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Upregulated Serum Glycated Albumin Contributes To Early Diabetic Nephropathy Diagnosis

Yunlai Liang, Kangkang Huang, Kun Wang, Jingzhong Liao, Bin Yi*

Department of Clinical Laboratory, Xiangya Hospital, Central South University, Changsha, China

Corresponding author: Bin Yi, Department of Clinical Laboratory, Xiangya Hospital, Central South University, Changsha, Hunan Province, China

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Abstract

Background Glycated albumin (GA) has been recently used as a glycemic marker for monitoring glucose control in type 2 diabetic mellitus (T2DM) patients, but its role in early diabetic nephropathy (EDN) in T2DM remains unclear. This study aims to investigate the clinical significance of GA in diagnosing EDN in T2DM patients.

Methods and Results 118 T2DM patients were enrolled and classified by the urine albumin/creatinine ratio (UACR) into groups of T2DM (UACR < 30 mg/g), EDN (early diabetic nephropathy 30 mg/g < UACR < 300mg/g) and ADN (advanced diabetic nephropathy, UACR > 300mg/g), and 36 healthy subjects were established as the control. Serum GA measured and the relevant clinical data were collected and analyzed. Our results disclosed significantly upregulated GA levels in EDN patients. Correlation analysis showed that in diabetes, GA was positively correlated with age(r=0.349, P=0.000), Ur(r=0.189, *P*=0.020), BMI(r=0.321, *P*=0.000), TBA(r=0.170, *P*=0.035), TG(r=0.227, *P*=0.005) and HbA1c(r=0.632, *P*=0.000), while negatively correlated with ALB(r=-0.227, *P*=0.001), mic-Alb(r=-0.271, *P*=0.004) and UAER(r=-0.475, *P*=0.003). Multiple linear regression found that GA was influenced by HbA1c and BMI. Univariate logistic regression demonstrated that upregulated GA, mic-Alb, ALB and Scr may be related to the progression of T2DM into EDN. Maybe due to insufficient sample size, mic-Alb rather than GA was included in the multivariate regression variance as a risk factor for the progression of T2DM to EDN. ROC analysis manifested that GA was a prominent indicator of EDN (AUC = 0.780, 95% CI 0.686 - 0.874, P<0.01) at cutoff values 16.705 % (sensitivity 0.900, specificity 0.525) in total T2DM patients. Noticeably, GA presented a better application value in the female where the AUC came up to 0.882 (95% CI: 0.768-0.997, P<0.01) with both high sensitivity (0.889) and high specificity (0.853) at the cutoff value of 23.365%.

Conclusion Upregulation of GA appears positively related to the presence of EDN and contributes to its diagnosis.

Keywords: Glycated Albumin; Early Diabetic Nephropathy; Type 2 Diabetes Mellitus; Diagnosis

Introduction

T2DM is one of the most clinical common metabolic diseases, characterized by many complications. The significant morbidity, disability and early mortality of T2DM resulting the related expenditure amounted to $165.3 billion in 2021 in China, ranking second in the world [1]. Approximately one-third of the T2DM patients develop into Diabetic Nephropathy (DN), which is a major cause of end-stage renal disease (ESRD) in advanced countries [2-4]. DN is the second most common cause of dialysis in ESRD patients in China [5] DN onsets insidiously and the rate of progression to end-stage renal disease is significantly accelerated once patients with DN go into a period of large volume proteinuria. It has been reported that diagnosis of early diabetic nephropathy (EDN) is of great significance to improve the quality of life and prolong the survival period of the patients [6]. As a result, early diagnosis and intervention of DN are pressingly needed. However, the present diagnostic methods fail to satisfy the clinical demands.

