Journal of Inflammation Research Dovepress

Open Access Full Text Article ORIGINAL RESEARCH

Serum Globulin and Albumin-to-Globulin Ratio are Associated with Diabetic Kidney Disease but Not Diabetic Retinopathy in Type 2 Diabetes Mellitus Patients: A Cross-Sectional Study

Ruo Zhang, Yang Jiao, Yuchao Wu, Lijing Yan, Chunhong Zhang, Jing Xu On behalf of the China National Diabetic Chronic Complications Study Group

Department of Endocrinology, The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi Province, People's Republic of China

Correspondence: Yang Jiao; Jing Xu, Department of Endocrinology, The Second Affiliated Hospital of Xi'an Jiaotong University, 157 Xiwu Road, Xi'an, Shaanxi Province, 710004, People's Republic of China, Tel +86 15029930210; +86 18092746638, Fax +862986320305, Email jyjoan@126.com; xujingjdefy85@163.com

Purpose: This study aimed to explore the association of globulin and albumin-to-globulin ratio (AGR) with diabetic kidney disease (DKD) and diabetic retinopathy (DR) in patients with type 2 diabetes mellitus (T2DM).

Methods: This study used data from the China National Diabetic Chronic Complications Study in Shaanxi Province. From April to May 2019, T2DM patients at disease surveillance sites in Shaanxi Province were investigated using a stratified multi-stage sampling method. The participants completed questionnaire surveys, anthropometric and blood pressure measurements, laboratory tests, and fundus photograph examinations. Multivariate Logistic regression and restricted cubic spline model were used to analyze the association of globulin and AGR with DKD and DR, and subgroup analysis was performed according to age, sex, and diabetes duration to test the stability of the results.

Results: A total of 1494 T2DM patients were enrolled in this study, including 495 patients with DKD (33.1%) and 341 patients with DR (22.8%). After adjusting for all covariates, globulin and AGR were linearly associated with DKD. For every 1g/L increase in globulin level, the risk of DKD increased by 7% (OR=1.07, 95% CI=1.04, 1.10). For every 1 unit increase in AGR, the risk of DKD was reduced by 55% (OR=0.45, 95% CI=0.28, 0.72). Subgroup analysis showed that the association between globulin and DKD was consistent across all subgroups, and the association between AGR and DKD was consistent across subgroups of age and diabetes duration; however, only in males, higher AGR was associated with a reduced risk of DKD. No association was found between globulin and AGR with DR.

Conclusion: Globulin is an independent risk factor and AGR is an independent protective factor for DKD. Screening for DKD should be performed in T2DM patients with high globulin and low AGR levels, especially in men.

Keywords: globulin, albumin-to-globulin ratio, diabetic kidney disease, diabetic retinopathy

Introduction

Type 2 diabetes mellitus (T2DM) is a common chronic disease, and its incidence has increased at an alarming rate in recent years. According to the International Diabetes Federation, the global prevalence of T2DM is expected to rise to 10.2% (578 million people) by 2030 and 10.9% (700 million people) by 2045.[1] Among them, China has the largest number of T2DM patients, accounting for about one-quarter of the total number of T2DM patients worldwide.[2] Shaanxi Province is located in the northwest region of China, where the staple food is wheat products such as steamed bread and noodles. Compared with southern and coastal areas of China, the economy here is less developed and the health literacy of residents is relatively weak,[3,4] all of which may affect the prevalence of T2DM. Three waves of surveys on chronic

Received: 14 September 2024
Accepted: 14 December 2024
Published: 24 December 2024

diseases and nutrition monitoring were conducted in 10 counties of Shaanxi Province in 2013, 2015, and 2018, and the data showed that the prevalence of T2DM was as high as 11.16%.[4]

The threat of T2DM to human health mainly comes from chronic complications, among which diabetic kidney disease (DKD) and diabetic retinopathy (DR) are the most common microvascular complications of T2DM. The occurrence of DKD and DR are closely related, and many studies have shown that DKD and DR can predict each other.[5–7] About 30–40% of T2DM patients have DKD,[8] and nearly 50% of them will eventually develop end-stage kidney disease,[9] shortening the life span of T2DM patients. About one-third of T2DM patients will have DR, which can rapidly progress to vision-threatening DR if not treated promptly, resulting in irreversible vision impairment.[10] Studies have shown that DR is the leading cause of acquired vision loss in the working-age population,[11] and is the fifth most common cause of blindness among people over 50 years old worldwide.[12] DKD and DR seriously affect the quality of life of T2DM patients and also bring heavy medical burdens to patients and society. Information on DKD and DR and related risk factors in Shaanxi Province is lacking. Therefore, it is necessary to comprehensively study the risk factors of DKD and DR, and conduct early screening for DKD and DR to improve the prognosis and quality of life of T2DM patients.

Studies have shown that controlling blood glucose alone cannot prevent the development of chronic microvascular complications of T2DM,[13] so attention has focused on the relationship between other risk factors such as inflammation and chronic microvascular complications. Inflammation plays a crucial role in the occurrence and progression of DKD and DR.[14] Serum albumin and globulin are biomarkers of systemic inflammation, and the relationship between lower levels of serum albumin and increased risk of DKD and DR has been well described,[15–20] but this is not the case for serum globulin. Globulin is synthesized and secreted by liver and plasma cells in response to inflammation and infection. Globulin is the main component of non-albumin in serum and is composed of a variety of proinflammatory proteins including immunoglobulin and acute phase proteins.[21] Elevated serum globulin concentrations are the result of the accumulation of immunoglobulins and acute inflammatory proteins, and these changes are key markers of the degree and severity of inflammation and immune.[22] However, its clinical significance in diabetic microvascular complications is unclear. A previous study in a US population has reported that high levels of globulin increase the risk of DKD in T2DM patients,[23] but that study did not collect information on DR in T2DM, which limits the exploration of the association between globulin and DR, as well as fail to take into account the effect of DR on the association between globulin and DKD since the occurrence of DKD and DR is closely related.[5–7] In addition, the study population was a US population, and there is a lack of research on the association of globulin with DKD and DR in the Chinese population. The albumin-to-globulin ratio (AGR) can comprehensively consider the levels of albumin and globulin and is also a marker of inflammation and infection in the body.[24] Recent studies have reported that AGR was an independent predictor of chronic kidney disease development.[25] Another study in adolescents with type 1 diabetes has found that reduced AGR was associated with early DKD.[26] However, there are no studies on the association of AGR with DKD and DR in T2DM patients.

Therefore, this study aimed to systematically explore the association of globulin and AGR with DKD and DR in a population in Northwest China, considering the effects of DKD and DR on each other's occurrence. Our primary hypothesis was there would be an association between globulin/AGR and DKD/DR.

Materials and Methods

Study Design and Participants

This study used the data of the China National Diabetic Chronic Complications Study (China DiaChronic Study) in Shaanxi Province. The China DiaChronic Study protocol has been described in detail previously.[27] In brief, the China DiaChronic Study was designed to investigate the prevalence of diabetes-related complications and the compliance rate of metabolic indicators in Chinese adults with diabetes between March 2018 and January 2020. The multi-stage stratified cluster random sampling method was used to sample study participants based on the China Chronic Disease and Risk Factors Surveillance points in 31 provinces, autonomous regions, and municipalities in China.[27] In Shaanxi Province, two disease surveillance points (DSPs) in urban areas and two DSPs in rural areas were first selected after considering urbanization levels; then, four neighborhoods in urban areas or four villages in rural areas were selected as study sites

from each DSP. After the total sample size was evenly distributed among study sites, 113 participants were sampled at each study site according to age- and sex- structure.

From April to May 2019, the study recruited T2DM patients aged 18–74 years who had resided at the sampling sites for 6 months or more of the last year before the survey in Shaanxi Province. Pregnant women and study subjects who could not participate because of serious illness were excluded. This study investigated 1777 T2DM patients in Shaanxi Province, after excluding participants with chronic kidney disease (n=91), liver disease (n=135), cancer (n=8), with missing value on urine albumin (n=13), without screening for DR (n=36), a total of 1494 participants were included in the final analysis (Figure 1).

Data Collection

Data collection of each participant included questionnaire surveys, anthropometric and blood pressure measurements, laboratory tests, and fundus photograph examinations. All data were collected by uniformly trained Chinese Diabetes Society (CDS) and Center for Disease Control and Prevention (CDC) medical staff at local community health service centers or hospitals. Social demographic characteristics, diabetes duration, blood glucose control methods, lifestyle, disease history, and family history of diabetes were collected by face-to-face interviews using a tablet computer.

