Notably, this dose-response relationship exhibits nonlinear characteristics, suggesting a potential threshold effect, which has important guiding value for clinical risk stratification.

In terms of predictive efficacy, the GA/HbA1c ratio demonstrated excellent diagnostic performance (AUC=0.869), with superior predictive value compared to single detection of traditional indicators such as HbA1c [15]. This result is consistent with the findings of Wang *et al.* [16], who reported a stronger correlation between the GA/HbA1c ratio and diabetic microvascular complications. Furthermore, this study found that when the optimal cut-off value of the GA/HbA1c ratio was set at 2.025, the sensitivity and specificity for predicting renal progression in T2DM patients were 85.00% and 75.00%, respectively. This critical value can serve as an important reference for clinical early warning. Unlike previous studies, this study used the RCS model innovatively to reveal the non-linear association between the GA/HbA1c ratio and renal lesion progression. This addressed the limitations of traditional linear analysis methods. This nonlinear relationship suggests that when the GA/HbA1c ratio exceeds a specific threshold, the risk of renal injury increases rapidly, which may be related to the "metabolic memory" effect induced by glycemic fluctuations [17].

In addition to the GA/HbA1c ratio, this study confirmed the roles of traditional risk factors such as hypertension, blood urea nitrogen, and cystatin C, which is consistent with existing literature reports [18-21]. However, these indicators mostly reflect the consequences rather than the causes of renal injury. In contrast, the GA/HbA1c ratio, as a dynamic indicator of glycemic control quality, has earlier warning value. It is worth mentioning that patients with an elevated GA/HbA1c ratio often exhibit more significant metabolic disorder characteristics [22], suggesting that this indicator may integrate information on multiple metabolic

abnormalities. From a clinical application perspective, the measurement of the GA/HbA1c ratio has the advantages of simple operation and low cost, and it is not affected by factors such as hemoglobin variants, making it suitable as a routine monitoring indicator. Combined with the results of ROC curve analysis, it is recommended to strengthen renal protection interventions for T2DM patients with a GA/HbA1c ratio >2.025, including optimizing glycemic control strategies and enhancing blood pressure management.

In conclusion, this study revealed a nonlinear dose-response relationship between the GA/HbA1c ratio and renal lesion progression in T2DM patients using the RCS model, confirming that this ratio is an independent risk factor and effective predictor of renal lesion progression. The innovative values of this study are as follows: first, it used an advanced statistical model to characterize the nonlinear association features; second, it determined a clinically applicable early warning threshold; third, it provided a new perspective for mechanistic research on glycemic fluctuations and renal injury. However, as a single-center observational study, this study has limitations such as a limited sample size and relatively short follow-up time. Future studies are needed to validate these findings in larger prospective cohorts and further explore the specific molecular mechanisms by which the GA/HbA1c ratio affects renal function. From the perspective of clinical translation, it is recommended to include the GA/HbA1c ratio in the routine monitoring system for T2DM patients and implement early interventions for high-risk individuals, which may provide new ideas for the prevention and treatment of DKD.