Many studies have pointed out that the urinary albumin, SBP and duration of diabetes are major risk factors for DN, but

glycemic control plays a dominant role in DN management [7]. Investigations have concluded that the onset and progression of DN in T2DM can be delayed by glycemic control [8]. So far, Fasting Plasma Glucose (FPG), 2 h postprandial plasma glucose (2 h PG) and random plasma glucose is tested as a routine to monitor the actual glucose levels in the body, however, these tests are easy to be affected by variable short-term lifestyle of the individuals. Glycated proteins have been proved to be good indicators of glycemic control over a period of time. For example, Hemoglobin A1c (HbA1c) has been widely used to reflect average glucose levels over the past 120 days [9]. The onset and progression of DN is affected by both sustained hyperglycemia and acute glucose fluctuations [10,11]. These evidences suggest that there are different rates of DN occurrence depending on the patient's glucose fluctuation status even at the same HbA1c level. What's worse, HbA1c level is influenced by several factors such as anemia, altered erythrocyte cycle and erythropoietin therapy [12,13]. Therefore, a specific indicator for monitoring glucose fluctuations and excursions is urgently needed in clinical practice to help predict the onset and development of DN.

Glycated albumin (GA) is an early Amadori‐type glycation product of the non-enzymatic glycation reaction between glucose and albumin that reflects glycemic control over the previous 14 to 21 days. It shows great advantage over HbA1c in reflecting glycemic excursion [9,14]. Moreover, GA is not affected by anemia, erythrocyte lifespan fluctuation or erythropoietin treatment [9,15], which frequently happen in the course of DN, and thus, it may be beneficial for these patients to evaluate their glycemic control.

In addition, GA is involved in many pathologic processes. Excessive GA can inappropriately provoke the Reactive Oxygen Species (ROS) system and the inflammatory cells, resulting in augmented production of angiotensin II (Ang II) and release of the growth factors [16,17]. Some researchers hold the opinion that GA plays a pivot role in the pathogenesis and prediction of DN in patients with T2DM [18]. These results imply that GA is strongly associated with the occurrence and development of DN. However, the relationship between variable GA levels and the development of EDN has rarely been evaluated. Therefore, by comprehensively analyzing the clinical data of a number of T2DM patients, we try to find the association between serum GA level and the presence of different stage of DN.

Materials and Methods

Subjects

118 consecutive T2DM patients (aged from 22 to 75 years) who agreed to participate in this study were enrolled between 1 April 2022 and 31 July 2022 from the endocrinology ward at Xiangya Hospital of Central South University. Biochemical indicators including GA were measured. This research was approved by the ethics committee of Xiangya Hospital of Central South University (No.202203083), and the relevant informed consent was obtained from all individuals.

Experiment design

All the patients were divided into three groups—EDN, ADN (advanced diabetic nephropathy) and T2DM, according to the diagnosis standard of DN and the urine albumin/creatinine ratio (UACR). T2DM patients with UACR ≧ 300 mg/g in the presence of diabetic nephropathy were classified into ADN group, while those with UACR between 30 and 300 mg/g accompanied by diabetic nephropathy at two or more follow-up examinations were included in the EDN group [19] and patients who had their UACR ≦30 mg/g were remained in the T2DM group. In addition, healthy control (HC) group was also established at the same time. Patients with cardio-cerebrovascular complications, thyroid dysfunction, liver dysfunction or malignant tumors were excluded. All clinical data relevant to this research were recorded and analyzed for differences between groups. Correlation analysis was conducted to find out the relationship between GA and other biochemical indicators, followed by multiple linear regression calculation for further selection of potential influence factors of GA. Univariate and multivariate logistic regression were performed to explore indicators associated with DN prevalence. Finally, ROC curve analysis was implemented to compare the utility of GA as an indicator of EDN.

General conditions of the patients

Parameters of the patients including age, sex, albumin (ALB), microalbuminuria (mic-Alb), body mass index (BMI), urinary albumin excretion (UAER) triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), GA, HbA1c, UACR, blood urea nitrogen (BUN), urine creatinine, serum creatinine（SCr, glomerular filtration rate (GFR), HDL to LDL ratio (HLR) evaluated as risk factors for DN in different stage in all subjects and their values were measured. GA was determined by enzymic method (Lucica GA-L protocol, Asahi Kasei Pharma Corp, Shizuoka, Japan), and GA% was calculated using the formula provided by the manufacturer's instruction as follows: GA%=(GA/ALB)/1.14*100+2.9.