Anthropometric measurements including height and weight were measured according to the standard protocol.[27] The measurement precision of height and weight was 0.1cm and 0.1kg, respectively. Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared. Blood pressure was measured in the left arm three times at 1-minute intervals with participants in a seated position after a 5-minute rest. The average of three blood pressure measurements was used in this study.

Blood samples after a 10-hour overnight fast and random urine samples were collected. Fasting plasma glucose (FPG) was tested by local laboratories with unified quality control within 48 hours. Blood and urine samples were stored, and after completing the survey in a neighborhood or village, the samples were transported in the temperature range of 2–8 °C to the Guangzhou KingMed Diagnostics Group Co., Ltd. (Guangzhou, China) for testing of hemoglobin A1c (HbA1c), serum creatinine, total cholesterol (TC), low-density lipoprotein (LDL_C), high-density lipoprotein (HDL_C), triglycerides (TG), alanine transaminase (ALT), aspartate transaminase (AST), serum albumin, serum globulin, urine albumin, and urine creatinine concentrations. AGR was calculated by dividing serum albumin by serum globulin. Urine albumin-to-creatinine ratio (UACR) was calculated by dividing urine albumin by urine creatinine.

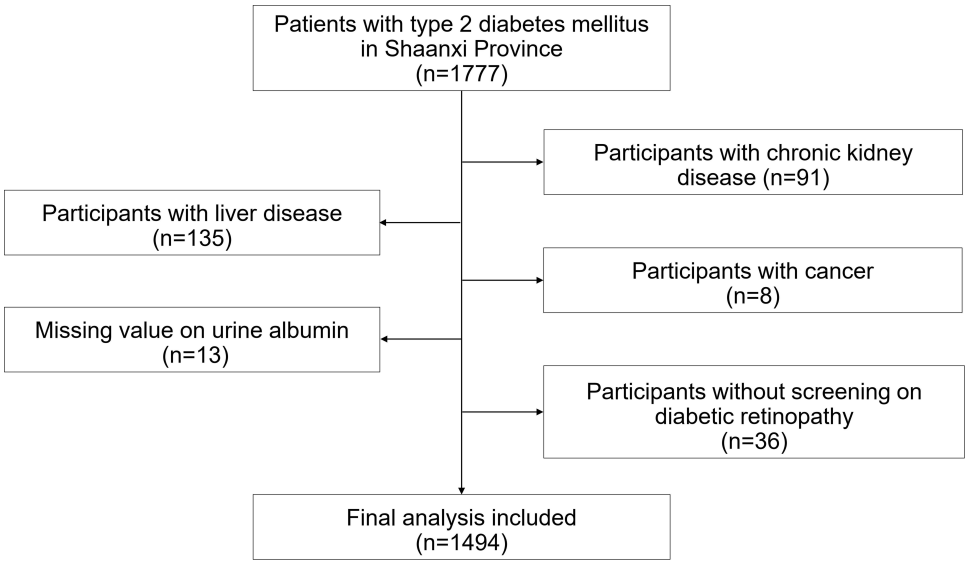

Figure 1 Flow chart of study participants.

Definition of DKD

The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI).[28] DKD was defined as eGFR<90 mL/min/1.73m^2 and/or UACR ≥ 30mg/g in the absence of signs of other causes of kidney damage.[29]

Definition of DR

Participants sat in a dark room with no windows and their pupils dilated naturally for fundus photograph examinations. A digital non-mydriatic retinal camera (Canon CR-2; Canon Inc., Tokyo, Japan or TRC-NW400; Topcon Corporation, Tokyo, Japan) was used to take two 45-degree color fundus photos of each of the subjects' eyes, one centered on the optic disc and the other centered on the macula. According to the 2002 International Clinical Diabetic Retinopathy Disease Severity Scales,[30] the photographs taken were reviewed and graded by a team of eight ophthalmologists from the Department of Ophthalmology of the Shanghai Sixth People's Hospital affiliated to Shanghai Jiao Tong University School of Medicine. The presence and severity of DR were identified and graded as no obvious DR, non-proliferative DR (including mild, moderate, and severe non-proliferative DR), and proliferative DR. These ophthalmologists underwent standardized training, and each photo was reviewed independently by two ophthalmologists. If the grading diagnosis of DR was inconsistent, a third senior ophthalmologist reviewed and obtained the final grading diagnosis. During the diagnosis process, all the ophthalmologists were blind to the participant's condition and the grading of the photographs by other ophthalmologists. In this study, DR was defined as the presence of any degree of DR in either eye (including mild non-proliferative, moderate non-proliferative, severe non-proliferative, and proliferative DR).

Statistical Analysis

All statistical analyses were performed using SAS (version 9.3, SAS Institute, Cary, NC, USA). A two-tailed $P<0.05$ was considered statistically significant. Continuous variables were expressed as median (25th percentile, 75th percentile) and compared between groups using the Wilcoxon rank test. Categorical variables were expressed as number (percentage) and compared between groups using the Chi-Square test.

The Logistic regression model was used to estimate the association of continuous and tertiles of globulin and AGR with DKD and DR. According to previous literature reports,[15,17,20,23] age, sex, educational level, family history of diabetes, diabetes duration, blood glucose control methods, hypertension, BMI, lipids, and other liver function biomarkers have been suggested as potential confounders. In our study, age, sex, educational level, diabetes family history, duration, glucose control methods, hypertension, BMI, FPG, HbA1c, TC, HDL_C, TG, AST, and ALT had significant differences between DKD and non-DKD groups or between DR and non-DR groups, and were selected as covariates. In addition, the occurrence of DKD and DR were also influenced by each other,[5–7] the other complication was also considered a covariate when studying one complication. Variance inflation factor (VIF) was used to detect the multicollinearity of these covariates. The covariates of VIF>5 (FPG and HDL_C) were removed from the model. Three models were established to control for covariates step by step: the unadjusted Model, Model 1, and Model 2. Model 1 adjusted for age, sex, and education level; Model 2 adjusted for age, sex, educational level, HbA1c, diabetes duration, blood glucose control methods, family history of diabetes, hypertension, BMI, TC, TG, AST, ALT and DR (the outcome was DKD) or DKD (the outcome was DR). For globulin, Model 2 additionally adjusted the level of albumin. To test the linear trend, the median value for each tertile of globulin and AGR was included in the regression model as a continuous variable. In addition, restricted cubic splines (RCS) with three knots at the 10th, 50th, and 90th percentiles of globulin and AGR were further used to explore the possible dose-response or non-linear relationship of globulin and AGR with DKD and DR. Lastly, subgroup analyses were conducted based on age, sex, and diabetes duration to test the robustness of the association of interest.

Results

Characteristics of the Study Participants

A total of 1494 T2DM patients were included in this study (Table 1). In general, the median age of the subjects was 57.7 years old (50.6, 65.5), with 406 (27.2%) individuals aged 65 years old and above. There were 495 (33.1%) patients with

Table 1 Characteristics of the Study Participants [a]