Conflict of interest The authors declare no competing interest

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· 论 著 ·

糖化白蛋白/糖化血红蛋白比值与2型糖尿病患者肾脏病变进展间的剂量-反应关系

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摘要: **目的** 基于限制性立方样条(RCS)模型分析糖化白蛋白(GA)/糖化血红蛋白(HbA1c)比值与2型糖尿病(T2DM)患者肾脏病变进展间的剂量-反应关系,为预测肾脏病变进展提供参考。**方法** 回顾性纳入安徽医科大学附属安庆第一人民医院2021年8月至2024年5月收治的T2DM患者90例,随访至2025年5月(终点事件为肾脏病变进展),根据是否发生肾脏病变进展事件分为进展组($n=19$)和无进展组($n=71$),比较两组GA/HbA1c比值及其他临床资料,采用多因素logistic回归模型分析影响T2DM患者肾脏病变进展的危险因素,采用RCS模型分析GA/HbA1c比值与T2DM患者肾脏进展的剂量-反应关系,并绘制受试者工作特征(ROC)曲线分析GA/HbA1c比值对T2DM患者肾脏病变进展的预测价值。**结果** 进展组高血压比例、血肌酐、血尿素氮、血尿酸、胱抑素C、GA/HbA1c比值高于无进展组($P<0.05$)。Logistic回归分析结果显示,合并高血压和血尿素氮、胱抑素C、GA/HbA1c比值升高是T2DM患者肾脏病变进展的独立危险因素($P<0.05$)。RCS模型显示GA/HbA1c比值与T2DM患者肾脏病变进展呈非线性剂量-反应关系($P=0.034$,非线性 $P=0.040$),T2DM患者肾脏病变进展事件发生风险随着GA/HbA1c比值的上升而逐渐增加。ROC曲线显示,GA/HbA1c比值预测T2DM患者肾脏病变进展的曲线下面积为0.869(95%CI:0.820~0.912),最佳截断值为2.025,灵敏度、特异度分别为85.00%、75.00%。**结论** GA/HbA1c比值与T2DM患者肾脏病变进展之间存在非线性剂量-反应关系,升高的GA/HbA1c比值与T2DM患者肾脏病变进展事件发生风险增加有关,对T2DM患者肾脏病变进展事件的发生有良好预测价值。

关键词: 2型糖尿病; 糖尿病肾病; 糖化白蛋白; 糖化血红蛋白; 限制性立方样条

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Abstract: Objective To analyze the dose-response relationship between the glycated albumin (GA)/glycated hemoglobin (HbA1c) ratio and renal lesion progression in patients with type 2 diabetes mellitus (T2DM) using a restricted cubic spline (RCS) model, and to provide a reference for predicting renal lesion progression. **Methods** A total of 90 T2DM patients admitted to Anqing First People's Hospital Affiliated to Anhui Medical University from August 2021 to May 2024 were enrolled, and followed up until May 2025 (the endpoint event was renal lesion progression). The patients were divided into the progression group ($n=19$) and non-progression group ($n=71$) according to whether renal lesion progression occurred. The GA/HbA1c ratio and other clinical data were compared between the two groups. Multivariate logistic regression analysis was used to identify the risk factors for renal lesion progression in T2DM patients. The RCS model was applied to analyze the dose-response relationship between the GA/HbA1c ratio and renal lesion progression in T2DM patients, and a receiver operating characteristic (ROC) curve was plotted to evaluate the predictive value of

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the GA/HbA1c ratio for renal lesion progression in T2DM patients. **Results** The proportion of hypertension, as well as the levels of serum creatinine, blood urea nitrogen, serum uric acid, cystatin C, and GA/HbA1c ratio in the progression group were higher than those in the non - progression group ($P<0.05$). Logistic regression analysis showed that hypertension, elevated blood urea nitrogen, cystatin C, and GA/HbA1c ratio were risk factors for renal lesion progression in T2DM patients ($P<0.05$). The RCS model revealed a non-linear dose-response relationship between the GA/HbA1c ratio and renal lesion progression in T2DM patients ($P=0.034$, P for nonlinear=0.040), and the risk of renal lesion progression events in T2DM patients gradually increased with the increase of the GA/HbA1c ratio. The ROC curve showed that the area under the curve of the GA/HbA1c ratio for predicting renal lesion progression in T2DM patients was 0.869 (95%CI:0.820-0.912), with an optimal cut-off value of 2.025, a sensitivity of 85.00%, and a specificity of 75.00%. **Conclusion** There is a nonlinear dose - response relationship between the GA/HbA1c ratio and renal lesion progression in T2DM patients. An elevated GA/HbA1c ratio is associated with an increased risk of renal lesion progression events in T2DM patients, and has good predictive value for the occurrence of renal lesion progression events in T2DM patients.

