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ORIGINAL ARTICLE

Baseline Glycated Albumin Predicts the Renal Dysfunction in a Five-Year Prospective Population-Based Study

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SUMMARY

Background: **Glycated albumin (GA) was reported to be associated with renal dysfunction in non-diabetic CKD population. This study assessed the correlation of GA and renal dysfunction and explored risk factors affecting renal progression in a general population-based study through a five-year follow-up.**
Methods: **Individuals who underwent a physical examination between September 2010 and September 2015 were enrolled. Multivariate linear regression was performed to assess the relationship between GA and eGFR change rate. The relationship between GA and renal progression was analyzed by multivariate logistic regression among 1,501 participants. Other risk factors were also explored and their predictive value was evaluated by ROC analysis, external validation was carried out in another 603 participants from the general population.**
Results: **The frequencies of subjects with renal progression increased obviously with the increment of baseline and mean GA according to quartile stratification (p for trend < 0.001). Baseline GA, age, and uric acid (p < 0.05) were identified as risk factors for renal dysfunction with a 30% or more decrease of eGFR. For every 1% increase of GA, the risk of deterioration of renal function increased to 1.585 in the population (95% CI, 1.299 - 1.935, p < 0.001). The predictive value of the model-building equation was confirmed by ROC analysis (AUC = 0.82, 95% CI: 0.773 - 0.832, p < 0.001) and in the validation group, predictive sensitivity and specificity were 85.7% and 73.5%.**
Conclusions: **Baseline GA is independently associated with renal dysfunction. Uric acid and age are also considered risk factors. GA combining with age, serum creatinine and uric acid can serve as predictive indicators for the progression of renal dysfunction.**
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INTRODUCTION

There is a rising incidence and prevalence of chronic kidney disease (CKD) which affects as many as 10 - 15% of the population worldwide with poor outcomes and carries an economic burden to society [1]. Research has shown that chronic renal insufficiency substantially increased the risk of cardiovascular disease, hospitalization, and death [2]. Elucidating the risk factors of renal dysfunction is vitally important to develop strategies for

early detection and intervention of CKD. Aging, hypertension, and diabetes are the most common risk factors for the decline of kidney function.

Glycated albumin (GA) is an early Amadori-type glycation protein of the non-enzymatic glycation reaction between glucose and serum albumin. GA was considered to be an alternative marker of hemoglobin A1c (HbA1c) for evaluating the glycemic control for diabetes, CKD, and dialysis patients and also for detecting prediabetes [3-5]. Several studies suggested that GA could be a screening marker for diabetes and even a predictive factor for mortality in hemodialysis patients [6-11]. Moreover, recent studies indicated GA may be a contributor to incident diabetes, acute kidney injury, and microvascular complications including diabetic retinopathy, diabetic nephropathy, coronary heart disease (CHD), and CKD [12-16].

Correlation between GA and renal dysfunction in non-diabetic CKD population was reported [17]. As our previous cross-sectional study indicated, elevated GA serves as a valuable risk marker for the assessment of decline in renal function in general population [18]. However, the impact of GA on long-term prognosis of renal function remains unclear. The present study aimed to assess the correlation between GA and renal dysfunction over a five-year period and to explore risk factors for progression of renal dysfunction. For further confirmation, we tested the prognostic value of risk factors in another population for external validation.

MATERIALS AND METHODS

This study was approved by the Ethics Committee of Peking University First Hospital, and each participant signed an informed consent before acceptance into and initiation of the study. All procedures were in compliance with the ethical standards and with the 1964 Helsinki Declaration and its later amendments.

Participants

Up to 3,260 individuals who underwent routine examination between September 2010 and September 2015 were recruited. We collected all data available from demographics to clinical disease history. We excluded 552 participants who did not attend the physical examination in 2015 and 604 participants who were missing complete baseline medical history or with invalid assessment values. Patients with a history of diabetes (n = 88), hypertension (n = 376), CHD (n = 50) or CKD (n = 142) were all included for analysis. In total, 2,104 individuals were enrolled in this prospective longitudinal study. Patients with both plasma and urine samples were distributed to the test group (n = 1,501) and those without urine sample into the validation group (n = 603). The flowchart of the current study is shown in Figure 1.

Laboratory assay

Blood samples were drawn from all subjects after an overnight fast (8 - 12 hours) for the measurement of fasting plasma glucose (FPG), hemoglobin A1c (HbA1c), GA, Scr, and lipid profile including triglycerides (TG), total cholesterol (TCHO), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). Scr levels were determined by Jaffe's method. FPG concentration was measured by glucose oxidase method. HbA1c was measured by the high-performance liquid chromatography (HPLC) method using a Tosoh G8 analyzer. Lipid markers were assayed by standard enzymatic procedures on an automated analyzer (7600 - 110, Hitachi, Tokyo, Japan). GA was analyzed by an enzymatic method using the LUCICA® GA-L kit (Asahi Kasei Pharma Corporation, Japan). The assay has an improved enzymatic GA measurement by using a glycated amino acid elimination reaction, and the results are highly correlated (r = 0.99) with values obtained by a high-performance liquid chromatography (HPLC) assay and is suitable for clinical use, as previously reported. Quality controls of high and low levels were carried out before daily work. Within-run CV was 1.30% and between-run CV was 4.75%.

