• Clinical Research •

Predictive value of triglyceride-glucose index and sex hormone-binding globulin in diabetic retinopathy

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Abstract

● **AIM:** To investigate the levels of the triglyceride-glucose (TyG) index and sex hormone-binding globulin (SHBG) in patients with type 2 diabetes mellitus (T2DM) with diabetic retinopathy (DR), and to explore their correlations with biochemical parameters and the homeostasis model assessment of insulin resistance (HOMA-IR) in DR patients.

● **METHODS:** Patients with T2DM and healthy individuals were enrolled. Age and body mass index (BMI) of the participants were collected, TyG of the subjects was calculated using the formula, SHBG level of the subjects was detected, and blood biochemical indexes were measured at the same time. The changes of each index among the groups were statistically analyzed, and the relationship between TyG, SHBG, DR and each index was analyzed.

● **RESULTS:** A total of 150 patients with T2DM and 64 healthy individuals as normal controls (NC, 28 males and 36 females, mean age 54.49±10.10y) were enrolled following ophthalmic evaluation. Patients were categorized into non-DR group (42 males and 36 females, mean age 56.68±8.02y) and DR group (35 males and 37 females, mean age, 53.83±11.10y). TyG levels were significantly elevated in both non-DR (7.25±0.62) and DR groups (8.02±0.82) compared to controls (6.85±0.48), with the DR group demonstrating higher TyG values than the non-DR group (P<0.05). The level of SHBG (nmol/L) in DR group (25.05±14.06) was lower than that in control group (41.90±22.6) and non-DR group (36.27±20.00; P<0.05). TyG exhibited significant inverse correlations with SHBG (r=-0.455) and high density lipoprotein (HDL; r=-0.430) levels (P<0.05). It was positively correlated with BMI, fasting blood glucose (FBG), 2h postprandial blood glucose (PBG), fasting C-peptide (FCP), glycated hemoglobin A1c (HbA1c), HOMA-IR, total cholesterol (TC) and triglycerides (TG) (r=0.406, 0.768, 0.386, 0.393, 0.475, 0.250, 0.242, 0.888, respectively, P<0.05). SHBG was negatively correlated with BMI, FBG, FCP, HbA1c and TyG (r=-0.440, -0.304, -0.407, -0.209, -0.455, respectively, P<0.05), and positively correlated with age, TG and HDL (r=0.238, 0.034, 0.227, respectively, P<0.05). Further multiple regression analysis showed that SHBG was negatively correlated with TyG (P=0.006).

● **CONCLUSION:** Elevated TyG index, reduces SHBG levels, and their negative correlation in the DR group suggest potential roles of TyG and SHBG in the pathogenesis and progression of DR. Combined assessment of SHBG and TyG may provide valuable insights for DR prediction and diagnosis.

● **KEYWORDS:** diabetic retinopathy; triglyceride-glucose index; sex hormone binding globulin; glycated hemoglobin; insulin resistance index

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INTRODUCTION

Diabetes mellitus is a chronic global health burden, characterized by a rising prevalence and significant public health implications. According to World Health Organization (WHO) statistics, the global prevalence of diabetes reached 10.5% in 2021, affecting approximately 536.6 million individuals, with projections indicating an increase to 12.2% (around 783.2 million individuals) by 2045[1]. Diabetic retinopathy (DR) represents a prevalent microvascular complication among diabetes patients and serves as one of the primary etiologies for vision loss[2]. DR adversely impacts

patients' quality of life and imposes substantial socioeconomic burdens on families and society[3]. Consequently, investigating effective early screening methodologies holds substantial significance for preventing and retarding DR progression.