Keywords: Type 2 diabetes mellitus; Diabetic kidney disease; Glycated albumin; Glycated hemoglobin; Restricted cubic spline

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2型糖尿病(type 2 diabetes mellitus, T2DM)作为一种常见的慢性病,其发病率在全球范围内呈逐年上升趋势^[1]。糖尿病肾病(diabetic kidney disease, DKD)是T2DM最主要的微血管并发症之一,不仅严重影响患者生活质量,也是导致终末期肾病的重要原因,给社会和家庭带来了沉重的经济负担^[2]。随着病情进展,T2DM患者一旦出现明显的肾脏病变,其治疗往往较为棘手,因此早期识别和干预肾脏进展的危险因素至关重要。血糖控制不佳是T2DM患者发生肾脏病变的关键因素之一^[3]。目前,临床上常用糖化血红蛋白(glycated hemoglobin, HbA1c)来评估患者的长期血糖控制情况,其反映了过去2~3个月的平均血糖水平,但HbA1c在反映短期血糖波动方面存在一定局限性^[4]。糖化白蛋白(glycated albumin, GA)则主要反映过去2~4周的血糖控制情况,与HbA1c相比,GA能更及时地反映近期血糖变化^[5]。近年来,GA/HbA1c比值逐渐受到关注,有研究表明该比值升高可能与糖尿病慢性并发症的发生风险增加密切相关^[6],但其与T2DM患者肾脏病变进展之间的关系尚不明确。限制性立方样条(restricted cubic spline, RCS)模型是一种灵活的非参数回归方法,能够有效探索连续变量之间复杂的非线性关系,避免对变量关系进行预先假设的局限性^[7]。本研究旨在基于RCS模型,分析GA/HbA1c比值与T2DM患者肾脏病变进展间的剂量-反应关系,为临床早期干预和防治DKD提供新的思路和理论依据。

1 资料与方法

1.1 一般资料 回顾性选取2021年8月至2024年5

月在安徽医科大学附属安庆第一人民医院治疗的T2DM患者90例,其中男性54例,女性36例;年龄45~75(60 ± 15)岁。纳入标准:(1)明确诊断为T2DM;(2)年龄 ≥ 18 岁;(3)临床资料完整;(4)自愿签署知情同意书。排除标准:(1)1型糖尿病或其他特殊类型糖尿病;(2)合并严重的肝、心、脑等器官疾病;(3)妊娠或哺乳期女性;(4)近3个月内有严重感染、创伤或重大手术史;(5)正在使用可能影响血糖或肾脏功能的特殊药物。本研究经安庆第一人民医院医学伦理委员会批准(伦理号AQYY-YXLL-LWLL-69)。

1.2 方法

1.2.1 GA/HbA1c比值计算 患者入院次日晨起采集空腹静脉血3 mL,GA水平测定采用酶法,HbA1c水平检测使用高效液相色谱技术,计算GA/HbA1c比值。检测系统及配套试剂均选用Roche品牌产品,实验操作全程严格遵循制造商提供的标准操作规程执行。

1.2.2 资料收集 收集患者入院24 h的临床资料,包括性别、年龄、身体质量指数(body mass index, BMI)、吸烟史、饮酒史、糖尿病家族史、糖尿病病程、合并症(高血压、冠心病)、白细胞计数、血小板计数、胆固醇、三酰甘油、高密度脂蛋白胆固醇(high-density lipoprotein cholesterol, HDL-C)、低密度脂蛋白胆固醇(low-density lipoprotein cholesterol, LDL-C)、血肌酐、血尿素氮、尿酸、胱抑素C、空腹血糖和GA/HbA1c比值。

1.2.3 随访与分组 采用定期门诊复诊结合电话随访,随访截止日期为2025年5月31日,主要观察终点为肾脏疾病进展,其判定标准为满足以下任意一项:

血肌酐水平倍增、估算肾小球滤过率降低超过25%、尿白蛋白肌酐比值>300 mg/g、需要肾脏替代治疗或发生任何原因导致的死亡^[8]。根据随访结果,将患者分为进展组(19例)和无进展组(71例)。