	Total (n=1494)	DKD+ (n=495)	DKD- (n=999)	P[b]	DR+ (n=341)	DR- (n=1153)	P[b]
Age, years	57.7 (50.6, 65.5)	60.8 (53.8, 67.4)	56.5 (49.4, 64.0)	<0.001	60.4 (54.4, 67.1)	57.0 (49.5, 65.0)	<0.001
Age, n(%)				<0.001			0.002
<65 years	1088 (72.8)	318 (64.2)	770 (77.1)		226 (66.3)	862 (74.8)	
≥ 65 years	406 (27.2)	177 (35.8)	229 (22.9)		115 (33.7)	291 (25.2)	
Sex, n(%)				0.002			0.341
Male	746 (49.9)	276 (55.8)	470 (47.0)		178 (52.2)	568 (49.3)	
Female	748 (50.1)	219 (44.2)	529 (53.0)		163 (47.8)	585 (50.7)	
Area, n(%)				0.617			0.325
Urban	723 (48.4)	235 (47.5)	488 (48.8)		173 (50.7)	550 (47.7)	
Rural	771 (51.6)	260 (52.5)	511 (51.2)		168 (49.3)	603 (52.3)	
Educational level, n(%)				<0.001			0.037
Primary school or below	408 (27.3)	162 (32.7)	246 (24.7)		111 (32.5)	297 (25.8)	
Middle school	488 (32.7)	175 (35.4)	313 (31.3)		108 (31.7)	380 (32.9)	
High school or above	598 (40.0)	158 (31.9)	440 (44.0)		122 (35.8)	476 (41.3)	
Current smoker, n(%)	358 (24.0)	115 (23.2)	243 (24.3)	0.642	80 (23.5)	278 (24.1)	0.805
Current drinker, n(%)	374 (25.0)	126 (25.5)	248 (24.8)	0.791	77 (22.6)	297 (25.8)	0.234
Diabetes family history, n(%)	559 (37.4)	194 (39.2)	151 (15.1)	0.318	156 (45.7)	403 (35.0)	<0.001
Duration, years	4.1 (1.7, 8.9)	5.6 (2.9, 11.2)	3.7 (1.2, 7.1)	<0.001	8.3 (4.0, 14.4)	3.6 (1.2, 6.9)	<0.001
Duration, n(%)				<0.001			<0.001
<5 years	839 (56.2)	224 (45.3)	615 (61.6)		119 (34.9)	720 (62.4)	
≥5 years	655 (43.8)	271 (54.7)	384 (38.4)		222 (65.1)	433 (37.6)	
Glucose control methods, n(%)				<0.001			<0.001
None	215 (14.4)	44 (8.9)	171 (17.1)		18 (5.3)	197 (17.1)	
Diet and exercise	251 (16.8)	59 (11.9)	192 (19.2)		42 (12.3)	209 (18.1)	
Hypoglycemic drugs	784 (52.5)	269 (54.3)	515 (51.6)		166 (48.7)	618 (53.6)	
Hypoglycemic drugs and insulin injection	244 (16.3)	123 (24.8)	121 (12.1)		115 (33.7)	129 (11.2)	
Hypertension, n(%)	875 (58.6)	376 (76.0)	499 (49.9)	<0.001	225 (66.0)	650 (56.4)	0.002
BMI, kg/m^2	25.1 (23.0, 27.2)	25.4 (23.3, 27.5)	24.9 (22.8, 26.9)	0.006	24.7 (22.8, 26.8)	25.1 (23.0, 27.3)	0.040
BMI, n(%)				0.015			0.177
<24 kg/m^2	541 (36.2)	155 (31.3)	386 (38.6)		128 (37.5)	413 (35.8)	
24–27.9 kg/m^2	669 (44.8)	233 (47.1)	426 (43.6)		160 (46.9)	509 (44.2)	
≥28 kg/m^2	284 (19.0)	107 (21.6)	177 (17.8)		53 (15.6)	231 (20.0)	
FPG, mmol/L	7.34 (5.80, 9.74)	8.63 (6.86, 11.60)	6.80 (5.58, 8.79)	<0.001	9.01 (6.90, 12.36)	6.99 (5.66, 8.99)	<0.001
HbA1c, %	7.0 (5.7, 8.6)	8.0 (6.6, 9.7)	6.5 (5.5, 7.9)	<0.001	8.2 (6.7, 10.0)	6.7 (5.6, 8.0)	<0.001
TC, mmol/L	4.58 (4.01, 5.21)	4.65 (4.04, 5.32)	4.55 (3.97, 5.17)	0.042	4.55 (4.02, 5.37)	4.58 (4.00, 5.19)	0.608

(*Continued*)

https://doi.org/10.2147/JIR.S492681

Table 1 (Continued).

	Total (n=1494)	DKD+ (n=495)	DKD- (n=999)	*P*[b]	DR+ (n=341)	DR- (n=1153)	*P*[b]
LDL_C, mmol/L	2.71 (2.12, 3.22)	2.71 (2.03, 3.27)	2.70 (2.15, 3.21)	0.812	2.68 (2.15, 3.30)	2.71 (2.11, 3.20)	0.458
HDL_C, mmol/L	1.24 (1.05, 1.48)	1.22 (1.03, 1.44)	1.26 (1.06, 1.49)	0.033	1.26 (1.05, 1.53)	1.24 (1.05, 1.47)	0.374
TG, mmol/L	1.68 (1.18, 2.48)	1.79 (1.26, 2.73)	1.62 (1.16, 2.36)	<0.001	1.63 (1.12, 2.43)	1.70 (1.19, 2.53)	0.241
ALT, U/L	17 (13, 23)	18 (14, 23)	17 (13, 22)	0.048	16 (12, 21)	18 (14, 23)	0.001
AST, U/L	18 (16, 22)	18 (16, 22)	18 (16, 22)	0.746	18 (15, 21)	18 (16, 22)	0.002
Urine albumin, mg/L	21.1 (7.8, 53.7)	85.1 (47.5, 201.3)	11.1 (5.3, 22.3)	<0.001	37.6 (12.0, 119.8)	18.1 (7.0, 45.5)	<0.001
Urine creatinine, g/L	1.3 (0.9, 1.8)	1.1 (0.8, 1.7)	1.3 (0.9, 1.8)	<0.001	1.1 (0.8, 1.6)	1.3 (0.9, 1.8)	<0.001
UACR, mg/g	15.3 (6.3, 41.7)	69.5 (42.0, 178.7)	8.5 (4.7, 15.8)	<0.001	30.4 (10.3, 130.0)	12.9 (5.7, 33.3)	<0.001
Serum creatinine, μmol/L	66 (57, 77)	69 (56, 82)	65 (57, 75)	<0.001	68 (57, 79)	66 (56, 76)	0.040
eGFR, mL/min/1.73 m^2	99.27 (89.78, 107.09)	95.46 (84.99, 105.18)	100.58 (91.83, 107.99)	<0.001	95.72 (85.93, 104.73)	100.11 (91.04, 107.84)	<0.001
Albumin, g/L	49.2 (47.3, 50.9)	49.1 (47.2, 50.9)	49.2 (47.3, 50.9)	0.557	48.7 (46.7, 50.4)	49.4 (47.5, 51.1)	<0.001
Globulin, g/L	29.1 (26.6, 31.8)	29.9 (27.6, 32.8)	28.7 (26.1, 31.3)	<0.001	29.7 (27.2, 32.2)	29.0 (26.4, 31.8)	0.026
AGR	1.69 (1.52, 1.87)	1.63 (1.47, 1.80)	1.70 (1.55, 1.91)	<0.001	1.65 (1.48, 1.80)	1.70 (1.54, 1.89)	<0.001

Notes: [a]Data were expressed as median (25^{th} percentile, 75^{th} percentile) for continuous variables or number (percentage) for categorical variables. [b]*P* values for the differences between groups were derived from the Wilcoxon rank test for continuous variables, and the Chi-Square test for categorical variables.

Abbreviations: AGR, albumin-to-globulin ratio; ALT, alanine aminotransferase; AST, aspartate transaminase; BMI, body mass index; DKD, diabetic kidney disease; DR, diabetic retinopathy; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HDL_C, high-density lipoprotein cholesterol; LDL_C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; UACR, urine albumin-to-creatinine ratio.

DKD and 341 (22.8%) patients with DR. Compared with patients without DKD or DR, those with DKD or DR had higher levels of globulin and lower levels of AGR. For other baseline characteristics, DKD or DR patients both had older age, longer duration of diabetes, a higher proportion of insulin use, a higher proportion of hypertension, higher BMI, higher levels of FPG, HbA1c, urinary albumin, UACR, serum creatinine, and ALT. They both had lower levels of education, urinary creatinine, and eGFR as compared with those without DKD or DR. Inconsistently, DKD patients had a higher proportion of male participants, higher levels of TC, TG, and lower levels of HDL_C, while DR patients had a higher proportion of diabetes family history and higher AST levels. The characteristics of participants according to the tertiles of globulin and AGR were shown in Supplementary Tables 1 and 2.

Association Between Globulin and AGR with DKD

Table 2 shows the association of continuous and tertiles of globulin and AGR with DKD by Logistic regression analysis. After adjusting for all covariates, we found that the highest and medium tertiles of globulin were associated with a higher risk of DKD in comparison to the lowest tertile (T3 vs T1: OR=2.09, 95% CI=1.52, 2.88; T2 vs T1: OR=1.44, 95% CI=1.06, 1.97), and the test for linear trend was significant (*P* for trend<0.001). For every 1g/L increase in globulin levels, the risk of DKD increased by 7% (OR=1.07, 95% CI=1.04, 1.10). As for AGR, the highest and medium tertiles of AGR were associated with a lower risk of DKD in comparison to the lowest tertile (T3 vs T1: OR=0.55, 95% CI=0.40, 0.76; T2 vs T1: OR=0.72, 95% CI=0.54, 0.96), and the test for linear trend was significant (*P* for trend=0.001). For every 1 unit increase in AGR, the risk of DKD was reduced by 55% (OR=0.45, 95% CI=0.28, 0.72). Then we used the RCS model to analyze whether there was a potential nonlinear association of globulin and AGR with DKD. As shown in Figure 2a and b, after adjusting for all covariates, the relationship of globulin (*P* for overall<0.001, *P* for non-linear=0.651) and AGR (*P* for overall=0.004, *P* for non-linear=0.601) with DKD were both linear. In summary, globulin was positively associated with DKD, and AGR was negatively associated with DKD.

