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Association between thyroid stimulating hormone levels and nonproliferative diabetic retinopathy: a cross-sectional study

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Abstract

Background The association between thyroid-stimulating hormone (TSH) and type 2 diabetes mellitus (T2DM) is well known. However, whether TSH is related to nonproliferative diabetic retinopathy (NPDR) has not been studied. This study aimed to explore the relationship between TSH and NPDR in Chinese patients with T2DM.

Methods In this cross-sectional study, 427 patients with T2DM were enrolled. The individuals were classified into two groups according to the fundus oculi examination: the non-diabetic retinopathy (NDR) group ($n=224$) and the non-proliferative diabetic retinopathy (NPDR) group ($n=203$). The individuals' demographic and clinical data were collected by reviewing medical records and direct interviews. The demographic data and biochemical parameters were compared between groups using the Student's t - test or the Mann–Whitney U test, anthropometric measurements, thyroid function, and NPDR were evaluated, and the associations between TSH and NPDR were assessed using logistic regression models.

Results No significant differences in age, sex, body mass index (BMI), incidence of alcohol consumption, and duration of diabetes were found between these two groups. The systolic blood pressure (SBP), incidence of smoking, TSH, blood urea nitrogen (BUN), and urinary micro-albumin (mALB) were significantly higher in the NPDR group than in the NDR group ($P<0.05$). Individuals in the NDR group had higher levels of thyroxine (T4), glutamic pyruvic transaminase (ALT), fasting C-peptide (FCP), and 2-hour C-peptide (2hCP) than individuals in the NPDR group ($P<0.05$). Spearman's correlation analysis revealed that the serum TSH levels were negatively associated with the HbA1c levels in all patients (r=-0.11, $P<0.05$). Serum TSH levels were negatively correlated with HbA1c levels (r = -0.19, $P<0.01$) and positively correlated with diabetes duration ($r=0.14$, $P<0.05$) in the NPDR group. Multivariate logistic regression analysis revealed that high TSH levels, sex, diabetes duration, high-density lipoprotein cholesterol (HDL-C), glycosylated hemoglobin (HbA1c), FCP, and SBP were associated with NPDR [odds ratio (OR) > 1, $P<0.05$]. Receiver operating characteristic curve analysis revealed that the optimal cutoff point of TSH for predicting NPDR was 2.235 mIU/L.

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Conclusion The TSH level is independently associated with NPDR in the Chinese population with T2DM. A high serum TSH level may be a potential risk factor for NPDR and an indicator for screening for diabetic microangiopathy.

Trial registration This study is registered with the Chinese Clinical Trial Registry (02/21/2025 ChiCTR2500097614).

Keywords Non-proliferative diabetic retinopathy, Type 2 diabetes mellitus, Thyroid stimulating hormone, Thyroid function

Introduction

Diabetes mellitus (DM) is a lifelong metabolic disease characterized by chronic hyperglycemia caused by multiple factors and has become a growing social and epidemiological problem. Type 2 diabetes mellitus (T2DM) accounts for more than 90% of diabetic patients. Hyperglycemia and metabolic disturbances lead to acute and chronic complications of diabetes, and chronic complications in particular are the leading cause of disability and death from diabetes. Diabetic retinopathy (DR) is a common complication of longstanding DM that affects up to 50% of diabetic patients and is the main cause of blindness among older adults [1]. In the initial phase of DR, hyperglycemia and altered metabolic pathways lead to oxidative stress and neurodegeneration. The typical clinical features of DR include microaneurysms, hemorrhages, hard exudates (lipid clusters), cotton wool spots (due to retinal ischemia), venous dilatation, bead-like changes, and intraretinal punctate hemorrhages [2, 3]. These symptoms can be categorized into two distinct stages of DR: non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) [3]. Vascular endothelial damage, micro-aneurysm formation, and intraretinal punctate hemorrhage are early features of NPDR. PDR is an angiogenic response to extensive ischemia and capillary obstruction (with neovascularization or/and intravitreal/retinal hemorrhage) and is more severe than NPDR.

Previously reported relevant factors that have been identified for the development of DR include hyperglycemia [4, 5], dyslipidemia [6], smoking [7], vitamin D deficiency [8], and cystatin C [9]. In addition, vascular diseases, including cardiovascular disease (CVD), peripheral arterial disease (PAD), and diabetic nephropathy (DN), are also closely related to DR [10]. Thyroid dysfunction and DM are also closely linked [11, 12]. Moreover, growing evidence indicates that thyroid hormones regulate metabolism and insulin resistance. Thyroid dysfunction can worsen glucose metabolism and induce hyperglycemia in patients with T2DM, thereby increasing the risk of diabetic complications. Hyperglycemia decreases thyroid-stimulating hormone (TSH) levels and the conversion of thyroxine (T4) to triiodothyronine (T3) in peripheral tissues [12]. However, the relationship between serum TSH and NPDR in Chinese patients with T2DM has not been specifically described. Moreover, there are few data on the potential association between TSH and NPDR, and the underlying mechanism of their interaction remains elusive. Although previous studies have probed into this association, the findings have been rather controversial. Owing to the paucity of data regarding the potential association between TSH and NPDR, this study aimed to clarify the possible link between TSH and NPDR in Chinese patients with T2DM.

Methods

Population

For this hospital-based cross-sectional study, a total of 427 patients with T2DM who visited the Department of Endocrinology at the Second People's Hospital of Chizhou between January 2021 and December 2023 were screened. The inclusion criteria were as follows: patients aged ≥ 18 years and diagnosed with T2DM according to the diagnostic criteria of T2DM established by the World Health Organization in 1999, T2DM was assessed as having a history of T2DM, or fasting plasma glucose (FPG) level ≥ 126 mg/dL (7.0 mmol/ L), or oral glucose tolerance test ≥ 200 mg/dL (11.1 mmol/L), or glycosylated hemoglobin (HbA1c) ≥ 6.5%. The following participants were excluded from the study: individuals with coronary heart disease, severe pulmonary disease, kidney disease, liver disease, severe infection, tumors, a history of thyroid disease with or without treatment, acute complications of diabetes, a history of hypothalamus or pituitary diseases, or a history of cerebral infarction were excluded. Pregnant or lactating women were also excluded.