Statistical analysis

SPSS Statistics 25.0 (SPSS Inc, Chicago, Illinois) adopted for statistical analysis. Normally distributed continuous variables presented as means ± SD, while non-normally distributed data were identified by median and quartile. Categorical and continuous variables among T2DM, EDN and ADN groups were compared by χ^2 analysis and independent t test respectively. Non-parametric test performed when continuous variables did not show a normal

distribution. Multiple linear regression employed to analyze influencing factors of GA. Univariate logistic regression was introduced to evaluate the independent indicators of DN. ROC analysis was applied to explore the efficiency of GA in diagnosing DN and to find the optimal cut-off point. $P < 0.05$ was considered to be statistically significant.

Ethical approval

Original study was approved by the Research Ethics Committees of Central South University, China with the permission number of 202203083. The work carried out in accordance with the Declaration of Helsinki. Participation in this study was voluntary and informed consent obtained from all participants.

Results

Clinical characteristics

We screened 137 patients with diabetes mellitus, and excluded 19 of them (cardio-cerebrovascular complications, n=13; type 1 diabetes, n=4; thyroid dysfunction, n=2). The final study sample for analysis comprised 118 patients with T2DM. The characteristics of study participants are shown in Table 1. The levels of mic-Alb and HbA1c in EDN group were significantly higher than those in T2DM group (P<0.05), but significantly lower than those in AND group (P<0.05). The ALB, TB, DB and GFR in EDN group were significantly higher than those in AND group (P<0.05), while Ur, Cr and UAER in EDN group were significantly lower than those in AND group (P<0.05). Notably, patients with EDN had the highest GA level among all groups and there was significant difference in GA between EDN and ADN groups (P<0.05). In addition, the serum GA of T2DM patients with HbA1c>6.4% (25.36±8.43) was significantly higher than that of patients with HbA1c<6.4% (19.10±5.84)

Groups/Indexes	Healthy(n=36)	T2DM(n=44)	EDN(n=30)	ADN(n=44)
Age*	49.13±7.73	59.65±12.17[a]	63.53±12.11[a]	60.50±10.01[a]
Gender(M/F)	20/16	26/18	21/9	29/15
ALB*	44.78±3.69	40.03±5.61[a]	37.11±5.58[a]	30.16±8.28[abc]
GFR*	85.33±11.50	80.97±18.36	72.81±20.29[a]	34.58±26.54[abc]
TB*	11.29±3.55	10.60±4.54	10.15±4.76	6.38±3.06[abc]
DB*	5.64±1.77	4.66±1.86	4.72±2.31	2.98±1.52[abc]
LDL[&]	3.02±0.67	2.74±0.86	2.92±1.40	3.06±0.99
TC[&]	4.92±0.88	4.33±1.24	4.77±2.18	4.85±1.36
GA[^]	13.42(12.65~14.39)	22.46(19.32~27.32)[a]	26.04(20.34~31.49)[a]	21.51(16.25~25.17)[ac]
Mic-Alb[^]	/	7.00(5.00~14.75)	44.00(30.00~96.00)[b]	1580.00(318.00~2380.00)[bc]
Ur[^]	4.50(3.62~5.58)	5.07(4.32~6.86)[a]	5.75(4.56~6.77)[a]	9.31(6.16~15.44)[abc]