In recent years, the triglyceride-glucose (TyG) index has garnered significant attention as a surrogate marker for assessing insulin resistance (IR), due to its simplicity and reliability[4]. Research indicates that the TyG index exhibits a strong correlation with both the onset and progression of DR[5-6]. Additionally, studies have demonstrated that fasting serum sex hormone-binding globulin (SHBG) levels are significantly lower in both DR and type 2 diabetes mellitus (T2DM) groups compared to normal controls (NC), with SHBG levels exhibiting inverse correlations with fasting glucose and glycated hemoglobin (HbA1c) levels[7]. However, the combined mechanistic role of the TyG index and SHBG in DR remains unclear, with limited research data currently available. Accordingly, this study aims to investigate the fluctuations in TyG index and SHBG levels among DR patients, examine their correlations with clinical biochemical parameters, and evaluate their predictive value for DR. The findings will provide a theoretical foundation for the early prevention and diagnosis of DR, with significant clinical and public health implications.

PARTICIPANTS AND METHODS

Ethical Approval Ethical clearance and approval were obtained from Ethics Committee of the First Affiliated Hospital of Xi'an Medical University (XYYFY2024LSKY-003), Shaanxi Province, China. All study participants were informed about the purpose of the study and additional information was given as they needed. Written informed consent was obtained from all participants. We had complied with the Declaration of Helsinki Ethical Principles for medical research involving human subjects.

General Information A total of 150 patients with T2DM who were hospitalized in the Department of Endocrinology at the First Affiliated Hospital of Xi'an Medical University between June 2023 and August 2024 were enrolled as study subjects.

Inclusion criteria: Patients were included if they met the diagnostic criteria for T2DM according to the Chinese Guidelines for the Prevention and Treatment of Type 2 Diabetes (2020 edition)[8]. This was defined as the presence of typical diabetic symptoms with one of the following: 1) random plasma glucose ≥11.1 mmol/L, 2) fasting plasma glucose ≥7.0 mmol/L, 3) 2-hour postprandial glucose ≥11.1 mmol/L during an oral glucose tolerance test (OGTT), 4) HbA1c ≥6.5%.

Exclusion criteria: The following conditions were grounds for exclusion: 1) Type 1 diabetes or other specific types of diabetes; 2) Pregnant or lactating women; 3) Presence of acute diabetic complications, severe infections, malignancies, or severe organ dysfunction (cardiac, hepatic, or renal); 4) Suspected familial hypertriglyceridemia [serum triglycerides (TG) >500 mg/dL]; 5) Presence of other ocular conditions that could potentially affect retinopathy assessment, such as optic neuritis, macular degeneration, cataracts, non-proliferative DR (NPDR) requiring acute treatment, or recent ocular surgery.

Based on fundoscopic examination and diagnostic criteria for DR from the Chinese Clinical Guidelines for Diabetic Retinopathy (2022 edition)[9], the enrolled T2DM patients were categorized into two groups: the non-DR group (n=78) and the DR group (n=72). Additionally, 64 healthy individuals with normal glycemic parameters who undergoing physical examinations during the same period were recruited as NC. The inclusion criteria for the NC group required normal glycemic indices, while the exclusion criteria encompassed a history of diabetes, ocular surgery, or impaired self-care capacity.

Measurement and Evaluation Methods for Observational Indicators Fasting venous blood samples (5 mL) were collected from the median cubital vein of all participants after a 10-hour overnight fast. The samples were centrifuged at 3000 r/min for 10min (centrifugation radius: 24.5 cm). The serum was then separated, aliquoted, and stored at -80°C for subsequent analysis.

Biochemical parameters Fasting blood glucose (FBG), postprandial blood glucose (PBG), total cholesterol (TC), TG, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) levels were measured using an automated biochemical analyzer (Olympus AU5800, USA) with manufacturer-matched reagent kits.

Hormonal and insulin parameters Thyroid-stimulating hormone (TSH), fasting insulin (FINS), 2-hour postprandial insulin (2h-PI), fasting C-peptide (FCP), and 2-hour postprandial C-peptide (2h-CP) were analyzed using a chemiluminescence analyzer (Abbott i2000, USA) with proprietary reagent kits.

Glycated hemoglobin HbA1c levels were determined using an automated high-performance liquid chromatography system (Bio-Rad D-100, USA).