1.3 统计学方法 采用SPSS 28.0软件分析数据。计数资料以例(%)表示,采用 χ^2 检验或校正 χ^2 检验;符合正态分布的计量资料以 $\bar{x}\pm s$ 表示,行 t 检验;采用logistic回归模型分析T2DM患者肾脏病变进展的影响因素,RCS模型分析GA/HbA1c比值与T2DM患者肾脏病变进展的剂量-反应关系,受试者工作特征(receiver operating characteristics, ROC)曲线分析GA/HbA1c比值对T2DM患者肾脏病变进展的预测价值。 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 进展组与无进展组临床资料比较 进展组高血压比例、血肌酐、血尿素氮、血尿酸、胱抑素C、GA/HbA1c比值高于无进展组($P<0.05$)。两组其他指标差异无统计学意义($P>0.05$)。见表1。

2.2 T2DM患者肾脏病变进展的危险因素分析 以T2DM患者是否发生肾脏病变进展事件为因变量(是=1,

否=0),以表1中 $P<0.05$ 的临床资料[高血压(是=1,否=0),血肌酐、血尿素氮、血尿酸、胱抑素C、GA/HbA1c比值均为连续变量,以原值代入]为自变量进行logistic回归分析,结果显示,合并高血压及高水平的血尿素氮、胱抑素C、GA/HbA1c比值是T2DM患者肾脏病变进展的独立危险因素($P<0.05$)。见表2。

2.3 GA/HbA1c比值与T2DM患者肾脏病变进展的剂量-反应关系 RCS模型以GA/HbA1c比值为横坐标,预测OR值为纵坐标,阴影部分代表95%CI。发现GA/HbA1c比值与T2DM患者肾脏病变进展呈非线性剂量-反应关系($P=0.034$,非线性 $P=0.040$),当GA/HbA1c比值 ≤ 2.025 (对应曲线拐点)时,T2DM患者肾脏病变进展事件发生风险上升趋势相对平缓;当GA/HbA1c比值超过2.025后,肾脏病变进展事件发生风险随比值的上升呈快速升高趋势。见图1。

2.4 GA/HbA1c比值对T2DM患者肾脏病变进展的预测价值 ROC曲线结果显示,GA/HbA1c比值预测T2DM患者肾脏病变进展的曲线下面积(area under the curve, AUC)为0.869(95%CI:0.820~0.912),最佳截断值为2.025,灵敏度、特异度分别为85.00%、75.00%。见图2。

表1 进展组与无进展组临床资料比较

Tab.1 Comparison of clinical data between the progression group and the non-progression group