In addition, morning urine samples were collected as possible to detect microalbumin and urine creatinine for the calculation of albumin-to-urine ratio (ACR). They were analyzed using an immunonephelometric and Jaffe's method, respectively, on automatic clinical analyzers of Immage 800 (Beckman Coulter) and Hitachi 7600-110 (Hitachi).

Other variable information

Personal information (age, gender, and smoking status), physical examinations (blood pressure, height, and weight), and detailed medical history of participants were recorded at the Health Management Centre. Body mass index (BMI) was calculated by dividing the patient's weight in kilograms by the height in meters squared. Estimated GFR was calculated using the equation according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). The estimated glomerular filtration rate (eGFR) change rate ([last eGFR - baseline eGFR]/[baseline eGFR] x 100%) was used as the variation indicator for the change of renal function. Mean GA equals (baseline GA + last GA)/2.

Diagnosis of diabetes was based on self-reported, current use of diabetes medications or according the criteria of American Diabetes Association (ADA): HbA1c $\geq$ 6.5% or FPG concentration $\geq$ 7.0 mmol/L [19]. Hypertension was defined as a systolic blood pressure of 140 mmHg or higher, diastolic blood pressure of 90 mmHg or higher or the current use of hypertension drugs. CKD was defined as baseline eGFR lower than 60 mL/minute/1.73m^2 or ACR higher than 30 mg/g according to the Kidney Disease: Improving Global Outcomes (KDIGO) guideline. Participants self-reported their history of CHD and smoking status.

Statistical analysis

SPSS software (Version 23.0; IBM, Inc., Armonk, NY, USA) and R software version 3.3.1 (http://www.R-project.org/) were used for all statistical analyses and a p-value lower than 0.05 was considered to be statistically significant. All variables are shown as means ± standard deviation (SD). Kruskal-Wallis tests and Chi-squared tests were used to compare the differences between groups. The multicollinearity was evaluated among potential factors using the variance inflation factor (VIF), and a VIF lower than 5 indicated no significant collinearity. Multivariate linear regression model was performed to assess the relationship between GA and eGFR change rate. Bonferroni correction was performed when comparing different biomarkers between groups. We conducted a multivariate logistic regression model analysis (Method = Forward: LR) to identify variables that contributed significantly to the incidence of renal dysfunction, then yielding the odds ratios. To validate the methodology, the receiver operating characteristic curve (ROC) was used to assess the sensitivity and specificity of the model. To verify the predictive value of the chosen risk factors for renal dysfunction in the general population, another 603 individuals were examined, using the study protocol.

RESULTS

Association between baseline GA and eGFR change rate

The analysis included 2,104 enrolled subjects, and their basic characteristics at baseline were summarized in Table 1. Figure 2 shows the progression of eGFR change rate descent relative to the increase in baseline GA value in the general population. Multivariate linear regression models of the eGFR change rate with GA and various factors were analyzed (Table 2). The baseline GA was independently associated with eGFR change rate after adjusting for up to 16 factors including demographic, clinical and lifestyle factors. An increase of baseline GA corresponded to the descent of eGFR change rate during five years ($\beta = -1.59$, $p < 0.001$). The higher binary group showed a significant decline of eGFR change rate than the lower binary group (B2 vs. B1: $\beta = -3.82$, $p < 0.001$). When we assessed baseline GA as tertiles and quartiles, the results seem to be robust for the continuous and the binary (T3 vs. T1: $\beta = -4.59$, $p < 0.001$; Q4 vs. Q1: $\beta = -5.10$, $p < 0.001$).

Study population

A total of 1,501 subjects were eligible for the test population in the present study according to abovementioned exclusion criteria. The mean age was 44.8 ± 14.5 years, 10.1% of population were men. American Food and Drug Administration once referred to a doubling of serum creatinine (Scr) from baseline (corresponding to a 57% reduction in eGFR) as an alternative endpoint for CKD progression [20]. However, it had clear limitations: some end events including cardiovascular events and mortality may occur before the doubling of Scr, and a decline of 30% in eGFR was more common than change of -57%. The CRIC study previously confirmed that using eGFR events (eGFR decrease of 25% and change in CKD stage) in the definition of kidney disease outcomes is appropriate in follow-up studies to identify risk factors for CKD progression [21]. It has been demonstrated that after adjusting for various confounders, a reduction of 30% in eGFR was associated with a 5-fold increased risk of end-stage renal disease (ESRD) [22]. Therefore, a 30% or more decrease of eGFR was defined as progression of renal dysfunction in this study. After a 5-year follow-up, 12.1% of the subjects experienced a progression of renal dysfunction. The enrolled subjects were then classified into non-progression group (n = 1,319) and progression group (n = 182) for comparisons. The demographic and laboratory characteristics of study population were shown in Table 3. All measurements were conducted at baseline unless stated otherwise.