Association Between Globulin and AGR with DR

Table 3 shows the association of continuous and tertiles of globulin and AGR with DR using Logistic regression analysis. No association was found between globulin and AGR with DR. Similarly, the RCS model also did not find any association between globulin and AGR with DR (Figure 2c and d). In summary, globulin and AGR were not associated with DR.

Table 2 Association of Globulin and AGR with DKD in the Logistic Regression Models

		Event (%)	OR (95% CI)		
			Unadjusted Model	Model 1[a]	Model 2[b]
Globulin (continuous)		495 (33.1)	1.08 (1.05, 1.11)	1.08 (1.05, 1.11)	1.07 (1.04, 1.10)
Globulin tertiles (g/L)	T3 (>30.7)	204 (41.0)	2.24 (1.70, 2.94)	2.21 (1.65, 2.96)	2.09 (1.52, 2.88)
	T2 (27.5–30.7)	174 (34.5)	1.69 (1.28, 2.24)	1.67 (1.25, 2.23)	1.44 (1.06, 1.97)
	T1 (≤27.4)	117 (23.7)	Ref	Ref	Ref
	P for trend[c]		<0.001	<0.001	<0.001
AGR (continuous)		495 (33.1)	0.32 (0.21, 0.49)	0.35 (0.22, 0.55)	0.45 (0.28, 0.72)
AGR tertiles	T3 (>1.80)	130 (25.8)	0.49 (0.37, 0.64)	0.52 (0.39, 0.69)	0.55 (0.40, 0.76)
	T2 (1.59–1.80)	163 (32.3)	0.67 (0.52, 0.87)	0.69 (0.53, 0.90)	0.72 (0.54, 0.96)
	T1 (≤1.58)	202 (41.6)	Ref	Ref	Ref
	P for trend[c]		<0.001	<0.001	<0.001

Notes: [a]Model 1: adjusted for age, sex and education level. [b]Model 2: adjusted for age, sex, educational level, HbA1c, duration, glucose control methods, diabetes family history, hypertension, BMI, TC, TG, AST, ALT, and DR, whereas for globulin, the level of albumin was additionally adjusted. [c]*P* for trend was obtained using the median value of each globulin or AGR tertile as a continuous variable in the regression models.

Abbreviations: AGR, albumin-to-globulin ratio; CI, confidence interval; DKD, diabetic kidney disease; OR, odds ratio.

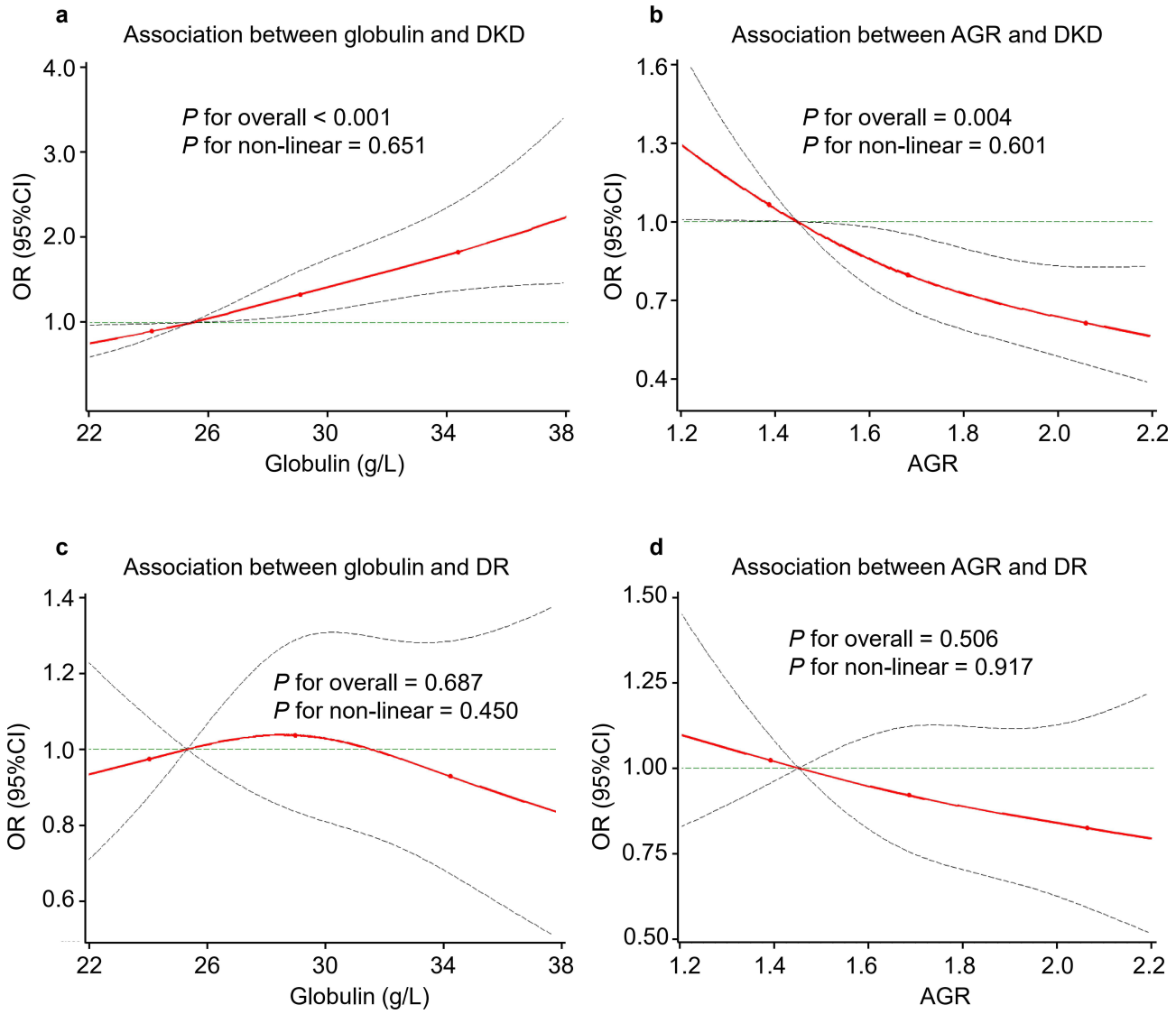

Figure 2 Dose-response relationship of globulin and AGR with DKD and DR using RCS regression. (**a**) Association between globulin and DKD. (**b**) Association between AGR and DKD. (**c**) Association between globulin and DR. (**d**) Association between AGR and DR.

Notes: ORs with a 95% CI were obtained from the multivariable model adjusted for age, sex, educational level, HbA1c, duration, glucose control methods, diabetes family history, hypertension, BMI, TC, TG, AST, ALT, and DR (the outcome was DKD) or DKD (the outcome was DR), whereas for globulin, the level of albumin was additionally adjusted. The globulin and albumin-to-globulin ratio was considered continuous exposure, and three knots (represented by dots) were placed at the 10th, 50th, and 90th percentiles of the distribution of globulin and albumin-to-globulin ratio in the entire population. The reference value for globulin and albumin-to-globulin ratio was the median value in the tertile 1 group of 25.4 g/L and 1.45, respectively. Solid lines indicate ORs and dashed lines indicate 95% confidence intervals.

Abbreviations: AGR, albumin-to-globulin ratio; CI, confidence interval; DKD, diabetic kidney disease; DR, diabetic retinopathy; OR, odds ratio; RCS, restricted cubic splines.

Subgroup Analysis of the Association Between Globulin and AGR with DKD and DR

We then stratified the participants according to age, sex, and diabetes duration to explore the association of globulin and AGR with DKD and DR respectively (Figure 3). For DKD, we found that the association between globulin and DKD was consistent across all subgroups, and the association between AGR and DKD was consistent across subgroups of age and diabetes duration; however, only in males, we found a higher AGR was associated with a reduced risk of DKD. The characteristics of participants according to sex and DKD status in different sexes were shown in Supplementary Tables 3 and 4. For DR, no association of globulin and AGR with DR was found in any subgroup.