SHBG SHBG concentrations were quantified using commercially available enzyme-linked immunosorbent assay (ELISA) kits.

The homeostasis model assessment of insulin resistance (HOMA-IR) index was using the following formula: HOMA-IR=FBG (mmol/L)×FINS (mIU/L)/22.5. Body mass index (BMI) was computed using the formula: BMI=weight (kg)/height² (m²). TyG index was derived as: TyG=Ln[TG (mg/dL)×FBG (mg/dL)/2].

Statistical Analysis Statistical analyses were performed using SPSS 27.0. Normally distributed continuous variables were expressed as mean±standard deviation and analyzed by one-

way ANOVA, while categorical variables were presented as counts and examined using χ^2 tests. Correlation analyses and multiple linear regression models were employed to evaluate associations between the TyG index and other clinical parameters in DR patients. The significance level was set at α=0.05 (two-tailed).

RESULTS

The non-DR group comprised 42 males and 36 females, with an age range of 34-68y (mean age, 56.68±8.02y). The DR group included 35 males and 37 females, with an age range of 33-69y (mean age, 53.83±11.10y). The NC group consisted of 28 males and 36 females, with an age range of 32-67y (mean age, 54.49±10.10y).

Intergroup comparisons revealed no statistically significant differences in age or gender distribution (P>0.05), ensuring baseline comparability among the groups.

Comparison of Serum TyG and SHBG Levels Among the Three Groups Serum TyG levels were significantly elevated in both the non-DR and DR groups compared to the control group (P<0.05). Moreover, the DR group exhibited higher TyG levels than the non-DR group (P<0.05). In contrast, SHBG levels were significantly lower in the DR group compared to both the control and non-DR groups (P<0.05; Table 1).

Comparative Analysis of Clinical Parameters Across Three Patient Groups No statistically significant differences were observed among the three groups in terms of age, FINS, FCP, LDL and HOMA-IR (P>0.05). Compared to the NC group, the non-DR group exhibited significantly higher levels of FBG, PBG, and HbA1c, while 2h-PI, 2h-CP, TSH, TC, and HDL were significantly lower (P<0.05). Patients with DR showed significantly higher BMI, FBG, PBG, HbA1c, and TG levels compared to the NC group, along with significantly lower 2h-CP, TSH, and HDL concentrations (P<0.05). Notably, the DR group had significantly higher BMI, FBG, PBG, HbA1c, and TG levels, and significantly lower HDL levels compared to the non-DR group (P<0.05; Table 2).

Correlation Between TyG and SHBG Levels and Clinical Indicators Pearson correlation analysis revealed that the TyG index was significantly inversely correlated with both SHBG and HDL levels (P<0.05). Additionally, the TyG index exhibited positive associations with BMI, FBG, PBG, FCP, HbA1c, HOMA-IR, TC, and TG (P<0.05; Table 3). Conversely, SHBG concentrations demonstrated negative correlations with BMI, FBG, FCP, HbA1c, and the TyG index (P<0.05), while showing positive relationships with age, TG, and HDL levels (P<0.05; Table 4). Multivariate regression analysis with the TyG index as the dependent variable, confirmed persistent positive associations with BMI, FBG, TG, and TC (P<0.05). Meanwhile, an inverse relationship was maintained with SHBG (P<0.05; Table 5).

Table 1 Comparison of serum TyG and SHBG level among the three groups mean±SD

Groups	TyG index	SHBG (nmol/L)
NC (n=64)	6.85±0.48	41.90±22.6
Non-DR (n=78)	7.25±0.62[a]	36.27±20.00
DR (n=72)	8.02±0.82[a,b]	25.05±14.06[a,b]
F	30.302	6.905
P	<0.001	0.001

[a]P<0.05 *vs* control group; [b]P<0.05 *vs* non-DR group. TyG: Triglyceride-glucose; SHBG: Sex hormone binding globulin; NC: Normal controls; DR: Diabetic retinopathy; SD: Standard deviation.