Cr^	77.00(64.00~87.00)	77.50(66.50~87.75)	83.50(73.50~114.05) [a]	170.90(125.00~411.00) [abc]
HbA1c^	5.40(5.20~5.55)	7.70(6.60~8.70)[a]	9.10(7.10~10.30) [ab]	6.75(6.13~8.28) [ac]
UAER^	/	0.10(0.09~0.11)	0.17(0.10~0.34)	4.77(2.81~6.01)[bc]
UCr^	/	5492.00(3663.25~10576.50)	51232.00(3211.00~8384.00)	4231.00(3190.00~5915.00)[b]
BMI^	21.38(19.43~22.61)	21.99(20.94~23.67)[a]	23.07(21.84~24.05) [a]	22.67(21.35~23.78) [a]
TBA^	3.00(2.00~4.90)	5.10(3.63~7.70)[a]	5.00(3.50~9.45) [a]	4.25(2.13~6.90) [a]
TG^	1.36(0.98~1.66)	1.65(1.07~2.37)	1.87(1.24~3.72) [a]	1.85(1.21~2.49) [a]
HDL^	1.331.11~1.63()	0.94(0.81~1.18) [a]	0.98(0.83~1.27) [a]	0.94(0.81~1.08) [a]
HLR^	0.46(0.35~0.59)	0.34(0.28~0.50) [a]	0.35(0.27~0.55)	0.31(0.24~0.38) [a]
a: The difference was statistically significant compared with the healthy group ; b: The difference was statistically significant compared with the T2DM group ; c : The difference was statistically significant compared with the EDN group ; d : The difference was statistically significant compared with the ADN group ; *:S-N-K test ; & : Dunet-T3 test ; ^: H test。				

Table 1: Characteristics of patients in the four groups.

Correlations between GA and other indexes in all subjects

Pearson's correlation was performed to evaluate the correlations between GA and other indicators in the total sample. As presented in Table 2, GA was positively correlated with age(r=0.349, *P*=0.000), Ur(r=0.189, *P*=0.020), BMI(r=0.321, *P*=0.000), TBA(r=0.170, *P*=0.035), TG(r=0.227, *P*=0.005) and HbA1c(r=0.632, *P*=0.000), while negatively correlated with ALB(r=-0.227, *P*=0.001), mic-Alb(r=-0.271, *P*=0.004) and UAER(r=-0.475, *P*=0.003). Although statistically significant correlations were found between GA and these measures mentioned above, their correlations were weak, except HbA1c.

	Age	ALB	mic-Alb	Ur	HbA1c	UAER	BMI	TBA	TG
r	0.349	-0.277	-0.271	0.189	0.632	-0.475	0.321	0.170	0.227
P	0.000	0.001	0.004	0.020	0.000	0.003	0.000	0.035	0.005

Table 2: Correlation between GA and other indicators in the total participants

Correlations between GA and other indexes among subgroups divided by BMI and HbA1c

As exhibited in Supplement Table 1, GA was positively correlated with Ur(r=0.273, *P*=0.002), TBA(r=0.223, *P*=0.013), TG(r=0.252, *P*=0.006) and HbA1c(r=0.632, *P*=0.000) and negatively correlated with ALB(r=-0.328, *P*=0.000) and mic-Alb(r=-0.224, *P*=0.037) in the subgroup of patients with BMI <24. While in subgroup of BMI > 24, GA was powerful relevance to HbA1c(r=0.654, *P*=0.003), BMI(r=0.775, *P*=0.000), or mic-Alb(r=-0.481, *P*=0.02). As described in Supplement Table 2, GA was significantly correlated to Alb(r=-0.379, *P*=0.015), Ur(r=0.576, *P*=0.00), GFR(r=-0.530, *P*=0.00), TB(r=-0.399, *P*=0.01) and DB(r=-0.424, *P*=0.006) in subgroup of patients with HbA1c<6.5%. Additionally, GA in subgroup of patients with HbA1c>6.5% was found to be strongly related to Alb(r=-0.218, *P*=0.046), BMI(r=0.379, *P*=0.00) and HbA1c(r=0.550, *P*=0.00).