Table 3 Association of Globulin and AGR with DR in the Logistic Regression Models

		Event (%)	OR (95% CI)		
			Unadjusted Model	Model 1[a]	Model 2[b]
Globulin (continuous)		341 (22.8)	1.03 (1.00, 1.06)	1.01 (0.98, 1.05)	0.99 (0.96, 1.03)
Globulin tertiles (g/L)	T3 (>30.7)	122 (24.5)	1.44 (1.06, 1.95)	1.28 (0.93, 1.76)	1.00 (0.70, 1.44)
	T2 (27.5–30.7)	128 (25.4)	1.50 (1.11, 2.04)	1.39 (1.02, 1.90)	1.15 (0.81, 1.62)
	T1 (≤27.4)	91 (18.5)	Ref	Ref	Ref
	P for trend[c]		0.026	0.175	0.944
AGR (continuous)		341 (22.8)	0.40 (0.25, 0.63)	0.48 (0.29, 0.78)	0.73 (0.42, 1.25)
AGR tertiles	T3 (>1.80)	91 (18.1)	0.57 (0.42, 0.77)	0.65 (0.47, 0.90)	0.83 (0.58, 1.18)
	T2 (1.59–1.80)	115 (22.8)	0.77 (0.58, 1.03)	0.81 (0.61, 1.09)	0.92 (0.67, 1.27)
	T1 (≤1.58)	135 (27.8)	Ref	Ref	Ref
	P for trend[c]		<0.001	0.008	0.295

Notes: [a]Model 1: adjusted for age, sex and education level. [b]Model 2: adjusted for age, sex, educational level, HbA1c, duration, glucose control methods, diabetes family history, hypertension, BMI, TC, TG, AST, ALT, and DKD, whereas for globulin, the level of albumin was additionally adjusted. [c]*P* for trend was obtained using the median value of each globulin or AGR tertile as a continuous variable in the regression models.
Abbreviations: AGR, albumin-to-globulin ratio; CI, confidence interval; DR, diabetic retinopathy; OR, odds ratio.

Discussion

Main Findings and Clinical Implications

This study comprehensively analyzed the association of serum globulin and AGR with DKD and DR in T2DM patients. We found there was a positive linear relationship between globulin and DKD, and a negative linear relationship between AGR and

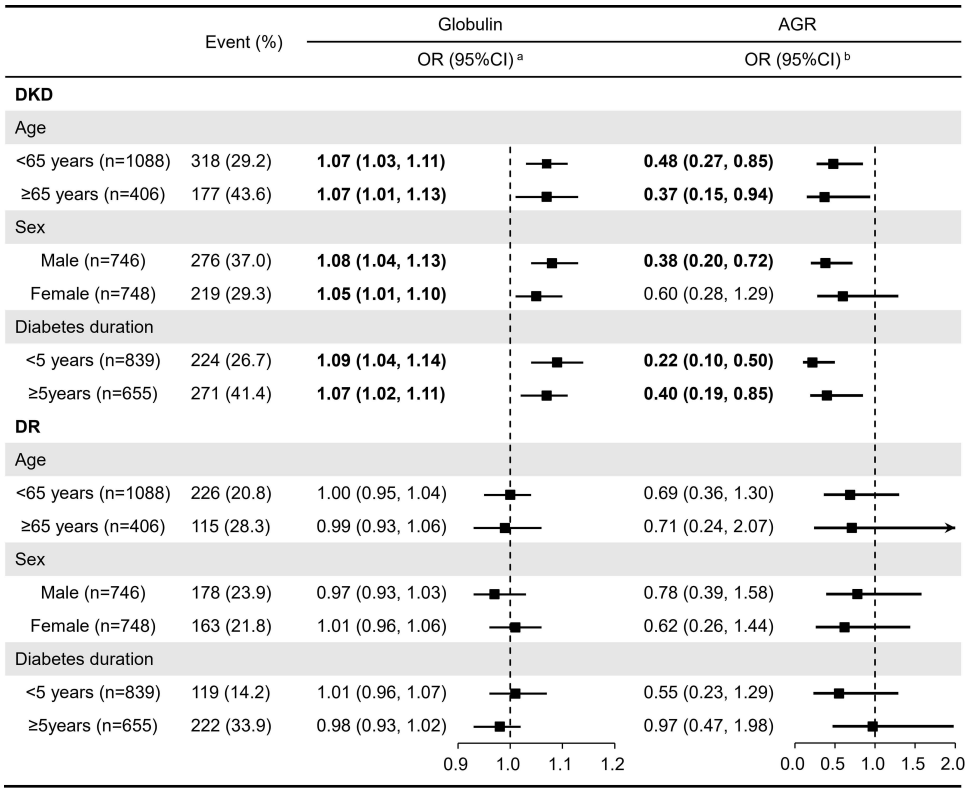

Figure 3 Subgroup analysis of the effect of globulin and AGR on DKD and DR.
Notes: [a]OR with a 95% CI was obtained from the multivariable Logistic regression model after adjusting for age, sex, educational level, HbA1c, duration, glucose control methods, diabetes family history, hypertension, BMI, TC, TG, AST, ALT, albumin, and DR (the outcome was DKD) or DKD (the outcome was DR) except for the stratification factor. [b]OR with a 95% CI was obtained from the multivariable Logistic regression model after adjusting for age, sex, educational level, HbA1c, duration, glucose control methods, diabetes family history, hypertension, BMI, TC, TG, AST, ALT, and DR (the outcome was DKD) or DKD (the outcome was DR) except for the stratification factor.
Abbreviations: AGR, albumin-to-globulin ratio; CI, confidence interval; DKD, diabetic kidney disease; DR, diabetic retinopathy; OR, odds ratio.

DKD. Further subgroup analysis showed that the association between globulin and DKD was consistent across all subgroups, and the association between AGR and DKD was consistent across subgroups of age and diabetes duration; however, only in males, higher AGR was associated with a reduced risk of DKD. These results suggest that DKD screening should be performed in T2DM patients with high globulin and low AGR levels, especially in men.

Globulin is Associated with DKD

Globulin levels are closely related to immune and inflammatory states, and studies have shown that globulin is positively correlated with the severity of chronic inflammation.[31] A previous cohort study of the Pima Indian population found that high levels of globulin were associated with T2DM,[32] confirming the role of globulin in the development of T2DM. In the past, one study analyzed the association between serum globulin and DKD risk in 4393 diabetes people in the United States, and found that high levels of globulin increased the risk of DKD (OR=1.10, 95% CI=1.07, 1.13, $P<0.001$);[23] however, DR, an important influencing factor of DKD, was not collected and adjusted in this study. Our study used multivariate Logistic regression and RCS model, and after adjusting a series of covariates such as DR and serum albumin, we also found a positive association between globulin and DKD, that is, globulin is an independent risk factor for DKD, and this association is linear.

In the inflammatory mechanism of DKD, the overexpression of proinflammatory cytokines and chemokines and the increase of endothelial cell adhesion molecules may promote the occurrence and development of DKD.[33] The underlying mechanism of globulin and DKD can be partially explained by several studies. Previous studies have shown that serum globulin is positively correlated with inflammatory cytokines such as IL-6, IL-8, and TNF-α, which are involved in the inflammatory process.[21,34] These inflammatory factors can increase the permeability of vascular endothelial cells, induce endothelial cell apoptosis, directly cause toxicity to renal cells, and participate in the occurrence of DKD.[35] On the other hand, an increase in globulin levels can stimulate the secretion of neutrophils.[36] It has been shown that the degree of neutrophil spontaneous adhesion was significantly greater in T2DM patients with overt proteinuria than that in T2DM patients with normal albuminuria. Increased spontaneous adhesion of neutrophils stimulated by the proinflammatory factors granulocyte-macrophage colony-stimulating factor (GM-CSF) and TNF may play a role in the progression of DKD.[37] In addition, globulin is a combination of multiple proteins with immunoglobulin as the main component, and the high globulin content may reflect the increased production of immunoglobulin and/or the increased humoral immune activity.[38] Large amounts of immunoglobulin deposits were found in the kidneys of diabetic patients.[39] Studies have shown that IgM deposits in the kidney bind directly to antigens expressed by damaged endothelial cells, leading to endothelial dysfunction of glomerular capillaries and accelerating the progression of DKD.[40] The deposition of IgG in the kidneys causes changes in the permeability of the glomerular filtration membrane, which leads to changes in the charge on both sides of the basement membrane, and ultimately leads to changes in the structure of the glomerular basement membrane, which is involved in the development of DKD.[41] The increase of IgA-positive B cells can increase the accumulation of IgA in the kidney, causing hematuria, proteinuria, and changes in renal function.[42]