Table 2 Comparison of clinical indexes in 3 groups mean±SD

Project	NC	Non-DR	DR
Cases (male/female)	64 (28/36)	78 (42/36)	72 (35/37)
Age (y)	54.49±10.10	56.68±8.02	53.83±11.10
BMI (kg/m^2)	24.54±3.31	24.43±3.57	26.41±3.58[a,b]
FBG (mmol/L)	5.35±0.52	6.91±1.72[a]	8.78±2.79[a,b]
PBG (mmol/L)	8.84±3.45	15.85±4.49[a]	18.47±3.94[a,b]
FINS (mU/L)	9.62±4.83	13.89±4.04	15.50±3.74
2h-PI (mU/L)	85.63±8.66	48.50±4.73[a]	64.09±17.88
FCP (ng/mL)	2.13±0.79	2.00±0.15	2.31±0.18
2h-CP (ng/mL)	9.95±0.60	6.36±0.44[a]	5.92±0.44[a]
HOMA-IR	2.34±0.23	4.54±1.32	5.63±1.02
HbA1c (%)	5.64±0.46	7.12±0.99[a]	8.25±1.44[a,b]
TSH (μIU/mL)	2.34±2.02	1.59±0.93[a]	1.58±0.84[a]
TC (mmol/L)	4.64±1.03	4.18±1.06[a]	4.45±0.90
TG (mmol/L)	1.20±0.56	1.47±0.85	2.73±1.86[a,b]
LDL (mmol/L)	2.92±0.85	2.59±0.88	2.61±0.73
HDL (mmol/L)	1.37±0.33	1.23±0.33[a]	1.07±0.26[a,b]

[a]P<0.05 *vs* NC group; [b]P<0.05 *vs* non-DR group. NC: Normal controls; DR: Diabetic retinopathy; BMI: Body mass index; FBG: Fasting blood glucose; PBG: 2h postprandial blood glucose; FINS: Fasting insulin; 2h-PI: 2h postprandial insulin; FCP: Fasting C-peptide; 2h-CP: 2h postprandial C-peptide; HOMA-IR: Homeostasis model-assessment of insulin resistant; HbA1c: Glycated hemoglobin A1c; TSH: Thyroid stimulating hormone; TC: Total cholesterol; TG: Triglycerides; LDL: Low density lipoprotein; HDL: High density lipoprotein; SD: Standard deviation.

DISCUSSION

IR is a pivotal pathogenic mechanism in T2DM and is associated with both macrovascular complications (such as coronary and carotid artery disease)[10] and microvascular complications[11]. Current evidence indicates that the HOMA-IR has been identified as an independent risk factor for the development of DR[12]. The TyG index has emerged as a robust tool for IR and diabetes risk stratification, with its predictive validity extensively validated across diverse ethnic populations[13]. Given the clinical practicality of glycemic and lipid profiling compared to insulin assays in primary care settings, the TyG index serves as a viable surrogate marker for detecting IR in ostensibly healthy individuals[14]. The TyG

Table 3 Association of TyG with clinical parameters

Project	*r*	*P*
Age (y)	-0.137	0.127
BMI (kg/m^2)	0.406	<0.001
FBG (mmol/L)	0.768	<0.001
PBG (mmol/L)	0.386	<0.001
FINS (mU/L)	0.080	0.375
2h-PI (mU/L)	-0.053	0.557
FCP (ng/mL)	0.393	<0.001
2h-CP (ng/mL)	-0.079	0.384
HOMA-IR	0.250	0.005
HbA1c (%)	0.475	<0.001
TSH (μIU/mL)	-0.057	0.526
SHBG (nmol/L)	-0.455	<0.001
TC (mmol/L)	0.242	0.007
TG (mmol/L)	0.888	<0.001
LDL (mmol/L)	0.096	0.285
HDL (mmol/L)	-0.430	<0.001

TyG: Triglyceride-glucose; BMI: Body mass index; FBG: Fasting blood glucose; PBG: 2h postprandial blood glucose; FINS: Fasting insulin; 2h-PI: 2h postprandial insulin; FCP: Fasting C-peptide; 2h-CP: 2h postprandial C-peptide; HOMA-IR: Homeostasis model-assessment of insulin resistant; HbA1c: Glycated hemoglobin A1c; TSH: Thyroid stimulating hormone; SHBG: Sex hormone binding globulin; TC: Total cholesterol; TG: Triglycerides; LDL: Low density lipoprotein; HDL: High density lipoprotein.