The BMI, blood pressures, HbA1c, lipid profile, ACR, UA, history of diabetes, CKD, CHD, and smoking status were relatively similar between groups at baseline. Persons with kidney endpoint were more likely to be older (49.6 ± 15.4 vs. 46.0 ± 15.2, $p = 0.002$) and hypertensive (26.9% vs. 20.0%, $p = 0.040$) as compared to persons without progression. The fasting glucose (5.1 ± 0.6 vs. 4.9 ± 0.6, $p < 0.001$), baseline GA (14.2 ± 1.2 vs. 13.7 ± 1.1, $p < 0.001$), mean GA (15.5 ± 1.7 vs. 14.8 ± 1.7, $p < 0.001$), urea (5.1 ± 1.3 vs. 4.8 ± 1.3, $p = 0.008$), and baseline eGFR (99.4 ± 16.4 vs. 91.2 ± 18.4, $p < 0.001$) were significantly higher in the progression group while the baseline Scr (61.6 ± 8.7 vs. 71.8 ± 13.2, $p < 0.001$) was lower than the non-progression group. The baseline eGFR and Scr in both groups were within the normal reference range and at the endpoint of follow-up, the subjects in the renal progression group had lower eGFR levels (65.1 + 12.1 vs. 78.76 + 15.4, $p < 0.001$) and higher serum creatinine levels (88.8 + 12.2 vs. 80.99 + 12.2, $p < 0.001$). In additional analyses, baseline GA was correlated with baseline HbA1c level ($r = 0.382$, $p < 0.001$) and mean GA significantly correlated with the mean FPG ($r = 0.567$, $p < 0.001$). There was evidence that Spearman's correlations revealed an inverse correlation of BMI with GA (Spearman's $r = -0.18$, $p < 0.001$) in persons without renal progression. This is in contrast to the positive correlation between BMI and HbA1c (Spearman's $r = 0.23$, $p < 0.001$).

The comparison of the risk of renal progression grouped by GA and HbA1c

All the subjects were divided into four groups on the basis of the quartiles of glycemic indices including baseline HbA1c, baseline GA, and mean GA. The range of quartiles for each index were demonstrated in Figure 3. The frequencies of subjects with renal progression of each group were computed and compared, and the line-

Table 1. Characteristics of general population (n = 2,104).

Variables		Population
n		2,104
Age, years		44.8 ± 14.5
BMI, kg/m2		23.4 ± 3.2
SBP, mmHg		115.3 ± 15.4
DBP, mmHg		73.4 ± 10.1
Triglycerides, mmol/L		1.2 ± 0.8
Total cholesterol, mmol/L		4.9 ± 0.9
LDL-C, mmol/L		2.9 ± 0.8
HDL-C, mmol/L		1.5 ± 0.3
Fasting glucose, mmol/L		4.9 ± 0.6
HbA1c, %		5.6 ± 0.4
GA, %		13.7 ± 1.1
Scr, μmol/L		70.5 ± 12.7
UA, μmol/L		302.5 ± 74.1
Baseline eGFR, mL/minute/1.73 m^2		93.0 ± 17.7
eGFR change rate, %		-15.9 ± 14.6
ACR, mg/g		9.1 ± 35.8
Diabetes mellitus, n (%)	No	2,020 (96.0)
	Yes	84 (4.0)
Hypertension, n (%)	No	1,732 (82.3)
	Yes	372 (17.7)
Smoking status, n (%)	Non-smoker	2,018 (95.9)
	Current smoker	86 (4.1)

Data are expressed as the Mean ± SD for continuous variables. n (%) for categorical variables.
Abbreviations: BMI - body mass index, SBP - systolic blood pressure, DBP - diastolic blood pressure, LDL-C - low-density lipoprotein cholesterol, HDL-C - high-density lipoprotein cholesterol, HbA1c - hemoglobin A1c, Scr - serum creatinine, UA - uric acid, eGFR - estimated glomerular filtration rate, ACR - albumin-to-creatinine ratio.

Table 2. The association between GA and eGFR change rate.

Glycated albumin		Total	eGFR change rate (Mean ± SD)	Crude Model		Model I	
				β (95% CI)	p-value	β (95% CI)	p-value
eGFR change rate							
Continuous		2,104	-15.86 ± 14.65	-1.31 (-1.86, -0.75)	< 0.001	-1.59 (-2.43, -0.74)	< 0.001
Binary	B1	1,052	-14.23 ± 13.33	0		0	
	B2	1,052	-17.48 ± 15.69	-3.24 (-4.49, -2.00)	< 0.001	-3.82 (-5.58, -2.06)	< 0.001
Tertiles	T1	681	-13.79 ± 13.34	0		0	
	T2	736	-16.25 ± 13.94	-2.47 (-3.99, -0.95)	0.002	-2.09 (-4.10, -0.08)	0.040
	T3	687	-17.48 ± 16.31	-3.69 (-5.24, -2.15)	< 0.001	-4.59 (-6.83, -2.35)	< 0.001
Quartiles	Q1	496	-13.50 ± 13.42	0		0	
	Q2	556	-14.89 ± 13.23	-1.40 (-3.16, 0.36)	0.120	-2.00 (-4.36, 0.35)	0.100
	Q3	554	-17.81 ± 13.93	-4.32 (-6.08, -2.55)	< 0.001	-4.88 (-7.24, -2.52)	< 0.001
	Q4	498	-17.11 ± 17.46	-3.61 (-5.42, -1.80)	< 0.001	-5.10 (-7.76, -2.43)	< 0.001

Adjusted for glycated albumin, age, gender, body mass index, smoking status, systolic blood pressure, diastolic blood pressure, fasting glucose, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, hemoglobin A1c, serum creatinine, uric acid, albumin creatinine rate, history of diabetes mellitus, hypertension, chronic kidney disease and coronary heart disease.