Data collection

Demographic data of the individuals and anthropometric parameters, including age, sex, body mass index (BMI), diabetes duration, alcohol consumption, daily number of cigarettes smoked, hypertension history, and history of other diseases, were collected in the hospital by reviewing medical records. Blood pressure was measured in the sitting position after a rest period of more than 10 min. Patients having systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg or having a history of hypertension were considered hypertensive. BMI was calculated as weight in kilograms divided by the square of height in meters.

Venous blood was drawn from all patients after an overnight fast to measure the following laboratory

parameters: FPG, C-peptide (CP), 2-hour C-peptide (2hCP), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), HbA1c, serum creatinine (Scr), blood urea nitrogen (BUN), uric acid (UC), urine micro-albumin (mALB), alanine aminotransferase (ALT), aspartate transaminase (AST), T3, T4, and TSH levels. The serum TSH, T3, and T4 concentrations were determined using a chemiluminescence immunoassay (Atellica IM 1600, Siemens Ltd., Berlin, Germany), and the corresponding normal reference concentrations were defined as 0.38–4.34 μIU/ml, 1.02–2.92 nmol/L, and 55.47–161.3 nmol/L, respectively.

All subjects were evaluated by two qualified retinal photographs using a CR-2AF (Canon, Tokyo, Japan) nonmydriatic camera at 45° (two eyes × two fields). Two experienced deputy chief ophthalmologists trained in retina and DR screening performed fundus examination. In the event of a discrepancy in diagnosis, a chief ophthalmologist was consulted to reach a consensus on the presence of DR. Mydriasis was achieved in all patients using Tropicamide 1% drops. DR was diagnosed and graded by mydriatic fundus photography and was further classified into NPDR and PDR according to the International Clinical Disease Severity Scale for DR and the Early Treatment of Diabetic Retinopathy Study (ETDRS). Only those patients afflicted with NPDR were integrated into this research.

Statistical analysis

All the statistical analyses were performed using SPSS software version 26.0. GraphPad Prism (version 8.0) was used to generate forest plots. The normality tests were examined using the Kolmogorov-Smirnov test. Continuous variables with a normal or non-normal distribution were presented as mean ± standard deviation (SD) or median (25th percentile, 75th percentile) respectively, and categorical variables as n (%). The characteristics of the participants in the NPDR group and the NDR group were compared using chi-square tests, Mann−Whitney U tests, or unpaired Student's t-tests, as appropriate. Spearman's correlation analysis was used to evaluate the correlations among different clinical characteristics in T2DM patients. Multiple logistic regression analysis was used to find the independent risk factors for NPDR. The receiver operating characteristic (ROC) curve was constructed to evaluate TSH, T3/TSH, and T4/TSH in patients with NPDR. The maximum Youden index was used to determine the optimal cutoff point. The optimal cutoff was calculated using the Youden index. Binary logistic regression analysis was performed to identify the independent determinants of NPDR. Baseline variables that were considered clinically relevant or that showed a univariate relationship with outcome (with a p value < 0.2) were entered into multivariate regression models. Variables for inclusion were carefully chosen, given the number of events available, to ensure parsimony of the final models. A P value < 0.05 at the two-tailed level was considered to indicate statistical significance.

Results

Demographic data

A total of 427 participants with T2DM were evaluated in our study, which consists of 251 (58.80%) male and 176 (41.20%) female, and the quartile of age was 57.0 (50–64) years. Among all participants, according to the results of ophthalmoscopy and fundus photography, 203 were diagnosed with NPDR, as NPDR group; and the other 224 without DR, as Non-DR (NDR) group. The clinical and laboratory characteristics of all participants are described in Table 1. Patients with NPDR exhibited higher prevalence of smoking and hypertension than those NDR. Furthermore, patients with NPDR exhibited a longer duration of diabetes. However, it was not statistically significant. A comparison of the serum biochemical indices (Table 1) revealed that the FCP and 2hCP levels were significantly lower in the NPDR group ($p < 0.01$). Significant differences in mALB and mALb/Ucr ratio were also observed between patients with NPDR and NDR ($p < 0.001$). For thyroid function, patients with NPDR exhibited significantly lower T4 ($P = 0.034$) and higher TSH ($P = 0.029$) levels than NDR group. All other characteristics were not significantly different between the two groups.

Relationships between TSH and other clinical features

Spearman's correlation analysis revealed a negative correlation between serum TSH levels and HbA1c levels (r = -0.11, $p < 0.05$) in all T2DM patients (Fig. 1a). In the NPDR group, the serum TSH level was negatively correlated with the HbA1c level (r=-0.19, $p < 0.01$) and positively correlated ($r = 0.14$, $p < 0.05$) with the duration of diabetes mellitus (Fig. 1c).

Risk factors for NPDR

A significant independent association between TSH and NPDR [odds ratio (OR) = 1.136, $P = 0.027$] was found by multiple logistic regression analysis adjusted for age, sex, diabetes duration, SBP, DBP, BMI, TG, LDL-C, HDL-C, HbA1c, FPG, FCP, UA, and mALB. Moreover, age (OR = 0.969), sex (OR = 0.290), diabetes duration (OR = 1.069), HbA1c level (OR = 1.277), FCP level (OR = 1.475), LDL-C level (OR = 0.386), HDL-C level (OR = 2.683), and SBP (OR = 1.034) were also found to be independent impact factors for NPDR (all $P < 0.01$) (Fig. 2).