Table 4 Association of SHBG with clinical parameters

Projects	*r*	*P*
Age (y)	0.238	0.008
BMI (kg/m^2)	-0.440	<0.001
FBG (mmol/L)	-0.304	<0.001
PBG (mmol/L)	-0.091	0.316
FINS (mU/L)	-0.089	0.324
2h-PI (mU/L)	-0.016	0.863
FCP (ng/mL)	-0.407	<0.001
2h-CP (ng/mL)	-0.146	0.105
HOMA-IR	-0.143	0.113
HbA1c (%)	-0.209	0.020
TSH (μIU/mL)	0.107	0.239
TyG index	-0.455	<0.001
TC (mmol/L)	0.034	0.705
TG (mmol/L)	0.034	<0.001
LDL (mmol/L)	0.096	0.711
HDL (mmol/L)	0.227	0.011

SHBG: Sex hormone binding globulin; BMI: Body mass index; FBG: Fasting blood glucose; PBG: 2h postprandial blood glucose; FINS: Fasting insulin; 2h-PI: 2h postprandial insulin; FCP: Fasting C-peptide; 2h-CP: 2h postprandial C-peptide; HOMA-IR: Homeostasis model-assessment of insulin resistant; HbA1c: Glycated hemoglobin A1c; TSH: Thyroid stimulating hormone; TyG: Triglyceride-glucose; TC: Total cholesterol; TG: Triglycerides; LDL: Low density lipoprotein; HDL: High density lipoprotein.

Table 5 Results of stepwise regression analysis

Variables	Regression coefficients	Standardized regression coefficients	*t*	95%CI	*P*
Constant	5.269		19.693	4.739-5.799	<0.001
BMI	0.018	0.081	2.459	0.003-0.032	0.015
FBG	0.113	0.325	6.999	0.081-0.145	<0.001
TG	0.360	0.602	15.993	0.315-0.404	<0.001
TC	0.045	0.023	0.059	0.000-0.091	0.050
SHBG	-0.004	-0.093	-2.796	-0.006 to -0.001	0.006

BMI: Body mass index; FBG: Fasting blood glucose; TG: Triglycerides; TC: Total cholesterol; SHBG: Sex hormone binding globulin; CI: Confidence interval.

index reflects systemic metabolic regulation and correlates strongly with the onset and progression of T2DM.

DR is a slowly progressive and insidious microvascular complication and is among the leading causes of visual impairment and blindness. Early screening and diagnostic interventions are of paramount importance for preventing and retarding DR progression. DR progression is significantly correlated with diminished quality of life and often precipitates psychological comorbidities[15]. Hyperglycemia and IR synergistically exacerbate lipotoxic effects on the microvasculature in diabetic patients. Emerging data indicate that IR may act as an early pathogenic factor in DR, independent of hyperglycemia[16]. Emerging evidence suggests that the TyG index may induce retinal damage through multiple pathways, including modulation of blood glucose levels, alteration of free fatty acid metabolism, and regulation of sodium-glucose cotransporter-2 (SGLT2) expression and function. These findings highlight the clinical significance of the TyG index for DR prevention and therapeutic intervention[5].