Multiple Linear regression analysis of the influencing factors of GA

In order to further explore the influencing factors of GA, multiple linear regression analysis was conducted. We took GA as the dependent variable and other indicators as independent variables (because of collinearity, GFR was excluded), with an entry value of α at 0.05 and a remove value at 0.1. The variables introduced to the equation were BMI and HbA1c. F-test showed F=3.817, *P*=0.014, indicating that the fitted multiple linear equation had statistical significance. The regression equation was $Y=2.758X_1+0.145X_2$ (Y=GA, X_1=HbA1c, X_2=BMI). The determination coefficient R^2 of this model was 0.868, implying that this model could account for 86.8% of GA variation and the remaining 13.2% was caused by other accidental factors (Table 3).

	B	SE	β	t	*P*
HbA1c	2.758	1.037	0.533	2.660	0.022
BMI	0.145	0.045	0.502	3.182	0.009

Table 3: Multiple Linear regression analysis of the influencing factors of GA.

Factors involved in the progression of T2DM into EDN

Risk factors that might promote the progression of T2DM to EDN were assessed by logistic regression, and the results were shown in Table 4. Univariate logistic regression demonstrated that GA, mic-Alb, ALB and Scr may be related to the progression. Subsequently, suffering from EDN was introduced as the dependent variable, and the above 4 indicators were included as independent variables for further analysis by multivariate regression. As described, elevated mic-Alb was a risk factor for the progression of T2DM to EDN. Unfortunately, although GA was strongly correlated with mic-Alb in some subgroups, it was not included in the regression model, which may be related to the small sample size of this study.

Variables	univariate regression		t (χ^2)	*P*	multivariate regression		*P*
	EDN (n=30)	T2DM (n=44)			OR	95%CI	
GA	28.08±11.08	23.38±6.28	-2.108	0.041			
ALB	37.11±5.58	40.31±5.61	2.197	0.031			
Micro-Alb	67.77±56.34	10.36±.24	-5.261	0.000	100.843	11.318-898.580	0.000
Scr	90.91±26.66	79.94±20.34	-1.991	0.05			

Table 4: Influence factors involved in the process from T2DM to EDN.

ROC curve analysis

An ROC curve analysis was used to calculate the areas under the curve (AUC) of GA for prediction of EDN presence (Figure 1A). GA showed an excellent AUC (AUC = 0.780, 95% CI 0.686 - 0.874, P<0.01). The cutoff values of GA that gave the highest sensitivity and specificity for the diagnosis of EDN in T2DM patients were 16.705 %(sensitivity 0.900, specificity 0.525). Noticeably, GA presented a better application value in the female where the AUC came up to 0.882 (95% CI: 0.768-0.997, P<0.01) with both high sensitivity (0.889) and high specificity (0.853) at the cutoff value of 23.365% (Figure 1B).

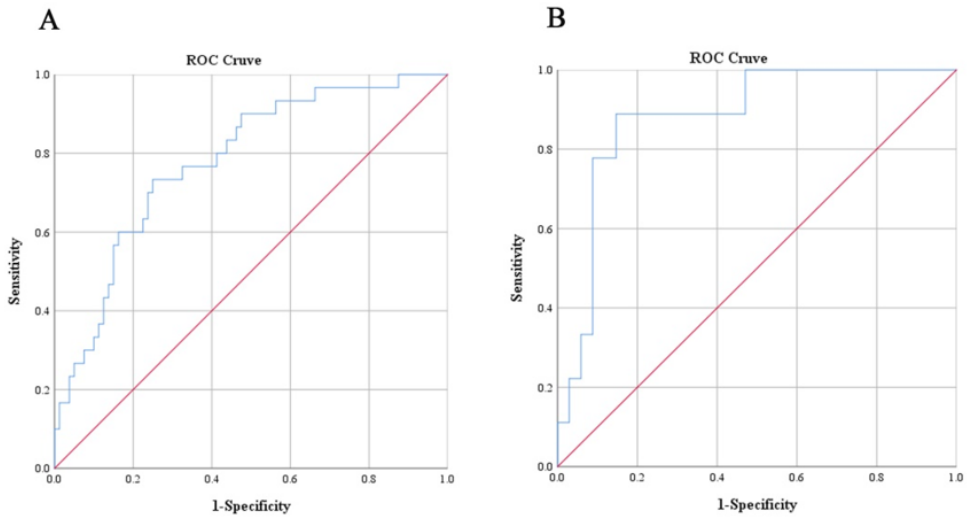

Figure 1: Receiver operating characteristic curve analysis for GA for the presence of EDN. A: In total population; B: In female.