Table 1 Comparison of clinical characteristics between T2DM patients with and without NPDR

Characteristics	Total (*n* = 427)	NPDR (*n* = 203)	NDR (*n* = 224)	*P*
Male/female	251/176	116/87	135/89	-
Age (years)	57.00 (50.00, 64.00)	57.45 ± 11.08	56.00 (48.00, 64.00)	0.217
Diabetes duration (years)	5.00 (1.00, 10.00)	8.00 (3.00, 12.00)	4.00 (0.80, 9.00)	0.451
Hypertension (%)	165 (38.64)	67 (33.00)	98 (43.75)	0.023*
SBP (mmhg)	136.00 (124.50, 148.00)	139.00 (130.00, 150.50)	134.00 (122.00, 145.00)	0.002**
DBP (mmhg)	85.00 (80.00, 90.00)	86.00 (79.00, 90.00)	85.00 (80.00, 90.00)	0.66
BMI (kg/m2)	24.11 (22.20, 26.44)	24.40 ± 3.50	24.20 (22.15, 26.55)	0.892
Smoking (%)	26.00	30.50	25.40	0.041*
Drinking (%)	14.52	15.76	13.39	0.487
FPG (mmol/L)	8.07 (6.61,10.29)	7.86 (6.49,10.34)	8.25 (6.70, 10.26)	0.546
2hPG (mmol/L)	18.87 ± 5.75	19.06 ± 5.76	18.71 ± 5.76	0.545
HbA1c (%)	9.10 (7.10, 11.00)	9.40 (7.10, 10.95)	8.75 (7.08, 11.03)	0.488
FCP (nmol/L)	1.57 (0.88, 2.26)	1.41 (0.74, 2.10)	1.75 (1.11, 2.41)	0.004**
2hCP (nmol/L)	5.20 (3.19, 7.63)	4.78 (2.60, 7.05)	5.65 (4.05, 8.09)	0.001**
FINS(pmol/L)	7.99 (4.99, 11.41)	7.91 (5.48, 12.27)	8.05 (4.80, 10.88)	0.581
2hINS (pmol/L)	33.91 (22.41, 55.24)	33.60 (20.67, 57.68)	34.36 (22.44, 54.50)	0.949
T3 (pmol/L)	1.63 (1.43, 1.80)	1.62 (1.44, 1.79)	1.63 (1.43, 1.81)	0.781
T4 (pmol/L)	107.23 ± 25.09	104.52 ± 23.37	109.72 ± 26.38	0.034*
TSH (mIU/L)	2.17 (1.44, 3.39)	2.33 (1.52, 3.58)	2.04 (1.36, 3.12)	0.029*
ALT (U/L)	24.00 (16.00, 35.00)	21.00 (15.00, 21.00)	26.00 (17.50, 38.50)	0.006**
AST (U/L)	22.00 (18.00, 28.00)	22.00 (17.00, 28.00)	23.00 (18.00, 29.00)	0.059
Scr (umol/L)	71.50 (58.00, 89.75)	72.00 (58.00, 91.25)	70.00 (57.00, 88.25)	0.457
BUN	5.70 (4.70, 6.90)	6.00 (4.70, 7.37)	5.55 (4.60, 6.60)	0.018*
eGFR (mL*min-1(1.73m2)-1)	97.56 (74.97, 116.76)	95.38 ± 35.49	98.58 (78.37, 118.26)	0.134
UA (mmol/L)	320.15 (259.25, 375.75)	325.50 (263.75, 375.25)	315.00 (247.00, 378.00)	0.410
TC (mmol/L)	4.46 (3.75, 5.27)	4.46 (3.72, 5.24)	4.47 (3.79, 5.28)	0.700
TG (mmol/L)	1.61 (1.15, 2.44)	1.61 (1.12, 2.14)	1.62 (1.16, 2.55)	0.347
HDL-C (mmol/L)	1.31 (1.10, 1.58)	1.33 (1.10, 1.64)	1.30 (1.10, 1.54)	0.315
LDL-C (mmol/L)	2.71 ± 0.86	2.63 ± 0.80	2.79 ± 0.90	0.066
VLDL-C (mmol/L)	0.74 (0.53, 1.11)	0.74 (0.51, 0.98)	0.74 (0.53, 1.16)	0.346
mALB	15.60 (6.65, 41.70)	21.00 (8.74, 70.45)	11.40 (5.89, 26.03)	< 0.001**
mALB/UCr	3.86 (1.08, 14.24)	5.62 (1.38, 25.69)	2.40 (0.94, 8.04)	< 0.001**

Data are expressed as means ± SD or median (25th–75th percentiles)

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure;

FPG, fasting plasma glucose; 2hPG, 2-hour plasma glucose; HbA1c, glycosylated hemoglobin;

FCP, fasting C-peptide; FINS, fasting insulin; 2hCP, 2-hour C-peptide; 2hINS, 2-hour insulin;

T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone;

ALT, Alaninetransaminase; AST, glutamic oxaloacetic transaminase;

Scr, serum creatinine; UA, uric acid; eGFR, estimated glomerular filtration rate;

TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol;

LDL-C, low-density lipoprotein cholesterol; VLDL-C, very low-density lipoprotein cholesterol;

mALB, urine micro-albumin; UCr, urine creatinine

* $P < 0.05$ compared NPDR with NDR two groups

** $P < 0.01$ compared NPDR with NDR two groups

The predictive value of TSH for NPDR

ROC curve analysis was used to verify the accuracy of TSH for predicting NPDR (Fig. 3). The results indicated that the optimal cutoff point of TSH was 2.235 mIU/L for predicting NPDR [area under curve (AUC) = 0.561; $P = 0.029$; Youden index = 0.122; sensitivity, 53.69%; specificity, 58.48%] (Fig. 3). The optimal cutoff point for the T4/TSH ratio was 52,502 pmol/mIU for predicting NPDR (AUC = 0.573; $P = 0.009$; Youden index = 0.148; sensitivity, 62.56%; specificity, 52.23%) (Fig. 3). The optimal cutoff point for the T3/TSH ratio was 755.1 pmol/mIU for predicting NPDR (AUC = 0.549; $P = 0.081$; Youden index = 0.111; sensitivity, 56.65%; specificity, 54.46%) (Fig. 3).