AGR is Associated with DKD

To the best of our knowledge, we are the first study on the association of AGR with DKD and DR. Our study found that a higher AGR level was a protective factor for DKD. Previous studies have also reported a negative correlation between AGR and chronic inflammation.[43] For example, studies in non-chronic kidney disease populations have found that low AGR was an independent predictor of the development of chronic kidney disease and had a stronger predictive value than other inflammatory markers such as white blood cell count and high-sensitivity C-reactive protein.[25] Under inflammatory and infectious conditions, there is an inverse relationship between albumin and globulin, resulting in a decrease in AGR.[44] In our study, patients with a higher AGR had higher albumin levels and lower globulin levels (Supplementary Table 2). Therefore, a higher AGR may be caused by high levels of albumin, low levels of globulin, or a combination of both. The positive association between serum globulin levels and DKD has been explained in the previous section. As for albumin, it has been reported to be negatively regulated by the acute phase reactants and is considered a biomarker of inflammation and nutritional status,[45] and it decreases after inflammatory stimulation.[46] Albumin is synthesized and secreted by liver cells and is the most abundant protein in peripheral plasma. Previous

studies have reported that high levels of albumin are protective factors for DKD,[15–17] while low levels of albumin are risk factors for DKD.[20] Research has shown that albumin was negatively correlated with the levels of inflammatory factors IL-6, IL-8, and TNF-α.[34] Besides, in the occurrence of DKD, the activation of nuclear factor kappa B (NF-κB) is associated with proteinuria and stromal cell infiltration.[35] NF-κB is a transcription factor and the main regulator of inflammatory factors.[47] Studies have shown that albumin can inhibit the activation of NF-κB, suppress the expression of vascular cell adhesion molecule-1 (VCAM-1) induced by TNF-α, and inhibit monocyte adhesion, thereby exerting anti-inflammatory effects.[20] In summary, high levels of albumin and/or low levels of globulin were associated with lower levels of inflammation and may explain a higher AGR associated with a lower risk of DKD.

Further subgroup analysis showed that the association between AGR and DKD was consistent in the subgroups of age and diabetes duration, but only in males, the increased AGR associated with a reduced risk of DKD. The sex difference between serum AGR and DKD has not been fully explored. Since globulin was associated with DKD in both sexes, the fact that the AGR was associated with DKD only in males may be due to differences in albumin. Our study found that serum albumin levels were significantly higher in males than in females (49.5 g/L vs 48.8 g/L, Supplementary Table 3). This result was consistent with the finding that serum albumin levels were 2% higher in males than in females, as reported in a hospital-based cohort study that enrolled nearly 300,000 patients.[48] The lower albumin levels in women may be explained by the fact that the mean serum albumin concentration in the population decreases with age, but the value decreases more rapidly in women.[49] AGR also decreases with decreasing albumin levels, thus making the association of AGR with DKD less observable in women. Prospective cohort designs are needed in future studies to separately assess the association of AGR with DKD in different sexes and to elucidate the sex-specific mechanisms involved.

Globulin and AGR are Not Associated with DR

In this study, we found that globulin was significantly higher and AGR was significantly lower in the DR population than in the non-DR population, but the association of globulin and AGR with DR lost its significance after adjusting for covariates and DKD. Previous studies have reported the association of albumin with DR,[16–20] and the absence of AGR with DR in the present study may be due to the fact that globulin was not associated with DR. The underlying mechanism by which globulin was associated with DKD but not with DR needs to be further explored, and previous studies may provide some clues. DKD and DR share common inflammatory pathways in pathogenesis, but differences in association between DKD and DR on inflammatory indicators have also been reported.[50] A previous study explored the association of neutrophil-to-lymphocyte ratio (an indicator of systemic inflammation) with DKD and DR in T2DM patients and found that the neutrophil-to-lymphocyte ratio was only associated with DKD, but not with DR.[50] It may be that the kidneys and the eyes, as two different organs, have unique physiologic processes and internal environments and their own specific influencing factors.[51] DR is a neurovascular disease caused by the destruction of the retinal neurovascular unit composed of retinal neurons, neuroglia, and vascular cells.[52] Premature neuronal death, structural, and biochemical changes in neurons and glial cells lead to neurodegeneration, and retinal neurodegeneration may cause functional abnormalities that are involved in the development of DR.[53] There may be potential specific influencing factors for DR that were not collected in our study. In the future, specific influencing factors for DR in larger populations are needed, and these influencing factors should be controlled when exploring the association between globulin/AGR and diabetic microvascular complications.

The Reno-Protective Effects of GLP-1 RA and SGLT2 Inhibitors in This Population

Our study found that high globulin and low AGR levels are associated with an increased risk of DKD in T2DM patients. In this population, lowering proteinuria levels and maintaining renal function are the main therapeutic goals.[54] Significant renal benefits have been reported in T2DM patients with the treatment of GLP-1 RA and SGLT2 inhibitors. GLP-1 RA was reported to reduce the risk of progression to end-stage renal disease and death due to renal disease,[55] and improvement in renal disease progression was primarily driven by reduced proteinuria levels.[54] Animal model studies have shown that GLP-1 RA can exert anti-inflammatory effects in the kidney by reducing ICAM1, TGF-β, and CD14 in the renal cortex and preventing monocyte infiltration.[56] Studies have shown that SGLT2 inhibitors can prevent major adverse renal outcomes in T2DM patients.[57] In T2DM patients with different stages of renal disease, SGLT2 inhibitors had a nephroprotective effect by reducing UACR and maintaining eGFR.[58] Attenuating inflammation-related molecular

processes may be one of the mechanisms underlying the reno-protective effect of SGLT2 inhibitors. In small-scale SGLT2 inhibitors trials, there were modest reductions in circulating inflammatory markers (eg, IL-6, TNF, and IFN-γ).[59] SGLT2 inhibitors have also been shown to reduce markers of inflammation and oxidative stress in an animal model of DKD.[60] Thus, the reno-protective effects of GLP-1 RA and SGLT2 inhibitors may be considered in T2DM patients, and the future could explore whether these drugs would affect serum globulin or AGR levels.

Strengths and Limitations

Our study has several strengths. First, this population-based study was carried out using a multi-stage stratified random sampling method after considering the level of urbanization, which made the sample more representative of the Shaanxi Province. Secondly, strict quality control was implemented in this study. Before the investigation, all researchers and investigators received unified training according to the guidelines. During the investigation, questionnaire surveys and anthropometric measurements were conducted according to the unified protocol, and laboratory tests and fundus photography examinations were conducted according to the unified testing laboratory and medical equipment, ensuring the reliability and consistency of the data. After the investigation, all data were uploaded to the information management platform for inspection and review. Third, in the diagnosis of DR, two fundus photographs were taken by professional ophthalmologists with uniform criteria for each eye of the participant, thus reducing the possibility of missed diagnosis of DR. Finally, this study collected a broad range of sociodemographic characteristics, health behaviors, family history, diabetes duration, blood glucose control methods, hypertension, BMI, blood glucose levels, lipid levels, and liver function, which allowed us to adjust for these confounders in assessing the association of globulin and AGR with DKD and DR.

Our study has several limitations. First, due to the cross-sectional study design, we cannot draw the causal relationship between globulin and AGR with DKD, and future prospective studies will be needed to clarify the causality of the associations. Second, the duration of T2DM and family history of diabetes in this study relied on self-reporting, which may introduce some reporting bias. Third, although we controlled for potential confounders to confirm these associations; however, there were still residual confounders that were not observed. Our findings would be much stronger if we had accessed and controlled other inflammatory indicators such as TNF-α in this study. Lastly, the sample in this study was from Shaanxi Province in Northwest China, and the study's generalizability might be limited if there are regional differences in disease management and outcomes.

Conclusion

In conclusion, our study suggests that globulin is an independent risk factor and AGR is an independent protective factor for DKD. Clinicians should consider monitoring globulin and AGR levels in patients with T2DM as part of routine screening for DKD, especially in men. Future longitudinal studies are warranted to explore the association of globulin subfractions with DKD and clarify the role of globulin and AGR in the development of DKD.