项目	进展组 (n=19)	无进展组 (n=71)	χ^2/t 值	P值
性别[例(%)]				
男性	12(63.16)	42(59.15)	0.100	0.752
女性	7(36.84)	29(40.85)		
年龄[例(%)]				
<60岁	8(42.11)	45(63.38)	2.802	0.094
≥60岁	11(57.89)	26(36.62)		
BMI(kg/m ² , $\bar{x}\pm s$)	25.77±4.96	25.02±5.26	0.558	0.578
吸烟史[例(%)]	12(63.16)	32(45.07)	1.962	0.161
饮酒史[例(%)]	8(42.11)	26(36.62)	0.192	0.661
糖尿病家族史[例(%)]	5(26.32)	10(14.08)	0.854	0.355
糖尿病病程(年, $\bar{x}\pm s$)	11.94±3.26	11.52±4.47	0.383	0.703
合并疾病[例(%)]				
高血压	12(63.16)	12(16.90)	16.400	<0.001
冠心病	8(42.11)	25(35.21)	0.307	0.580
白细胞计数($\times 10^9/L$, $\bar{x}\pm s$)	6.88±2.12	7.84±2.71	1.429	0.156
血小板计数($\times 10^9/L$, $\bar{x}\pm s$)	198.49±48.64	207.61±44.56	0.780	0.438
胆固醇(mmol/L, $\bar{x}\pm s$)	3.75±1.41	3.94±1.25	0.599	0.551
三酰甘油(mmol/L, $\bar{x}\pm s$)	1.73±0.55	1.74±0.63	0.063	0.950
HDL-C(mmol/L, $\bar{x}\pm s$)	1.21±0.30	1.27±0.43	0.571	0.569
LDL-C(mmol/L, $\bar{x}\pm s$)	2.30±0.72	2.13±0.53	1.147	0.255
血肌酐($\mu\text{mol/L}$, $\bar{x}\pm s$)	62.35±8.07	55.12±8.47	3.336	0.001
血尿素氮(mmol/L, $\bar{x}\pm s$)	8.56±2.96	5.89±1.52	5.426	<0.001
血尿酸(mmol/L, $\bar{x}\pm s$)	365.21±47.06	331.92±32.66	3.573	0.001
胱抑素C(mmol/L, $\bar{x}\pm s$)	1.51±0.45	0.98±0.52	4.378	<0.001
空腹血糖(mmol/L, $\bar{x}\pm s$)	12.99±2.75	11.87±2.44	1.730	0.087
GA/HbA1c比值($\bar{x}\pm s$)	1.97±0.36	1.74±0.22	3.492	<0.001

表2 影响T2DM患者肾脏病变进展的多因素logistic回归分析
Tab.2 Multivariate logistic regression analysis of factors influencing renal lesion progression in patients with T2DM

因素	β	SE	Wald χ^2	P值	OR值	95%CI
高血压	2.078	0.917	5.132	0.023	7.987	1.324~48.189
血肌酐	0.098	0.054	3.295	0.069	1.103	0.992~1.226
血尿素氮	0.871	0.321	7.350	0.007	2.389	1.273~4.482
血尿酸	0.015	0.012	1.462	0.227	1.015	0.991~1.039
胱抑素C	2.176	0.925	5.534	0.019	8.807	1.437~53.976
GA/HbA1c比值	3.831	1.582	5.864	0.015	46.103	2.075~1 024.129

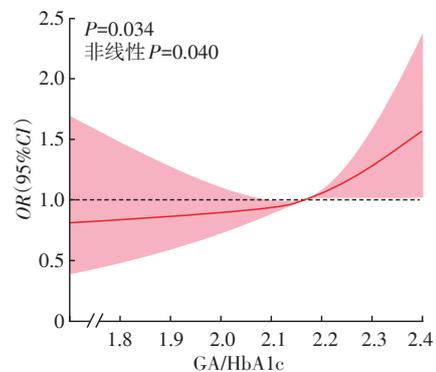


图1 GA/HbA1c比值与T2DM患者肾脏病变进展的剂量-反应关系

Fig.1 Dose-response relationship between the GA/HbA1c ratio and renal lesion progression in patients with T2DM

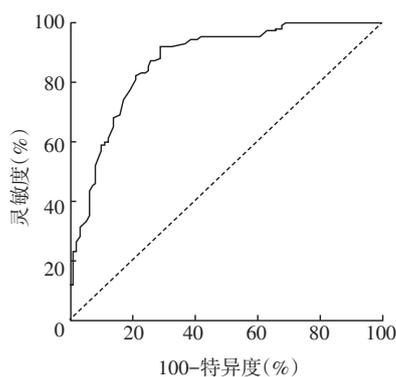


图2 GA/HbA1c 比值预测 T2DM 患者肾脏病变进展的 ROC 曲线

Fig.2 The ROC curve of the GA/HbA1c ratio in predicting renal lesion progression in patients with T2DM