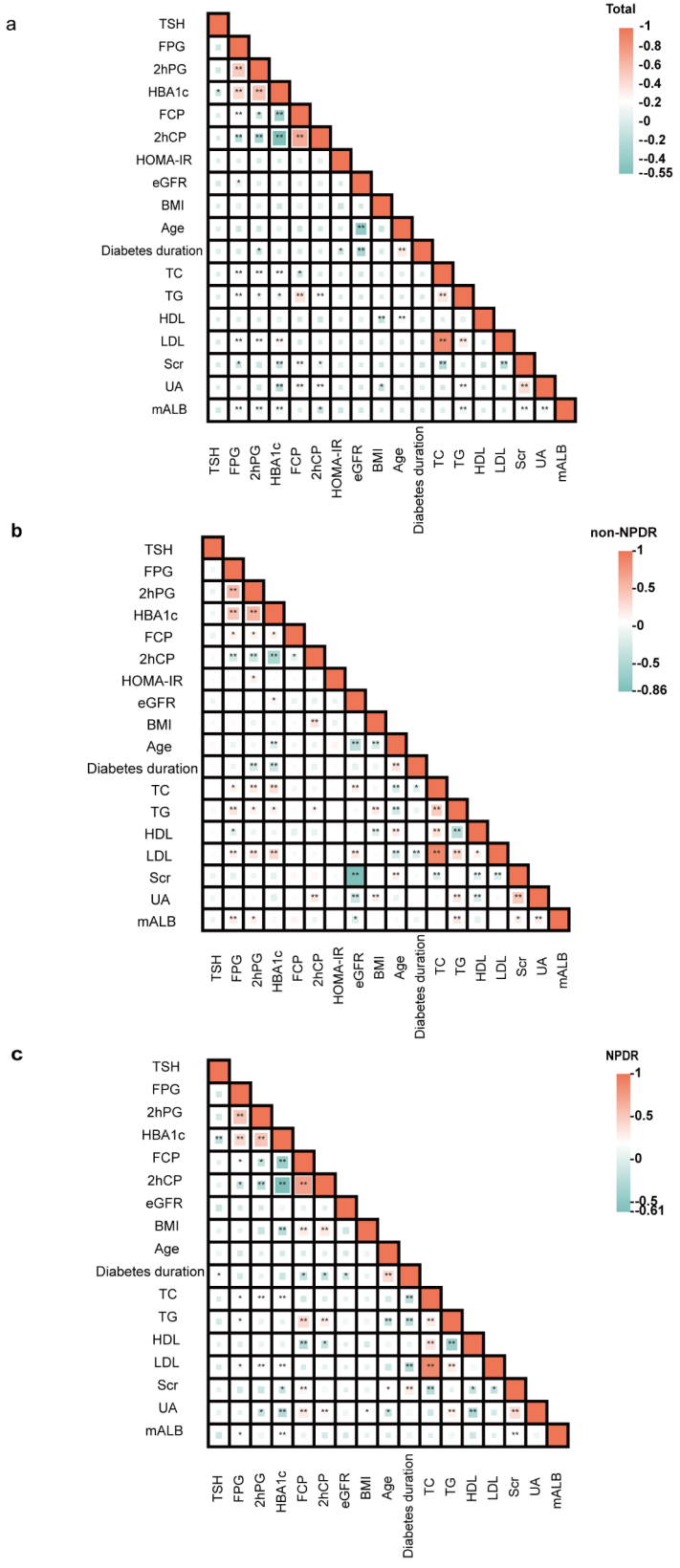

Fig. 1 Correlation between TSH and other clinical features. Heatmap showing Spearman's rank correlation between selected clinical features in all T2DM patients **(a)**, in group of NDR **(b)** and in group of NPDR **(c)**. *$P < 0.05$; **$P < 0.01$

characteristics	P Value	OR（95%CI）
Age	0.009	0.969 (0.947 - 0.992)
Sex	<0.001	0.290 (0.158 - 0.532)
Duration of diabetes	0.001	1.069 (1.027 - 1.112)
BMI	0.372	0.967 (0.899 - 1.041)
TG	0.752	0.977 (0.848 - 1.127)
LDL-C	<0.001	0.386 (0.277 - 0.537)
HDL-C	0.007	2.683 (1.307 - 5.506)
SBP	<0.001	1.034 (1.016 - 1.052)
DBP	0.055	0.972 (0.945 - 1.001)
HbA1c	<0.001	1.277 (1.135 - 1.438)
FPG	0.313	0.955 (0.874 - 1.044)
FCP	<0.001	1.475 (1.246 - 1.747)
TSH	0.027	1.136 (1.014 - 1.272)
UA	0.642	1.001 (0.998 - 1.003)
mALB	0.162	1.001 (1.000 - 1.002)

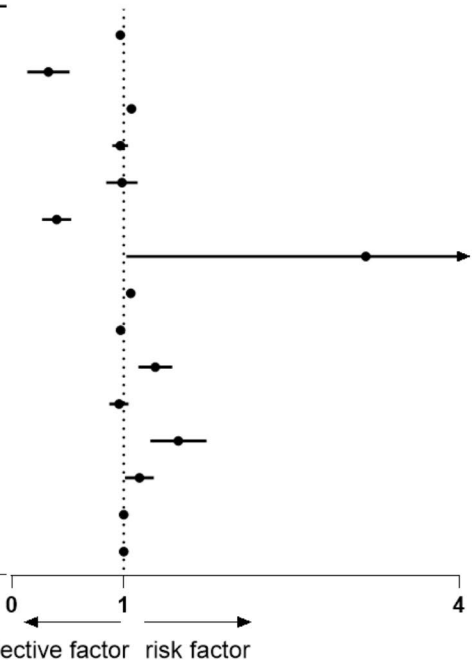

Fig. 2 Multiple regression analysis of NPDR with different clinical characteristics. Multiple regression analysis of variables independently associated with NPDR in all participants. The model was adjusted for age, sex, diabetes duration, BMI, TG, HDL-C, LDL-C, SBP, DBP, HbA1c, FPG, FCP, UA, and mALB. UA, uric acid; mALB, urine micro-albumin; BMI, body mass index; HbA1c, hemoglobin A1c; FPG, fasting plasma glucose; FCP, fasting C-peptide; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; TSH, thyroid stimulating hormone. **P* < 0.05; ***P*<0.01

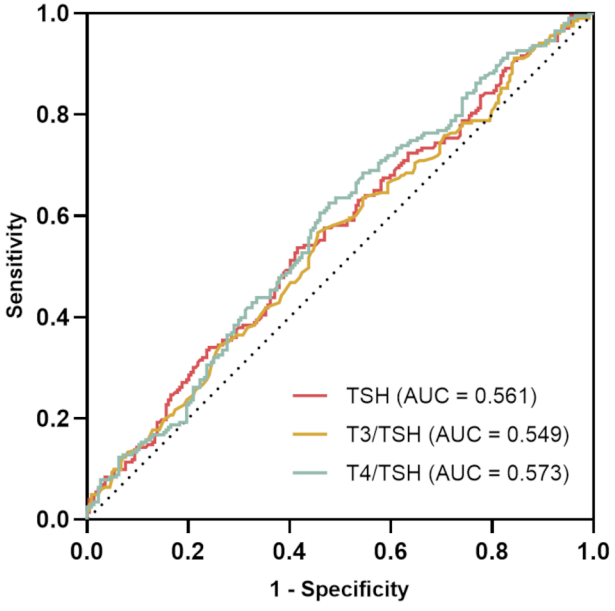

Fig. 3 ROC curve analysis of TSH, T3/TSH ratio and T4/TSH ratio to indicate NPDR. ROC, receiver operating characteristic; NPDR, non-proliferative diabetic retinopathy; T3, triiodothyronine1; T4, thyroxine; TSH, thyroid stimulating hormone