Table 3. Distribution of characteristics in participants of test group (n = 1,501).

Variables		Renal dysfunction		p-value
		Non-progression	Progression	
n		1,319	182	
Gender, n (%)	Male	141 (10.7)	2 (1.1)	< 0.001
	Female	1,178 (89.3)	180 (98.9)	
Age, years		46.0 ± 15.2	49.6 ± 15.4	0.002
BMI, kg/m^2		23.6 ± 3.3	23.6 ± 3.3	0.859
SBP, mmHg		116.6 ± 15.7	116.9 ± 17.3	0.927
DBP, mmHg		74.1 ± 10.4	72.8 ± 10.2	0.204
Triglycerides, mmol/L		1.2 ± 0.9	1.2 ± 0.8	0.515
Total cholesterol, mmol/L		5.0 ± 0.9	5.0 ± 0.9 *	0.233
LDL-C, mmol/L		2.9 ± 0.8	3.0 ± 0.8 *	0.365
HDL-C, mmol/L		1.5 ± 0.3	1.5 ± 0.3	0.286
Fasting glucose, mmol/L		4.9 ± 0.6	5.1 ± 0.6 *	< 0.001
HbA1c, %		5.6 ± 0.4	5.6 ± 0.4	0.264
GA, %		13.7 ± 1.1	14.2 ± 1.2 *	< 0.001
Mean GA, %		14.8 ± 1.7	15.5 ± 1.7	< 0.001
Endpoint GA, %		16.0 ± 2.6	16.8 ± 2.7	< 0.001
Baseline Scr, µmol/L		71.8 ± 13.2	61.6 ± 8.7	< 0.001
Mean Scr, µmol/L		76.4 ± 12.0	75.2 ± 10.0	0.174
Endpoint Scr, µmol/L		80.99 ± 12.2	88.8 ±12.2	< 0.001
Baseline eGFR, mL/minute/1.73 m^2		91.2 ± 18.4	99.4 ± 16.4 *	< 0.001
Mean eGFR, mL/minute/1.73 m^2		85.0 ±16.0	82.3 ± 14.1	0.025
Endpoint eGFR, mL/minute/1.73 m^2		78.76 ± 15.4	65.1 ± 12.1	< 0.001
eGFR change rate, %		-12.8 ± 11.2	-34.7 ± 4.3	< 0.001
ACR, mg/g		9.2 ± 35.5	8.4 ± 38.4	0.260
UA, µmol/L		305.2 ± 76.7	302.4 ± 69.4	0.66
Urea, mmol/L		4.8 ± 1.3	5.1 ± 1.3 *	0.008
Diabetes mellitus, n (%)	No	1,262 (95.7)	168 (92.3)	0.068
	Yes	57 (4.3)	14 (7.7)	
Hypertension, n (%)	No	1,055 (80.0)	133 (73.1)	0.040
	Yes	264 (20.0)	49 (26.9)	
CKD, n (%)	No	1,193 (90.4)	173 (95.1)	0.058
	Yes	126 (9.6)	9 (4.9)	
CHD, n (%)	No	1,280 (97.0)	178 (97.8)	0.735
	Yes	39 (3.0)	4 (2.2)	
Smoking status, n (%)	Non-Smoker	1,264 (95.8)	179 (98.4)	0.147
	Current Smoker	55 (4.2)	3 (1.6)	

Data are expressed as the Mean ± SD for continuous variables. n (%) for categorical variables.
*** - normal distributions.**
Abbreviations: BMI - body mass index, SBP - systolic blood pressure, DBP - diastolic blood pressure, LDL-C - low-density lipoprotein cholesterol, HDL-C - high-density lipoprotein cholesterol, Scr - serum creatinine, HbA1c - hemoglobin A1c, eGFR - estimated glomerular filtration rate, ACR - albumin-to-creatinine ratio, UA - uric acid, CKD - chronic kidney disease, CHD - coronary heart disease.

Table 4. Logistic regression analysis between renal dysfunction and variables.

Characteristics	B	SE	Wald	p-value	OR (95% CI)
Age	0.039	0.009	17.937	< 0.001	1.039 (1.021 - 1.058)
GA	0.461	0.102	20.505	< 0.001	1.585 (1.299 - 1.935)
Scr	-0.118	0.013	84.252	< 0.001	0.889 (0.867 - 0.911)
UA	0.005	0.002	6.414	0.011	1.005 (1.001 - 1.008)
Constant	-3.924	1.494	6.9	0.009	-

Adjusted for age, glycated albumin, gender, body mass index, smoking status, systolic blood pressure, diastolic blood pressure, fasting glucose, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, hemoglobin A1c, serum creatinine, uric acid, albumin creatinine rate, history of diabetes mellitus, hypertension, chronic kidney disease, and coronary heart disease.

ar test for trend was analyzed. The highest quartile of baseline HbA1c indicated a larger frequency of progressor than any other quartile. The frequencies of subjects with renal progression increased obviously with the increment of baseline GA and mean GA according to quartile stratification (p for trend < 0.001).