New research has found that the TyG index is positively correlated with DR. Patients with DR and a greater duration of disease had a higher TyG index. Moreover, patients with severe NPDR and PDR have the highest TyG index, suggesting that IR may provide some clues to the severity of DR[17]. A Meta-analysis has revealed a significant positive correlation between elevated TyG index and increased prevalence of DR in T2DM populations[18]. Moreover, a dose-dependent relationship

has been observed, with each 0.1-unit increment in the TyG index conferring a 9.5% increased risk of DR[19]. This finding underscores the pathophysiological significance of the TyG index in the pathogenesis of DR. Our study findings showed that TyG indices were significantly higher in the DR group compared to both the control and non-DR groups, which corroborates previous observations by Neelam *et al*[4]. Notably, positive correlations were identified between the TyG index and BMI, FBG, HbA1c, and HOMA-IR, thereby reinforcing its utility as a robust predictor for both IR and adiposity severity. The TyG index exhibited incremental elevation with suboptimal control of HbA1c and FBG, suggesting its clinical applicability for rapid IR assessment and DR risk stratification. Although fluorescein fundus angiography remains the diagnostic gold standard for DR, its invasive nature and substantial cost limit its widespread utilization. Compounding this limitation, primary care facilities often lack essential equipment for fundoscopy, retinal photography, and optical coherence tomography (OCT)[20]. In contrast, the TyG index offers a practical, non-invasive, and cost-effective computational alternative for monitoring the onset and progression of DR.

SHBG is a glycoprotein synthesized by hepatocytes and plays a pivotal role in modulating the circulating concentrations of bioactive sex hormones and regulating tissue cellular functions. Extensive evidence indicates that obesity, IR, and T2DM are frequently associated with reduced SHBG levels, establishing SHBG as a clinically significant biomarker for predicting these metabolic disorders. Longitudinal research by Seipone *et al*[21] demonstrated SHBG's predictive capacity for dysglycemia progression in middle-aged African males. Furthermore, inverse correlations has been observed between SHBG and HbA1c, postprandial glucose excursions, and the conversion from prediabetes to diabetes in female populations[22]. Diminished SHBG levels have also been shown to correlate with early-onset gestational diabetes mellitus and serve as a reliable indicator of IR severity during pregnancy[23]. Sun *et al*[6] reported an inverse relationship between SHBG concentrations and the prevalence of DR, suggesting that low serum SHBG levels may constitute an independent risk factor for DR development. Our results revealed significantly lower SHBG levels in the DR group compared to both control and non-DR groups, along with a negative correlation between SHBG and HbA1c. These findings align with the hypothesis that reduced SHBG levels may contribute to the pathogenesis of DR. However, contradictory results have also been reported. Sun *et al*[6] noted elevated SHBG levels in DR patients compared to non-DR individuals, highlighting the complexity and potential heterogeneity in the relationship between SHBG and DR. This discrepancy underscores the need for further investigation into the precise role of SHBG in DR pathogenesis, as well as the potential influence of confounding factors such as ethnicity, sex, and metabolic status.

Our study identified a significant inverse correlation between the TyG index and SHBG levels, suggesting that progressive reductions in SHBG correspond with elevations in the TyG index and are associated with increased risks of diabetes and DR. Furthermore, the TyG index demonstrated a negative association with HDL, while SHBG exhibited a positive correlation with HDL. These findings reveal intricate interrelationships among these parameters and suggest that SHBG may play a potential regulatory role in lipid metabolism.

In addition, this study has certain limitations. First, the lack of subgroup analysis based on DR severity, such as comparisons between NPDR and PDR, fails to reveal potential differences in the TyG index and SHBG across different stages of the disease. Second, the single-center, cross-sectional design and limited sample size constrain the generalizability and causal inference of the findings. Future large-scale, stratified prospective studies are needed to further validate whether the TyG index and SHBG levels change significantly with DR progression and whether their predictive utility differs between early and advanced stages.

In summary, this study highlights the clinical significance of the TyG index and SHBG in DR. The TyG index promotes DR development, while SHBG has an inhibitory effect. These findings provide a scientific basis for DR prevention and control strategies. The TyG index is a practical screening tool for DR risk in primary care due to its simplicity and reliance on routine blood tests. Combining TyG index with SHBG levels enhances the accuracy of DR prediction and diagnosis, improving patient outcomes and reducing healthcare burden.

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