Discussion

Regarding the timeline of DR development, the initial phase of DR (NPDR) typically does not exhibit any noticeable clinical symptoms. However, advanced DR (PDR) can cause substantial clinical pain, such as neovascularization, fundus hemorrhage, and loss of vision. Despite its gradual onset, NPDR can persist for a significant duration even in the absence of noticeable clinical signs. Investigating the fluctuations in serum TSH levels in patients with NPDR is highly intriguing for identifying a new perspective on the correlation between serum TSH and NPDR in patients with T2DM.

This cross - sectional study included a total of 427 patients with T2DM and was conducted to analyze the relationship between TSH and NPDR in Chinese patients diagnosed with T2DM. We confirmed that TSH had a notable influence on NPDR in the Chinese T2DM population, regardless of other variables.

The pathophysiology of DR is complex and still unknown. The pathophysiologic alterations in DR include [1] oxidative stress, in which the generation of reactive oxygen clusters may be connected with the progression of DR [13]; and [2] inflammation, in which early DR is characterized by increased vascular permeability, increased retinal blood flow, neutrophil infiltration, macrophage infiltration, glial activation, complement

activation, and tissue edema [14] [3]. Neovascularization: The pathophysiology of DR is significantly influenced by neovascularization. Elevated blood glucose exacerbates retinal ischemia and hypoxia, damages capillary endothelial cells, and leads to the formation of microaneurysms, which further obstruct and necrotize capillaries, ultimately resulting in neovascularization [15]. According to some research, endothelial cell dysfunction alone is enough to cause DR [4]. Neuronal degeneration: oxidative stress, compromised antioxidant defense mechanisms, and an imbalance of neuroprotective factors in neurons cause neuronal and glial changes in the retina before neovascularization; from this perspective, DR can also be viewed as a neurodegenerative disease [16] [5]. Gut flora: The composition, modification, and disruption of the gut microbiota affect important physiological processes in the body, and the gut microbiota may contribute to diseases such as chronic inflammation, immune system imbalance, T2DM, chronic kidney disease, and rheumatoid arthritis [17]. Hyperglycemia in T2DM patients leads to dysbiosis of the intestinal flora, leading to bacterial translocation and deposition of intestinal endotoxin, which further induces intestinal inflammation. Recently, several scholars proposed the concept of the "gut-retina axis" and investigated the relationships among the gut microbiota, DM, and DR and found that there is a strong correlation between the gut flora and its metabolites, which suggests that the gut-retina axis could be used as a biomarker for future clinical diagnosis and treatment of DR [18]. In this study, we found that FCP, 2-h CP, and 2-h insulin levels were significantly lower in patients with T2DM combined with NPDR than in the NDR group, and HbA1c was elevated in the former compared with the latter, suggesting that the pancreatic islet function in the T2DM combined with NPDR group was poorer than that in the NDR group and that glycemic control was poor. Sex, diabetes duration, systolic blood pressure, HbA1c, FCP, and TSH levels were found to be independent risk factors for NPDR patients, whereas age, LDL-C, and HDL-C were found to be protective factors against NPDR. To our knowledge, few studies have focused on the relationship between TSH and NPDR, and the nature of this relationship remains incompletely understood. Consistent with the findings of previous studies, the present study showed that serum TSH levels were greater and T4 levels were lower in patients in the NPDR group than in patients in the NDR group, and the serum TSH concentration was an independent risk factor for NPDR. TSH, T3/TSH and T4/TSH were used in this study to predict NPDR, with AUCs of 0.561, 0.549, and 0.573, respectively. In addition, the optimal cutoff points for TSH, T3/TSH, and T4/TSH according to the ROC curves were estimated in this study and were 2.235 μIU/ml, 755.1 pmol/mIU, and 52,502 pmol/mIU, respectively. Similarly, the AUCs of TSH and T4/TSH were significantly different ($P<0.05$), but the difference in the comparison of the AUCs of T3/TSH was not statistically significant ($P>0.05$). The upper TSH limit advised by the American Society of Clinical Biochemistry is 2.5 μIU/ml [19]. The TSH threshold in this study is similar to that reported in earlier epidemiologic studies, with more than 95% of the normal population having TSH levels < 2.5 μIU/mL, beyond which the incidence of some diseases may increase. Therefore, lowering TSH levels may be a potentially positive measure for preventing NPDR. However, recently, several scholars have suggested that TSH is not correlated with DR [20, 21, 22]. This finding contradicts the findings of Yang [23] et al., who concluded that patients in the subgroup with higher TSH levels ($2.0 \le TSH < 4.0$ IU/ml) had a greater incidence of DR than did those in the subgroup with lower TSH levels ($0.4 \le TSH < 2.0$ IU/ml). Considering that the reason for the inconsistency between the results of the present study and those of the above studies is that only Wu [22] et al. included subjects with normal thyroid function among patients with T2DM, the reason for the inconsistency between the results of the present study and the results of the other studies may be that all of them included individuals with normal thyroid function among those with T2DM who had a combination of subclinical hypothyroidism, which may explain the inconsistency in the results. Several existing studies have demonstrated the potential mechanism of TSH in the occurrence and development of DR [24, 25, 26, 27, 28]. Lin [24] et al. detected functional TSH receptors in peripapillary retinal cells, which may promote the effect of high TSH levels on high glucose-induced loss of PC through TSH receptor-dependent apoptosis of mitochondrial cells. In addition, high TSH levels have been reported to be associated with early retinal changes, including narrowing of small retinal arteries and changes in visual protein expression [27, 28, 29]. Currently, international guidelines recommend screening for thyroid dysfunction in children, adolescents, and adults with type 1 diabetes (T1DM), but there is a lack of screening recommendations for T2DM. In conclusion, our findings suggest that in T2DM patients, additional attention should also be given to the potential impact of thyroid function, especially TSH, on the development of DR in clinical practice. In the future, well-designed longitudinal studies are necessary to further substantiate the role of TSH in the risk management of diabetic complications and to explore the reference range of "normal" TSH.