Risk factors for renal dysfunction progression

Using multivariate logistic regression analysis adjusted for up to 19 factors, age, baseline GA, Scr, and UA were identified as the four factors contributing to the prediction of renal dysfunction (Table 4). As the participant gets older, the risk of suffering from renal dysfunction progression increased yearly by 1.039 times (95% CI, 1.021 - 1.058, p < 0.001). For every 1% increase of GA, the risk of deterioration of renal function increased 1.585 in the population (95% CI, 1.299 - 1.935, p < 0.001). If a participant's UA increased by 1 μmol/L, renal dysfunction would be possibly present with the risk of 1.005 times (95% CI, 1.001 - 1.008, p = 0.011). The logistic equation was as follows: Log (P) = -3.924 + 0.039 x X1 + 0.461 x X2 - 0.118 x X3 + 0.005 x X4, where X1 stands for age, X2 stands for baseline GA, X3 stands for Scr and X4 stands for UA.

Predictive capability of the factors for renal dysfunction in population

To confirm whether our four mentioned factors could be used as valid predictors for renal dysfunction in population, receiver-operating characteristic (ROC) analysis was applied. It turned out that when Youden's Index was the highest, the cutoff point was -2.28 for the equation. Thus, we could positively predict renal dysfunction progression of a participant if the abovementioned Log(P) was equal to or greater than -2.28. Accordingly, the area under curve (AUC) was 80.2% (95% CI, 0.773 - 0.832; p < 0.001), and the sensitivity and specificity were 85.2% and 64.0%, respectively (Figure 4).

External validation

Based on the above findings, an external validation needed to be performed for further confirmation. Another 603 general population participants were enrolled as the validation group at the same time. The basic characteristics of participants are summarized in Table 5. By the end of the follow-up, 49 participants (8.1%) who met our criteria (30% decrease or more of eGFR) were identified as progressors of renal dysfunction. The fact that all the progressors were female showed a gender difference (p < 0.001). The prevalence of diabetes, hypertension, CKD, and CHD were 2.8%, 10.4%, 1.2%, and 1.2%, respectively. There were no significant differences in the chronic diseases mentioned and other demographic characteristics between groups. However, the progression group had a higher level of glycemic indices (FPG and mean GA, p < 0.001) and baseline eGFR (p < 0.001) and a lower Scr (p < 0.001) level than the non-progression group.

We applied both the criteria and proposed predictive paradigm to the validation group. The proposed predictive paradigm consisted of four risk factors and a constant that was presented earlier. The results showed that in the 603 subjects, 42 of 49 progressors and 407 of 554 non-progression subjects were predicted correctly using the above factors with a sensitivity of 85.7% and a specificity of 73.5% (Table 6).

DISCUSSION

The present study suggested that an increased baseline GA level is related to a poor renal outcome over a 5-year period in a large cohort of general population. The model, combined baseline GA with age, Scr, and UA, has a rather predictive value for progression of renal dysfunction.

Since CKD has been a major reason for ESRD and significantly impacts the health quality and economic burden of patients, much attention had been paid to its treatment and prevention [23]. Great efforts were made to detect and diagnose the early stage of renal dysfunction before the occurrence of renal disease or other microvascular disease in diabetic patients. GA was considered to have a better monitoring value for glucose con-

Table 5. Distribution of characteristics in participants of validation group (n = 603).

Variables		Renal dysfunction		p-value
		Non-progression	Progression	
n		554	49	
Gender, n (%)	Male	69 (12.5)	0	0.017
	Female	485 (87.5)	49 (100)	
Age, years		40.6 ± 11.3	43.3 ± 14.2	0.114
BMI, kg/m^2		23.1 ± 3.0	22.7 ± 2.3 *	0.557
SBP, mmHg		112.1 ± 13.9	112.2 ± 14.7 *	0.955
DBP, mmHg		72.0 ± 9.6	71.9 ± 8.2	0.946
Triglycerides, mmol/L		1.1 ± 0.8	1.1 ± 0.8	0.706
Total cholesterol, mmol/L		4.9 ± 1.0 *	4.8 ± 1.0 *	0.941
LDL-C, mmol/L		2.9 ± 0.8 *	2.9 ± 0.8 *	0.843
HDL-C, mmol/L		1.4 ± 0.3	1.5 ± 0.4 *	0.922
Fasting glucose, mmol/L		4.8 ± 0.6	4.9 ± 0.5 *	0.012
HbA1c, %		5.5 ± 0.4	5.6 ± 0.3	0.231
GA, %		13.6 ± 1.1	13.8 ± 1.0	0.083
Mean GA, %		14.6 ± 1.4	15.0 ± 1.4 *	0.036
Endpoint GA, %		15.6 ±2.0	16.1 ± 2.2	0.042
Baseline Scr, µmol/L		71.4 ± 11.2	59.5 ± 7.0	< 0.001
Mean Scr, µmol/L		75.9 ±10.5	73.6 ±15.8	0.004
Endpoint Scr, µmol/L		80.4 ±11.1	87.7 ±26.4	< 0.001
Baseline eGFR, mL/minute/1.73 m^2		95.0 ± 14.6 *	106.1 ± 13.9 *	< 0.001
Mean eGFR, mL/ minute/1.73 m^2		88.7 ±12.9 *	88.1 ±12.8 *	0.760
Endpoint eGFR, mL/minute/1.73 m^2		82.4 ±13.5 *	70.2 ±12.2	< 0.001
eGFR change rate, %		-12.7 ± 11.0	-34.3 ± 6.7	< 0.001
UA, µmol/L		298.1 ± 70.3	281.1 ± 56.7 *	0.110
Urea, mmol/L		4.7 ± 1.2	5.0 ± 1.4 *	0.114
Diabetes mellitus, n (%)	No	539 (97.3)	47 (95.9)	0.915
	Yes	15 (2.7)	2 (4.1)	
Hypertension, n (%)	No	498 (89.9%)	42 (85.7)	0.501
	Yes	56 (10.1)	7 (14.3)	
CKD, n (%)	No	548 (98.9)	48 (98.0)	0.549
	Yes	6 (1.8)	1 (2.0)	
CHD, n (%)	No	548 (98.9)	48 (98.0)	0.549
	Yes	6 (1.8)	1 (2.0)	
Smoking status, n (%)	Non-Smoker	527 (95.1)	49 (100)	0.114
	Current Smoker	27 (4.9)	0	