Discussion

Up to now, clinical diagnosis of ND mainly depends on micro albumin excretion. Microalbuminuria is currently the most reliable biomarker of DN, however, recent evidences have posed challenges to this notion. Hohenadel D et al. have argued that microalbuminuria is more likely to revert to normal urinary albumin than the overt proteinuria [20], implying that microalbuminuria may be no longer a suitable predictor of progression. The application of HbA1c in the diagnosis of ND also has the limitation. Since the degree of hemoglobin glycosylation depends not only on the level of glycemic control, but also on the lifespan of erythrocyte, DN patients with hemoglobin disorders or anemia may have erroneous HbA1c levels, and consequently receive insufficient therapy [21]. As a result, a more efficient biomarker to facilitate DN diagnosis, especially in the early stage, urgently needed. GA is a non-enzymatic glycosylation product of plasma albumin and glucose, which reflects the glycemic control of the diabetic patients in the last 2 to 3 weeks [22]. Several recent studies have revealed that upregulated GA is significantly related to the presence of DN [23,24].

To our best knowledge, it is the first time that GA levels in the groups of T2DM, EDN and ADN found to be obviously increased and reached its peak in EDN, compared to that in the healthy. It is reasonable to assume that the non-enzymatic glycosylation of albumin in patients with T2DM is dramatically enhanced when glycemic control of the body is poor, leading to a large amount of GA accumulation [25] and the successive renal function impairment, propelling the patients into the stage of EDN. When patients undergo clinical treatment for glycemic control, their blood sugar levels may decrease or the production of GA may slow down, nevertheless, GA is constantly transformed into advanced glycation end products (AGEs) [28]. This transformation continues in the case of invariable or reduced generation of GA, which causes continuous reduction of the GA level in ADN. In this regard, GA is expected to be a indicator of early renal injury in diabetes mellitus as well as to monitor the progress of T2DM toward ND, so as to help clinicians understand the real-time changes of the patients' condition to better control and alleviate the disease from further deterioration.

To evaluate the correlation between GA and other indicators, including those involved in glycometabolism, we analyzed data from patients with T2DM, EDN and ADN. GA was found to related to Ur(r=0.189, *P*=0.020), BMI(r=0.321, *P*=0.000), HbA1c(r=0.632, *P*=0.000) mic-Alb(r=-0.271, *P*=0.004), UAER(r=-0.475, *P*=0.003) and so on. Although statistically significant correlations found between GA and these measures mentioned above, their correlations were weak, except HbA1c. In analyses stratified by BMI categories, the pattern of differences in correlation coefficients between pairs of markers was broadly similar, except BMI itself. We noted that studies have shown that GA is negatively correlated with BMI in T2DM or poor glycemic control [25,26], which is quite contrary to the results of our current study. We speculated that the essence of this difference lies in the different proportions of the effects of glycaemia and obesity-related chronic inflammation on GA at different period. If obesity induced inflammation affects GA levels for reasons (increasing albumin catabolism and deficiency of insulin secretion) other than degree of glycaemia, GA is negatively correlated with BMI, as mentioned above. However, when the influence of hyperglycemia exceeds the obesity-induced chronic inflammation, the accumulation of GA

will surpass the decomposition induced by the inflammation, and GA will be positively correlated with BMI. In analyses divided by HbA1c categories, the pattern of correlation between GA and other indexes was quite different. GA was mainly related to liver and kidney function when patients were under ideal blood glucose control (HbA1c<6.5%). However, a strong association between GA and HbA1c and BMI observed when glycemic control was poor. These data strongly suggest the potential value of GA for glycemic control or monitoring.