Previous studies [30, 31]have shown that the incidence of complications in patients with T2DM increases with the duration of the disease, the prevalence of DR in patients with a disease duration of more than 10 years is approximately 24.8%, and with increasing HbA1c,

the incidence of chronic complications in patients with T2DM also increases, which is considered to be related to the increase in the degree of damage to micro-vessels and nerve cells in the long-term high glucose treatment [32]. Compared with T1DM, diabetes duration has a greater impact on patients with T2DM combined with NPDR. The results of this study showed that the duration of diabetes was an independent risk factor for NPDR, and the mean risk increased by 1.069 times for each unit increase in the duration of the disease. This finding is similar to that of Singh [33] et al. The prevalence of DR in patients with a disease duration greater than 15 years was five times higher than that in patients with a disease duration less than 5 years.

Gender has recently been reported to be associated with the risk of developing diabetes-related complications [34, 35]. Middle-aged men are significantly more likely to develop T2DM, suggesting that sex-related factors are involved in the pathogenesis of T2DM and its complications to some extent in middle-aged populations [36, 37]. Several studies [38, 39, 40, 41] revealed sex correlations with fat distribution, activation of inflammatory signaling pathways, and T2DM risk. There are sex differences in disease progression and pathogenesis in middle-aged T2DM patients, and the present study revealed that men were at approximately 0.290-fold greater risk than women. Male sex is significantly associated with DR in middle-aged populations. Studies based on data from national databases in the UK and Finland showed that male sex is an independent risk factor for DR in the middle to late stages of T2DM and also for disease progression [42, 43]. Although the pathological mechanisms by which sex influences DR progression are currently unknown, significant differences between sexes imply the use of different individualized care measures. Prevention strategies that target modifiable risk factors are critical for the middle-aged T2DM population. The relationship between lipid levels and the development of DR is poorly understood. A case-control study [44] conducted in 13 countries revealed that diabetic micro-angiopathy (especially DN) was associated with increased triglyceride levels and decreased HDL-C levels in patients with well-controlled LDL-C. However, the results of several randomized controlled trials [e.g., action to control cardiovascular risk in diabetes study (ACCORD) and fenofibrate intervention and event lowering in diabetes study (FIELD)] have shown that fenofibrate significantly reduces the onset and progression of retinopathy in diabetic patients with dyslipidemia and that the risk of retinopathy is decreased by 30% [45]. In contrast, fenofibrate had little effect on patients with uncomplicated DR in the ACCORD study. Unlike those of the ACCORD study, the results of the FIELD study showed a benefit of DR progression independent of changes in lipid levels. Although the ADA guidelines [46] strongly recommend optimizing lipid levels to slow DR progression, the efficacy of fibrates in the primary prevention of DR is unclear. Thus, the exact beneficial effects of fibrates, as well as the exact role of higher HDL-C levels in DR, remain to be elucidated. However, in the scenario mentioned above, the most interesting result in our study was that in multivariate logistic regression analysis, high LDL-C appeared to be a potential protective factor for NPDR, and high HDL-C appeared to be a potential independent risk factor for NPDR, with a 2.683-fold increase in the mean risk of NPDR for each unit increase in HDL-C. These findings have not been confirmed in the previous literature; however, most studies have demonstrated an independent association between low HDL-C and renal disease and macro-vascular complications in T2DM patients and between all-cause mortality and a reduction in cardiac macro-vascular event rates and low HDL-C levels. In contrast, there is no evidence of a correlation between HDL-C and DR [47]. Previously, only Ferdinando Carlo Sasso [48] et al. conducted a large cross-sectional, multicenter, observational study and reported that DR was independently associated with HDL-C levels (OR 1.042; 95% CI 1.012 ~ 1.109; $p = 0.004$), with an ROC curve defining the potential cutoff value for HDL-C (40 mg/dL), this scholar also proposed a hypothesis regarding the association between HDL-C and DR, recognizing that the link may be incidental to an unknown pathophysiological abnormality. Therefore, additional large-scale cross-sectional and longitudinal studies are needed in the future to further investigate the relationship between retinopathy and high HDL-C levels.

Several limitations in the present study need to be explained. First, it is impossible to infer causality because of the cross-sectional design of this study. Thus, further studies are needed to determine the relative risk between thyroid hormones and NPDR risk in T2DM patients. Second, due to the hospitalization time limit, the thyroid function of subjects was assayed only once, so there may be some statistical bias. Third, the sample size is relatively small, which may lead to bias in the results, and it is necessary to further increase the sample size in later studies. Fourth, diabetes increases the risk of low T3 syndrome and hypothyroidism. As this study did not assess the trans-T3 levels of the participants, the relationship between thyroid function and NPDR risk may have been distorted. Fifth, the data on potential risk factors of NPDR, including physical activity, education, hypoglycemic, hypolipidemic and antihypertensive drug were not available in the present study. Therefore, the possibility of residual confounding could not be excluded. Lastly, all the subjects were from a single center where all participants were Chinese. As a result, our findings may not apply to all Chinese patients with T2DM or patients of

other ethnicities. Despite these potential limitations, this study has several advantages. To minimize confounding factors, we strictly excluded patients with positive thyroid autoantibodies or a history of thyroid disease or other endocrine diseases that can alter thyroid function. Moreover, few studies have specifically studied the correlation between thyroid hormones and NPDR. Ours is the first cross - sectional study in China that solely includes NPDR patients.

Conclusion

Current study indicates that relatively high TSH levels may also be independently associated with NPDR. This finding suggest that the residual risk of DR might be partially attributable to suboptimal thyroid function. In clinical practice, greater attention should be paid to the potential impact of TSH and the T4/TSH ratio on the management of NPDR. Prospective cohort studies are also warranted to assess the relation between thyroid hormones and NPDR in T2DM patients.