Abbreviations

AGR, albumin-to-globulin ratio; ALT, alanine aminotransferase; AST, aspartate transaminase; BMI, body mass index; CI, confidence interval; DKD, diabetic kidney disease; DR, diabetic retinopathy; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HDL_C, high-density lipoprotein cholesterol; LDL_C, low-density lipoprotein cholesterol; OR, odds ratio; RCS, restricted cubic splines; TC, total cholesterol; TG, triglycerides; UACR, urine albumin-to-creatinine ratio.

Data Sharing Statement

The datasets generated for this study are available from the corresponding author for reasonable use.

Ethical Approval and Informed Consent

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Shanghai Sixth People's Hospital (No: 2018-010) and was registered in the Chinese Clinical Trial Registry (ChiCTR1800014432). Written informed consent to participate in the study was obtained from all study participants.

Acknowledgments

The authors thank all investigators and all participants in the China National Diabetic Chronic Complications Study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; have agreed on the journal to which the article has been submitted; have reviewed and agreed on all versions of the article before submission, during revision, the final version accepted for publication, and any significant changes introduced at the proofing stage; and agree to be accountable for all aspects of the work.

Funding

This research was funded by the Shaanxi Provincial Natural Science Basic Research Program, grant number 2022JQ-887.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Saeedi P, Petersohn I, Salpea P. et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the International Diabetes Federation Diabetes Atlas, 9(th) edition. *Diabet Res Clin Pract*. 2019;157:107843. doi:10.1016/j.diabres.2019.107843
2. Hou X, Wang L, Zhu D, et al. Prevalence of diabetic retinopathy and vision-threatening diabetic retinopathy in adults with diabetes in China. *Nat Commun*. 2023;14(1):4296. doi:10.1038/s41467-023-39864-w
3. Hu M, Wan Y, Yu L, et al. Prevalence, awareness and associated risk factors of diabetes among adults in Xi'an, China. *Sci Rep*. 2017;7(1):10472. doi:10.1038/s41598-017-10797-x
4. Qiu L, Wang W, Sa R, Liu F. Prevalence and risk factors of hypertension, diabetes, and dyslipidemia among adults in Northwest China. *Int J Hypertens*. 2021;2021:5528007. doi:10.1155/2021/5528007
5. Zhang J, Wang Y, Li L, et al. Diabetic retinopathy may predict the renal outcomes of patients with diabetic nephropathy. *Ren Fail*. 2018;40 (1):243–251. doi:10.1080/0886022x.2018.1456453
6. Lee MK, Han KD, Lee JH, et al. Normal-to-mildly increased albuminuria predicts the risk for diabetic retinopathy in patients with type 2 diabetes. *Sci Rep*. 2017;7(1):11757. doi:10.1038/s41598-017-11906-6
7. Zhang K, Liu X, Xu J, et al. Deep-learning models for the detection and incidence prediction of chronic kidney disease and type 2 diabetes from retinal fundus images. *Nat Biomed Eng*. 2021;5(6):533–545. doi:10.1038/s41551-021-00745-6
8. Chen H, Wang DG, Yuan L, et al. Clinical characteristics of patients with diabetic nephropathy on maintenance hemodialysis: a multicenter cross-sectional survey in Anhui Province, Eastern China. *Chin Med J*. 2016;129(11):1291–1297. doi:10.4103/0366-6999.182832
9. Cheng HT, Xu X, Lim PS, Hung KY. Worldwide epidemiology of diabetes-related end-stage renal disease, 2000–2015. *Diabetes Care*. 2021;44 (1):89–97. doi:10.2337/dc20-1913
10. Clinical application of Diabetic Retinopathy Study (DRS) findings DRN. Photocoagulation treatment of proliferative diabetic retinopathy. Clinical application of Diabetic Retinopathy Study (DRS) findings, DRS Report Number 8. The Diabetic Retinopathy Study Research Group. *Ophthalmology*. 1981;88(7):583–600.
11. Ting DS, Cheung GC, Wong TY. Diabetic retinopathy: global prevalence, major risk factors, screening practices and public health challenges: a review. *Clin Exp Ophthalmol*. 2016;44(4):260–277. doi:10.1111/ceo.12696
12. GBD 2019 Blindness and Vision Impairment Collaborators, Vision Loss Expert Group of the Global Burden of Disease Study. Causes of blindness and vision impairment in 2020 and trends over 30 years, and prevalence of avoidable blindness in relation to VISION 2020: the right to sight: an analysis for the Global Burden of Disease Study. *Lancet Glob Health*. 2021;9(2):e144–e160. doi:10.1016/s2214-109x(20)30489-7
13. Coca SG, Ismail-Beigi F, Haq N, Krumholz HM, Parikh CR. Role of intensive glucose control in development of renal end points in type 2 diabetes mellitus: systematic review and meta-analysis intensive glucose control in type 2 diabetes. *Arch Int Med*. 2012;172(10):761–769. doi:10.1001/archinternmed.2011.2230
14. Barrett EJ, Liu Z, Khamaisi M, et al. Diabetic microvascular disease: an endocrine society scientific statement. *J Clin Endocrinol Metab*. 2017;102 (12):4343–4410. doi:10.1210/jc.2017-01922
15. Hui D, Zhang F, Lu Y, et al. A multifactorial risk score system for the prediction of diabetic kidney disease in patients with type 2 diabetes mellitus. *Diabetes Metab Syndr Obes*. 2023;16:385–395. doi:10.2147/dmso.S391781
16. Iwasaki T, Togashi Y, Terauchi Y. Significant association of serum albumin with severity of retinopathy and neuropathy, in addition to that of nephropathy, in Japanese type 2 diabetic patients. *Endocr J*. 2008;55(2):311–316. doi:10.1507/endocrj.k07-086
17. Zhu Y, Cai X, Liu Y, et al. Serum albumin, but not bilirubin, is associated with diabetic chronic vascular complications in a Chinese type 2 diabetic population. *Sci Rep*. 2019;9(1):12086. doi:10.1038/s41598-019-48486-6
18. Wang GX, Fang ZB, Li JT, et al. The correlation between serum albumin and diabetic retinopathy among people with type 2 diabetes mellitus: NHANES 2011-2020. *PLoS One*. 2022;17(6):e0270019. doi:10.1371/journal.pone.0270019
19. Klein R, Sharrett AR, Klein BE, et al. The association of atherosclerosis, vascular risk factors, and retinopathy in adults with diabetes: the atherosclerosis risk in communities study. *Ophthalmology*. 2002;109(7):1225–1234. doi:10.1016/s0161-6420(02)01074-6