In addition, our results of multiple linear regression disclosed that the influencing factors of GA were BMI and HbA1c, which were consistent with the results of correlation analysis. The regression equation containing these three indicators could explain 86.8% of the GA variation. HbA1c and GA are early Amadori type glycosylated products of hemoglobin and albumin, and both of them are affected by blood glucose levels [27]. More and more evidences supported the relationship between BMI and GA have been presented [28]. Our analysis of univariate logistic regression determined that GA, mic-Alb, ALB and Scr may be related to the progression of T2DM to EDN. DN refers to specific pathologic structural and functional alterations of kidneys in patients with diabetes, characterized clinically by a persistent reduction in GFR and/or increased serum creatinine and urinary excretion of ALB [29]. There were evidences that the reabsorption rate of GA in glomeruli was higher than that of albumin alone, and the accumulation of GA in glomeruli could adversely impact the renal glomerular capillary's structure, function and metabolism by activating Protein Kinase C (PKC) and transforming growth factor-β (TGF-β) system [30,31]. The above findings together with our results indicate that GA may be massively involved in the process of DN. Unfortunately, the regression equation obtained by multivariate analysis with the above 4 indicators as independent variables only included mic-Alb. Although GA strongly correlated with mic-Alb, it was not included in the regression equation. This does not negate the important role of GA in the progression of DN. We suspect that GA not statistically considered as a risk factor due to insufficient sample size.

Another encouraging finding of our work is that GA has the potential to be an excellent biomarker for diagnosing EDN in T2DM. Previous report stated that GA and the GA: HbA1c ratio could be more strongly associated with the presence of DN than HbA1c alone [32]. GA levels may be helpful for evaluating the risk of mortality in hemodialysis patients with or without DM [33]. Even though some studies considered GA as a useful marker for diagnosing DN in DM patients, there is little investigation on the significance of GA in EDN occurrence. According to our ROC curve data, GA exhibited an excellent AUC (AUC = 0.780, 95% CI 0.686 - 0.874, P<0.01). The cutoff values of GA that gave the highest sensitivity and specificity for the diagnosis of EDN in T2DM patients were 16.705% (sensitivity 0.900, specificity 0.525). It is worth mentioning that the diagnostic efficiency of GA in female, where the AUC was 0.882 (95% CI: 0.768-0.997, P<0.01) with both high sensitivity (0.889) and high specificity (0.853) at the cutoff value of 23.365%. So far, there is little relevant information available to explain this phenomenon. We suppose that some high level of sex hormones such as estrogen or progesterone in the female, may affect the metabolism of GA, causing the fluctuation of GA more obvious in the early stage of DN. Although further evidences needed to support this speculation, the results suggest that the female patients with T2DM may benefit more from the application of GA in predicting EDN.

Our study has several limitations. Primarily, this was a cross-sectional study in a single center, and not every patient received a continuous follow-up visit. Second, the sample size was relatively small and needs to be enlarged to make the conclusion more convincible. Finally, the albumin catabolism rate not taken into account in our analysis. Therefore, a multicenter interventional study with a larger number of patients is in urgent need to confirm the utility of GA level for EDN prediction in clinic.

In conclusion, this work compared the GA level in T2DM with that in T2DM with EDN or ADN, and analyzed the association between GA and DN in the presence of different disease stages. Our findings suggest that upregulation of GA appears to be positively related to the presence of EDN and contributes to its diagnosis, especially in the female.

Disclosure

Competing interests: The authors have declared that no competing interest exists.

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Authors' Contributions: YL wrote the main manuscript text, KH and KW prepared the table 1-4, JL and YL made the figure1. BY amended the first draft and approved the final version. All authors reviewed the manuscript.

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