Abbreviations

ACCORD	Action to Control Cardiovascular Risk in Diabetes Study
ALT	glutamic pyruvic transaminase
AST	Aspartate transaminase
AUC	Area under curve
BMI	Body mass index
BUN	Blood urea nitrogen
2hCP	2-hour C-peptide
2hINS	2-hour insulin
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DM	Diabetes mellitus
DR	Diabetic retinopathy
DN	Diabetic nephropathy
eGFR	Estimated glomerular filtration rate
ETDRS	Early Treatment of Diabetic Retinopathy Study
FCP	Fasting C-peptide
FPG	Fasting plasma glucose
FIELD	Fenofibrate Intervention and Event Lowering in Diabetes Study
FINS	Fasting insulin
HbA1c	glycosylated hemoglobin
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
mALB	urine micro-albumin
NDR	Non-DR
NPDR	Non-proliferative diabetic retinopathy
PDR	Proliferative diabetic retinopathy
PVD	Peripheral arterial disease
RCT	Randomized controlled trial
ROC	Receiver operating characteristic
SBP	Systolic blood pressure
Scr	Serum creatinine
SD	Standard deviation
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TC	Total cholesterol
TG	Triglyceride
TSH	Thyroid-stimulating hormone
T4	Thyroxine
T3	Triiodothyronine
UC	Uric acid
UCr	Urine creatinine
VLDL-C	very low-density lipoprotein cholesterol

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Author contributions
Yiqi Xu formulated research goals and aims, designed methodology, wrote the manuscript and made statistical analysis. Biwu Dong, Youyun Tang, Feng Jiang, and Yan Jiang collected and processed the data. Junsheng Chen and Wei Xing supervised the project. Fengping Zhu proposed and supervised the project. All authors read and approve the final submitted manuscript.

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Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the Ethics Committees of the Institutional Ethics Committee of the Second People's Hospital of Chizhou (CZEY 20240520). Informed consent was obtained from each participant. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. White NH, Pan Q, Knowler WC, Schroeder EB, Dabelea D, Chew EY, et al. Risk factors for the development of retinopathy in prediabetes and type 2 diabetes: the diabetes prevention program experience. Diabetes Care. 2022;45(11):2653–61.
2. Frank RN. On the pathogenesis of diabetic retinopathy. A 1990 update. Ophthalmology. 1991;98(5):586–93.
3. Wong TY, Cheung CM, Larsen M, Sharma S, Simó R. Diabetic retinopathy. Nat Reviews Disease Primers. 2016;2:16012.
4. Hainsworth DP, Bebu I, Aiello LP, Sivitz W, Gubitosi-Klug R, Malone J, et al. Risk factors for retinopathy in type 1 diabetes: the DCCT/EDIC study. Diabetes Care. 2019;42(5):875–82.
5. Song KH, Jeong JS, Kim MK, Kwon HS, Baek KH, Ko SH, et al. Discordance in risk factors for the progression of diabetic retinopathy and diabetic nephropathy in patients with type 2 diabetes mellitus. J Diabetes Invest. 2019;10(3):745–52.
6. Estacio RO, McFarling E, Biggerstaff S, Jeffers BW, Johnson D, Schrier RW. Overt albuminuria predicts diabetic retinopathy in Hispanics with NIDDM. Am J Kidney Diseases: Official J Natl Kidney Foundation. 1998;31(6):947–53.
7. Cai X, Chen Y, Yang W, Gao X, Han X, Ji L. The association of smoking and risk of diabetic retinopathy in patients with type 1 and type 2 diabetes: a meta-analysis. Endocrine. 2018;62(2):299–306.
8. Chen X, Wan Z, Geng T, Zhu K, Li R, Lu Q, et al. Vitamin D status, vitamin D receptor polymorphisms, and risk of microvascular complications among