20. Zhang J, Deng Y, Wan Y, He S, Cai W, Xu J. Association between serum albumin level and microvascular complications of type 2 diabetes mellitus. *Diabetes Metab Syndr Obes*. 2022;15:2173–2182. doi:10.2147/dmso.S373160
21. Wang Y, Li C, Wang W, et al. Serum albumin to globulin ratio is associated with the presence and severity of inflammatory bowel disease. *J Inflamm Res*. 2022;15:1907–1920. doi:10.2147/jir.S347161
22. Hsieh YP, Tsai SM, Kor CT, Chiu PF. Serum globulin is a novel predictor of mortality in patients undergoing peritoneal dialysis. *Sci Rep*. 2023;13 (1):1139. doi:10.1038/s41598-023-27688-z
23. Wang J, Liu F, Kong R, Han X. Association between globulin and diabetic nephropathy in type 2 diabetes mellitus patients: a cross-sectional study. *Front Endocrinol*. 2022;13:890273. doi:10.3389/fendo.2022.890273
24. Ye Y, Chen W, Gu M, et al. Serum globulin and albumin to globulin ratio as potential diagnostic biomarkers for periprosthetic joint infection: a retrospective review. *J Orthop Surg Res*. 2020;15(1):459. doi:10.1186/s13018-020-01959-1
25. Park J, Kim HJ, Kim J, Choi YB, Shin YS, Lee MJ. Predictive value of serum albumin-to-globulin ratio for incident chronic kidney disease: a 12-year community-based prospective study. *PLoS One*. 2020;15(9):e0238421. doi:10.1371/journal.pone.0238421
26. Burlaka IA, Mityuryayeva IO, Shevchenko TA, Holoborodko AD, Kovalchuk IV, Lantukh LO. Clinical, laboratory, instrumental, anamnestic characteristics in children with type I diabetes mellitus and early stage of diabetic nephropathy. *Glob Pediatr Health*. 2021;8:2333794x211063052. doi:10.1177/2333794x211063052
27. Hou XH, Wang LM, Chen SY, et al. Data resource profile: a protocol of China national diabetic chronic complications study. *Biomed Environ Sci*. 2022;35(7):633–640. doi:10.3967/bes2022.078
28. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Internal Med*. 2009;150(9):604–612. doi:10.7326/0003-4819-150-9-200905050-00006
29. American Diabetes Association.Microvascular complications and foot care: standards of medical care in diabetes-2021. *Diabetes Care*. 2021;44 (Suppl 1):S151–s167. doi:10.2337/dc21-S011
30. Wilkinson CP, Ferris FL, Klein RE, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. *Ophthalmology*. 2003;110(9):1677–1682. doi:10.1016/s0161-6420(03)00475-5
31. Wu PP, Hsieh YP, Kor CT, Chiu PF. Association between albumin-globulin ratio and mortality in patients with chronic kidney disease. *J Clin Med*. 2019;8(11):1991. doi:10.3390/jcm8111991
32. Lindsay RS, Krakoff J, Hanson RL, Bennett PH, Knowler WC. Gamma globulin levels predict type 2 diabetes in the Pima Indian population. *Diabetes*. 2001;50(7):1598–1603. doi:10.2337/diabetes.50.7.1598
33. DeFronzo RA, Reeves WB, Awad AS. Pathophysiology of diabetic kidney disease: impact of SGLT2 inhibitors. *Nat Rev Nephrol*. 2021;17 (5):319–334. doi:10.1038/s41581-021-00393-8
34. Chen Y, Chen Y, Zhao L, et al. Albumin/Globulin ratio as Yin-Yang in rheumatoid arthritis and its correlation to inflamm-aging cytokines. *J Inflamm Res*. 2021;14:5501–5511. doi:10.2147/jir.S335671
35. Toth-Manikowski S, Atta MG. Diabetic kidney disease: pathophysiology and therapeutic targets. *J Diabetes Res*. 2015;2015:697010. doi:10.1155/2015/697010
36. Nakazawa D, Masuda S, Tomaru U, Ishizu A. Pathogenesis and therapeutic interventions for ANCA-associated vasculitis. *Nat Rev Rheumatol*. 2019;15(2):91–101. doi:10.1038/s41584-018-0145-y
37. Takahashi T, Hato F, Yamane T, et al. Increased spontaneous adherence of neutrophils from type 2 diabetic patients with overt proteinuria: possible role of the progression of diabetic nephropathy. *Diabetes Care*. 2000;23(3):417–418. doi:10.2337/diacare.23.3.417
38. Hashash JG, Koutroumpakis F, Anderson AM, et al. Elevated serum globulin fraction as a biomarker of multiyear disease severity in inflammatory bowel disease. *Ann Gastroenterol*. 2022;35(6):609–617. doi:10.20524/aog.2022.0748
39. Ilyas Z, Chaiban JT, Krikorian A. Novel insights into the pathophysiology and clinical aspects of diabetic nephropathy. *Rev Endocr Metab Disord*. 2017;18(1):21–28. doi:10.1007/s11154-017-9422-3
40. Tang X, Li H, Li L, et al. The clinical impact of glomerular immunoglobulin M deposition in patients with type 2 diabetic nephropathy. *Am J Med Sci*. 2018;356(4):365–373. doi:10.1016/j.amjms.2018.07.001
41. Zhou T, Fang YL, Tian TT, Wang GX. Pathological mechanism of immune disorders in diabetic kidney disease and intervention strategies. *World J Diabetes*. 2024;15(6):1111–1121. doi:10.4239/wjd.v15.i6.1111
42. Forshaw MJ, Guirguis O, Hennigan TW. IgA nephropathy in association with Crohn's disease. *Int J Colorectal Dis*. 2005;20(5):463–465. doi:10.1007/s00384-004-0696-z
43. Zeng M, Liu Y, Liu F, Peng Y, Sun L, Xiao L. Association between albumin-to-globulin ratio and long-term mortality in patients with chronic kidney disease: a cohort study. *Int Urol Nephrol*. 2020;52(6):1103–1115. doi:10.1007/s11255-020-02453-7
44. Yoshino Y, Taguchi A, Shimizuguchi T, et al. A low albumin to globulin ratio with a high serum globulin level is a prognostic marker for poor survival in cervical cancer patients treated with radiation based therapy. *Int J Gynecol Cancer*. 2019;29(1):17–22. doi:10.1136/ijgc-2018-000025
45. Don BR, Kaysen G. Serum albumin: relationship to inflammation and nutrition. *Semin Dial*. 2004;17(6):432–437. doi:10.1111/j.0894-0959.2004.17603.x
46. Levitt DG, Levitt MD. Human serum albumin homeostasis: a new look at the roles of synthesis, catabolism, renal and gastrointestinal excretion, and the clinical value of serum albumin measurements. *Int J Gene Med*. 2016;9:229–255. doi:10.2147/ijgm.S102819
47. Lin YC, Chang YH, Yang SY, Wu KD, Chu TS. Update of pathophysiology and management of diabetic kidney disease. *J Formos Med Assoc*. 2018;117(8):662–675. doi:10.1016/j.jfma.2018.02.007
48. Grimm G, Haslacher H, Kampitsch T, et al. Sex differences in the association between albumin and all-cause and vascular mortality. *Eur J Clin Invest*. 2009;39(10):860–865. doi:10.1111/j.1365-2362.2009.02189.x
49. Weaving G, Batstone GF, Jones RG. Age and sex variation in serum albumin concentration: an observational study. *Ann Clin Biochem*. 2016;53(Pt 1):106–111. doi:10.1177/0004563215593561
50. Ciray H, Aksoy AH, Ulu N, Cizmecioglu A, Gaipov A, Solak Y. Nephropathy, but not angiographically proven retinopathy, is associated with neutrophil to lymphocyte ratio in patients with type 2 diabetes. *Exp Clin Endocrinol Diabetes*. 2015;123(5):267–271. doi:10.1055/s-0035-1547257
51. Tang S, An X, Sun W, et al. Parallelism and non-parallelism in diabetic nephropathy and diabetic retinopathy. *Front Endocrinol*. 2024;15:1336123. doi:10.3389/fendo.2024.1336123

52. Ji L, Tian H, Webster KA, Li W. Neurovascular regulation in diabetic retinopathy and emerging therapies. *Cell Mol Life Sci*. 2021;78(16):5977–5985. doi:10.1007/s00018-021-03893-9
53. Barber AJ. Diabetic retinopathy: recent advances towards understanding neurodegeneration and vision loss. *Sci China Life Sci*. 2015;58(6):541–549. doi:10.1007/s11427-015-4856-x
54. Karakasis P, Patoulias D, Fragakis N, Klisic A, Rizzo M. Effect of tirzepatide on albuminuria levels and renal function in patients with type 2 diabetes mellitus: a systematic review and multilevel meta-analysis. *Diabetes Obes Metab*. 2024;26(3):1090–1104. doi:10.1111/dom.15410
55. Kristensen SL, Rørth R, Jhund PS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol*. 2019;7(10):776–785. doi:10.1016/s2213-8587(19)30249-9
56. Kodera R, Shikata K, Kataoka HU, et al. Glucagon-like peptide-1 receptor agonist ameliorates renal injury through its anti-inflammatory action without lowering blood glucose level in a rat model of type 1 diabetes. *Diabetologia*. 2011;54(4):965–978. doi:10.1007/s00125-010-2028-x
57. Neuen BL, Young T, Heerspink HJL, et al. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol*. 2019;7(11):845–854. doi:10.1016/s2213-8587(19)30256-6
58. Karakasis P, Popovic DS, Patoulias D, et al. The effect of sodium-glucose cotransporter inhibitors on renal function as adjunctive to insulin in adults with type 1 diabetes: an updated multilevel meta-analysis of randomized controlled trials. *Diabetes Ther*. 2024;15(2):521–532. doi:10.1007/s13300-023-01523-0
59. Bonnet F, Scheen AJ. Effects of SGLT2 inhibitors on systemic and tissue low-grade inflammation: the potential contribution to diabetes complications and cardiovascular disease. *Diabetes Metab*. 2018;44(6):457–464. doi:10.1016/j.diabet.2018.09.005
60. Jaikumkao K, Pongchaidecha A, Chueakula N, et al. Dapagliflozin, a sodium-glucose co-transporter-2 inhibitor, slows the progression of renal complications through the suppression of renal inflammation, endoplasmic reticulum stress and apoptosis in prediabetic rats. *Diabetes Obes Metab*. 2018;20(11):2617–2626. doi:10.1111/dom.13441