3 讨论

本研究通过 RCS 模型探讨了 GA/HbA1c 比值与 T2DM 患者肾脏进展间的剂量-反应关系。结果显示,GA/HbA1c 比值与肾脏病变进展风险呈显著非线性正相关,且这种关联具有明确的剂量依赖性特征,这与既往研究发现的 GA 和 HbA1c 单独与 DKD 相关的结论有所不同^[9-10]。可能的机制在于,GA/HbA1c 比值升高反映了短期血糖波动与长期血糖控制的失衡状态,这种代谢紊乱可能通过多重途径加速肾脏损伤:一方面,血糖波动导致氧化应激和炎症反应加剧,促进肾小球基底膜增厚和系膜基质扩张^[11-12];另一方面,持续的高血糖环境引起晚期糖基化终末产物积聚,通过激活晚期糖基化终产物受体加重肾脏纤维化进程^[13-14]。需要特别指出,本研究发现这种剂量-反应关系呈现非线性特征,提示可能存在阈值效应,这对临床风险分层具有重要指导价值。

从预测效能来看,GA/HbA1c 比值展现出优异的诊断性能(AUC=0.869),其预测价值优于传统指标(如 HbA1c)单独检测^[15]。这一结果与 Wang 等^[16]的研究发现相呼应,他们报道 GA/HbA1c 比值与糖尿病微血管并发症的相关性更强。此外,本研究发现 GA/HbA1c 比值最佳截断值为 2.025 时,预测 T2DM 患者肾脏进展的灵敏度为 85.00%、特异度为 75.00%,该临界值可作为临床预警的重要参考。与既往研究相比,本研究创新性地采用 RCS 模型揭示了 GA/HbA1c 比值与肾脏病变进展的非线性关联模式,弥补了传统线性分析方法的不足。这种非线性关系提示,当 GA/HbA1c 比值超过特定阈值后,肾脏损伤风险呈现加速上升趋势,这可能与血糖波动引发的“代谢记忆”效应有关^[17]。

除 GA/HbA1c 比值外,本研究还确认了高血压、血尿素氮、胱抑素 C 等传统危险因素的作用,与现有文献

报道一致^[18-21]。但这些指标多反映肾脏损伤的结果而非原因,相比之下,GA/HbA1c 比值作为血糖控制质量的动态指标,具有更早预警价值。值得一提的是,GA/HbA1c 比值升高的患者往往伴随更显著的代谢紊乱特征^[22],这提示该指标可能整合了多重代谢异常信息。从临床应用角度,GA/HbA1c 比值的测量具有操作简便、成本较低的优势,且不受血红蛋白变异等因素干扰,适合作为常规监测指标。结合 ROC 曲线分析结果,建议对 GA/HbA1c 比值>2.025 的 T2DM 患者加强肾脏保护干预,包括优化血糖控制策略、强化血压管理等。

综上所述,本研究通过 RCS 模型揭示了 GA/HbA1c 比值与 T2DM 患者肾脏病变进展间的非线性剂量-反应关系,证实该比值是肾脏病变进展的独立危险因素和有效预测指标。本研究的创新价值在于:第一,采用先进统计模型刻画了非线性关联特征;第二,确定了具有临床实用性的预警阈值;第三,为血糖波动与肾脏损伤的机制研究提供了新视角。但本研究作为单中心观察性研究,存在样本量有限、随访时间较短等局限性。未来需要更大规模的前瞻性队列验证这些发现,并进一步探索 GA/HbA1c 比值影响肾脏功能的具体分子机制。从临床转化角度,建议将 GA/HbA1c 比值纳入 T2DM 患者的常规监测体系,对高风险个体实施早期干预,这可能为 DKD 的防治提供新思路。

利益冲突 无

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对严重水肿患者测定准确性较低,未来可采用双能X线吸收法等方法进行交叉验证^[16]。计划下一步实施基于MFR分层的干预研究,以探讨代谢调整对肾脏预后的影响。

综上所述,MFR升高是DKD肾功能受损及CGA分期进展的独立保护因素,其作用机制或与肌肉-脂肪轴失调有关。今后需通过长期随访与干预试验,将MFR整合进DKD个体化管理策略,有望为DKD的个体化精准治疗提供新的策略与证据支持。

利益冲突 无

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