Data are expressed as the Mean ± SD for continuous variables. N (%) for categorical variables.
*** - Normal distributions.**
Abbreviations: BMI - body mass index, SBP - systolic blood pressure, DBP - diastolic blood pressure, LDL-C - low-density lipoprotein cholesterol, HDL-C - high-density lipoprotein cholesterol, Scr - serum creatinine, HbA1c - hemoglobin A1c, eGFR - estimated glomerular filtration rate, UA - uric acid, CKD - chronic kidney disease, CHD - coronary heart disease.

Table 6. The diagnostic test of logistic multivariate regression.

Logistic multivariate regression	Renal progression standard		Total
	+	-	
+	**42**	**147**	**189**
-	**7**	**407**	**414**
Total	**49**	**554**	**603**

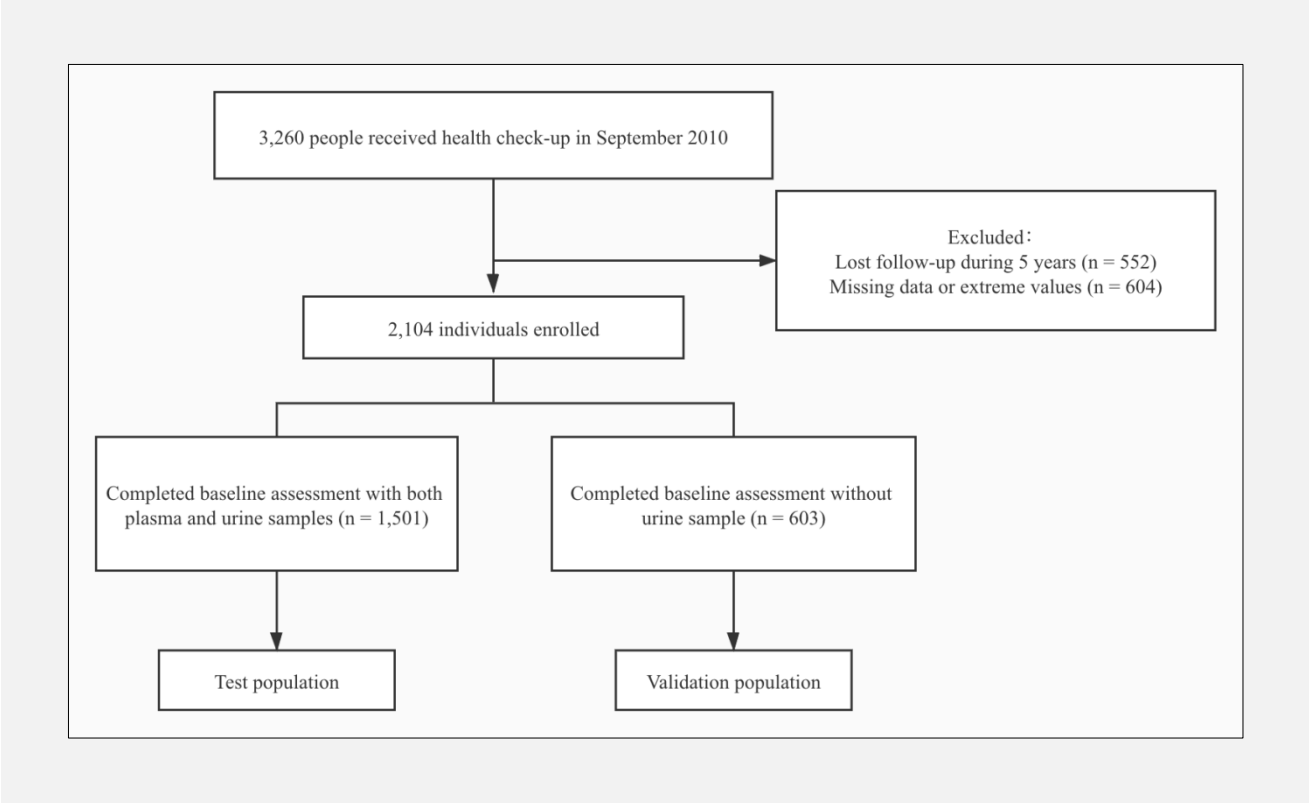


Figure 1. Flowchart of participants in the current study.