individuals with type 2 diabetes: A prospective study. Diabetes Care. 2023;46(2):270–7.
9. Xiong K, Zhang S, Zhong P, Zhu Z, Chen Y, Huang W, et al. Serum Cystatin C for risk stratification of prediabetes and diabetes populations. Diabetes Metabolic Syndrome. 2023;17(11):102882.
10. Vujosevic S, Aldington SJ, Silva P, Hernández C, Scanlon P, Peto T, et al. Screening for diabetic retinopathy: new perspectives and challenges. Lancet Diabetes Endocrinol. 2020;8(4):337–47.
11. Zhang L, Krzentowski G, Albert A, Lefebvre PJ. Risk of developing retinopathy in diabetes control and complications trial type 1 diabetic patients with good or poor metabolic control. Diabetes Care. 2001;24(7):1275–9.
12. Mendoza A, Hollenberg AN. New insights into thyroid hormone action. Pharmacol Ther. 2017;173:135–45.
13. Giacco F, Brownlee M. Oxidative stress and diabetic complications. Circul Res. 2010;107(9):1058–70.
14. Miyamoto K, Khosrof S, Bursell SE, Rohan R, Murata T, Clermont AC, et al. Prevention of leukostasis and vascular leakage in streptozotocin-induced diabetic retinopathy via intercellular adhesion molecule-1 Inhibition. Proc Natl Acad Sci USA. 1999;96(19):10836–41.
15. Qin Y, Zhang J, Babapoor-Farrokhran S, Applewhite B, Deshpande M, Megarity H, et al. PAI-1 is a vascular cell-specific HIF-2-dependent angiogenic factor that promotes retinal neovascularization in diabetic patients. Sci Adv. 2022;8(9):eabm1896.
16. Barber AJ, Lieth E, Khin SA, Antonetti DA, Buchanan AG, Gardner TW. Neural apoptosis in the retina during experimental and human diabetes. Early onset and effect of insulin. J Clin Investig. 1998;102(4):783–91.
17. Cai Y, Kang Y. Gut microbiota and metabolites in diabetic retinopathy: insights into pathogenesis for novel therapeutic strategies. Volume 164. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie; 2023. p. 114994.
18. Liu K, Zou J, Fan H, Hu H, You Z. Causal effects of gut microbiota on diabetic retinopathy: A Mendelian randomization study. Front Immunol. 2022;13:930318.
19. Kratzsch J, Fiedler GM, Leichtle A, Brügel M, Buchbinder S, Otto L, et al. New reference intervals for Thyrotropin and thyroid hormones based on National academy of clinical biochemistry criteria and regular ultrasonography of the thyroid. Clin Chem. 2005;51(8):1480–6.
20. Qi Q, Zhang QM, Li CJ, Dong RN, Li JJ, Shi JY, et al. Association of Thyroid-Stimulating hormone levels with microvascular complications in type 2 diabetes patients. Med Sci Monitor: Int Med J Experimental Clin Res. 2017;23:2715–20.
21. Ramis JN, Artigas CF, Santiago MA, Mañes FJ, Canonge RS, Comas LM. Is there a relationship between TSH levels and diabetic retinopathy in the Caucasian population? Diabetes Res Clin Pract. 2012;97(3):e45–7.
22. Wu J, Li X, Tao Y, Wang Y, Peng Y. Free Triiodothyronine levels are associated with diabetic nephropathy in euthyroid patients with type 2 diabetes. Int J Endocrinol. 2015;2015:204893.
23. Yang JK, Liu W, Shi J, Li YB. An association between subclinical hypothyroidism and sight-threatening diabetic retinopathy in type 2 diabetic patients. Diabetes Care. 2010;33(5):1018–20.
24. Lin D, Qin R, Guo L. Thyroid stimulating hormone aggravates diabetic retinopathy through the mitochondrial apoptotic pathway. J Cell Physiol. 2022;237(1):868–80.
25. Zhang S, Feng G, Kang F, Guo Y, Ti H, Hao L, et al. Hypothyroidism and adverse endpoints in diabetic patients: A systematic review and Meta-Analysis. Front Endocrinol. 2019;10:889.
26. Han C, He X, Xia X, Li Y, Shi X, Shan Z, et al. Subclinical hypothyroidism and type 2 diabetes: A systematic review and Meta-Analysis. PLoS ONE. 2015;10(8):e0135233.
27. Eom YS, Wilson JR, Bernet VJ. Links between thyroid disorders and glucose homeostasis. Diabetes Metabolism J. 2022;46(2):239–56.
28. Lee S, Farwell AP. Euthyroid sick syndrome. Compr Physiol. 2016;6(2):1071–80.
29. Énzsöly A, Hajdú RI, Turóczi Z, Szalai I, Tátrai E, Pálya F, et al. The predictive role of thyroid hormone levels for early diabetic retinal changes in experimental rat and human diabetes. Investig Ophthalmol Vis Sci. 2021;62(6):20.
30. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy. II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. Archives Ophthalmol (Chicago Ill: 1960). 1984;102(4):520–6.
31. Hong T, Mitchell P, de Loryn T, Rochtchina E, Cugati S, Wang JJ. Development and progression of diabetic retinopathy 12 months after phacoemulsification cataract surgery. Ophthalmology. 2009;116(8):1510–4.
32. Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. Diabetes. 2005;54(6):1615–25.
33. Singh RP, Elman MJ, Singh SK, Fung AE, Stoilov I. Advances in the treatment of diabetic retinopathy. J Diabetes Complicat. 2019;33(12):107417.
34. Huebschmann AG, Huxley RR, Kohrt WM, Zeitler P, Regensteiner JG, Reusch JEB. Sex differences in the burden of type 2 diabetes and cardiovascular risk across the life course. Diabetologia. 2019;62(10):1761–72.
35. Peters SAE, Woodward M. Sex differences in the burden and complications of diabetes. Curr Diab Rep. 2018;18(6):33.
36. Sattar N. Gender aspects in type 2 diabetes mellitus and cardiometabolic risk. Best Pract Res Clin Endocrinol Metab. 2013;27(4):501–7.
37. Li J, Ni J, Wu Y, Zhang H, Liu J, Tu J, et al. Sex differences in the prevalence, awareness, treatment, and control of diabetes mellitus among adults aged 45 years and older in rural areas of Northern China: A Cross-Sectional, Population-Based study. Front Endocrinol. 2019;10:147.
38. Pulit SL, Karaderi T, Lindgren CM. Sexual dimorphisms in genetic loci linked to body fat distribution. Biosci Rep. 2017;37(1).
39. de Ritter R, de Jong M, Vos RC, van der Kallen CJH, Sep SJS, Woodward M, et al. Sex differences in the risk of vascular disease associated with diabetes. Biology Sex Differences. 2020;11(1):1.
40. Henstridge DC, Abildgaard J, Lindegaard B, Febbraio MA. Metabolic control and sex: A focus on inflammatory-linked mediators. Br J Pharmacol. 2019;176(21):4193–207.
41. Winkler TW, Justice AE, Graff M, Barata L, Feitosa MF, Chu S, et al. The influence of age and sex on genetic associations with adult body size and shape: A Large-Scale Genome-Wide interaction study. PLoS Genet. 2015;11(10):e1005378.
42. Kostev K, Rathmann W. Diabetic retinopathy at diagnosis of type 2 diabetes in the UK: a database analysis. Diabetologia. 2013;56(1):109–11.
43. Looker HC, Nyangoma SO, Cromie D, Olson JA, Leese GP, Black M, et al. Diabetic retinopathy at diagnosis of type 2 diabetes in Scotland. Diabetologia. 2012;55(9):2335–42.
44. Sacks FM, Hermans MP, Fioretto P, Valensi P, Davis T, Horton E, et al. Association between plasma triglycerides and high-density lipoprotein cholesterol and microvascular kidney disease and retinopathy in type 2 diabetes mellitus: a global case-control study in 13 countries. Circulation. 2014;129(9):999–1008.
45. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, et al. Effects of long-term Fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet (London England). 2005;366(9500):1849–61.
46. 2. Classification and diagnosis of diabetes: standards of medical care in Diabetes-2019. Diabetes Care. 2019;42(Suppl 1):S13–28.
47. Morton J, Zoungas S, Li Q, Patel AA, Chalmers J, Woodward M, et al. Low HDL cholesterol and the risk of diabetic nephropathy and retinopathy: results of the ADVANCE study. Diabetes Care. 2012;35(11):2201–6.
48. Sasso FC, Pafundi PC, Gelso A, Bono V, Costagliola C, Marfella R, et al. High HDL cholesterol: A risk factor for diabetic retinopathy? Findings from NO BLIND study. Diabetes Res Clin Pract. 2019;150:236–44.

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