trol than HbA1c in dialysis and anemia patients, since it is not influenced by the lifespan of red blood cells or erythropoietin treatment [24,25]. In our study, baseline GA was correlated with baseline HbA1c level and mean GA significantly correlated with the mean FPG. These results reaffirmed the validity of GA as a monitoring marker of glucose level compared with traditional markers. Also, BMI, taken into consideration for obesity, was a risk factor for CKD. Spearman's correlations revealed an inverse correlation of BMI with GA in persons without renal progression and this finding is consistent with a previous report [26]. BMI was concluded as a confounder in the later multivariate regression analyses.

Linear regression analysis showed that high levels of baseline GA were associated with the decline of eGFR change rate. Also, by dividing subjects into quartiles, we found that a high level of baseline GA is related to the larger frequency of progression of renal dysfunction in our population. Among other studies, GA was proven to be independently associated with a decrease of renal function in specific population like non-diabetic or CKD patients [17]. The glycation of albumin plays a varied role in the deterioration of renal function. Our previous research showed GA can induce injury and inflammation in human proximal tubular epithelial cells [27]. Another study also demonstrated GA contributed to the activation of NADPH oxidase and led to the stimulation of TGF-β, resulting in increased extracellular matrix production in mesangial cells, a characteristic of

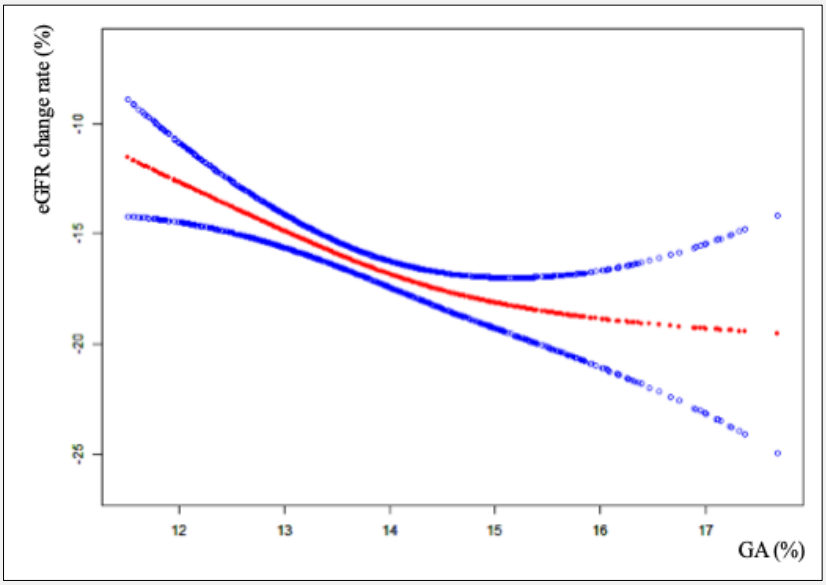
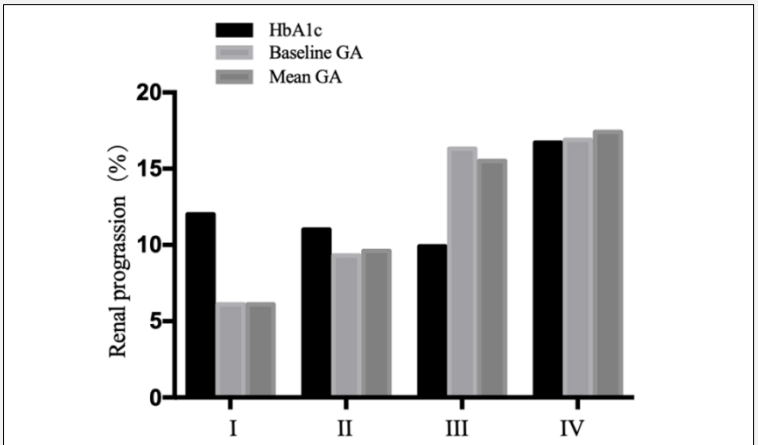


Figure 2. Trend for eGFR change rate relative to baseline GA.

The middle line represents the eGFR change rate corresponding to the GA value and the lines on sides reflect the 95 percentile confidence intervals.



Variate	Q1	Q2	Q3	Q4
baseline HbA1c (%)	<5.3	5.3-5.5	5.5-5.8	>5.8
baseline GA (%)	<13.0	13.0-13.7	13.7-14.5	>14.5
mean GA (%)	<13.8	13.8-14.7	14.7-15.7	>15.7

Figure 3. The frequencies of subjects with renal progression by quartiles of GA and HbA1c.

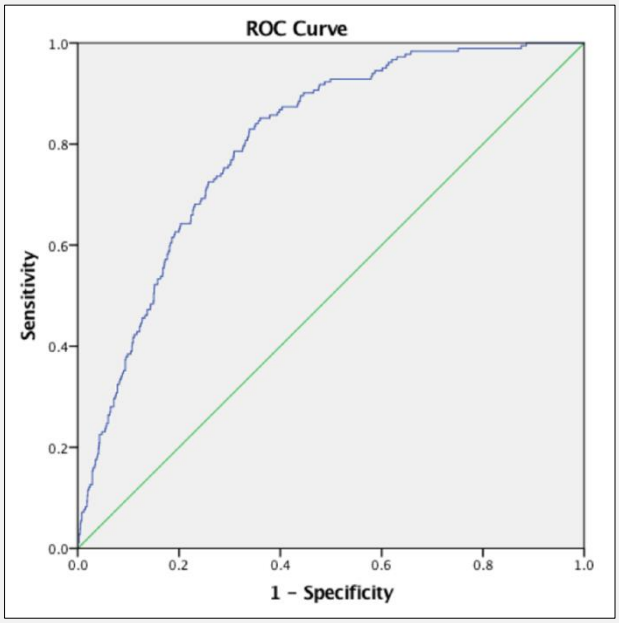


Figure 4. The receiver-operating characteristic curve of the multivariate logistic regression equation for predicting renal dysfunction.

The longitudinal axis means sensitivity to predict the probability of renal dysfunction. The x-axis (abscissa) means the false positive rate (1-specificity) of the prediction. The 45° straight line of the graph stands is the reference line, representing sensitivity being equal to false positive rate. The curve is farther from the reference line and nearer to the upper left corner of the graph. Area under the curve was 0.802 (95% confidence interval: 0.773 to 0.832, $p < 0.001$).

renal disease [28].

Combining our results and the above evidence, we hypothesized that GA would be a risk factor for renal insufficiency. The analysis showed that baseline GA had a greater impact on renal outcome than the mean GA, thus the predictive value of GA was preliminarily confirmed. We also found GA combined with other risk factors would be helpful to detect the early stage of renal dysfunction. When using logistic regression, we concluded 19 potential factors that may contribute to renal dysfunction based on literature review [29-31]. In the end, baseline GA, age, and UA were identified as risk factors for renal dysfunction. Another index influencing the outcome was Scr, and the above four elements constituted the equation for prediction model.

It is generally accepted that renal function decreases with age and analyses between cross-sectional and longitudinal studies were carried out [32]. Several studies have focused on the relationship between UA and renal function since hyperuricemia, the clinical manifestation of monosodium urate crystal deposition, is common in patients with CKD [33]. In an ambispective cohort study, the value of UA was significantly reduced among CKD patients receiving multidisciplinary care with improved eGFR decreases [34]. In our model, UA is a mild risk factor for renal dysfunction. Similar to our finding, several other studies also demonstrated that elevated UA independently predicts the risk of new-onset CKD and an increased likelihood of eGFR decline [35, 36]. Moreover, recent data suggest that UA may be an important factor in the pathogenesis of CKD and hypertension as well as AKI in general [37]. Hence, UA may not only be a marker but also a potential therapeutic target in kidney disease. Its association between multifactorial disorders of the kidney is worthy of more attention and more studies to clarify.

Elevated Scr is generally considered a sign of declining renal function, but it was not a risk factor in our model. This result may be limited to its baseline level and the extent of the change during our follow-up period. In this study, the endpoint of the event was defined by the rate of change in eGFR, and the changing degree of eGFR and Scr was noted (the average eGFR and Scr level did not differ between the two groups during follow-up). The endpoint Scr level in the progression group was significantly higher than the non-progression group, and the measured values during the follow-up period were within the normal reference interval. The performance

of the Scr in the model may be due to the fact that patients with higher baseline creatinine levels have less fluctuation range during follow-up and are less prone to renal function progression.

After building our model, we need further validations of its predictive effect. The ROC analysis was carried out in the same population and external validation was performed on another population using the equation obtained earlier. The predictive value of ROC was rather high with an AUC of 82% in the test population. For the validation group, it yielded a sensitivity of 85.7% and a specificity of 73.5% in predicting the renal dysfunction risk. These results confirmed the validity of the formula and ensured the predictive value of our model which may provide guidance for clinical detection of renal dysfunction.

In conclusion**,** GA not only has a wider range of application in the evaluation of blood glucose, but also can prompt renal function damage in a few years. It is not only simple and quick to measure, but also cost-effective for the patients. The test of GA costs ¥70 and it is covered by medical insurance. At present, GA is a supplementary indicator of HbA1c for short-term glucose monitoring for diabetic patients. In the future, it can also be used in the screening of the general population to ring the bell for potential renal dysfunction.

The strengths of our study comprise the use of data generated from a large-scale cohort, the availability of baseline medical information for participants, and the ability to adjust for well-recognized risk factors as needed. Moreover, our tests are non-invasive and cost-effective compared to renal biopsy. The population may be the greatest limitation of the study, both the test and validation people were from a single center and the impact of risk factors may vary by race and/or ethnicity. Our study was conducted in a Chinese population gathered in Beijing due to the objective condition. This may bias our results and whether the findings from this study can be extrapolated to other populations requires further verification.

CONCLUSION

This study provided support that glycated albumin was a risk factor for renal deterioration and the combination including baseline glycated albumin, age, serum creatinine, and uric acid had a proper predictive value for renal dysfunction.

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Declaration of Interest:
The authors did not declare any potential conflicts of interest.

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