ORIGINAL RESEARCH

Correlation Between Thyroid-Related Hormones and Diabetic Retinopathy in Type 2 Diabetes Mellitus Patients with Normal Thyroid Function: A Retrospective Study

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Purpose: To investigate the correlation between thyroid-related hormones and diabetic retinopathy (DR) in euthyroid patients with type 2 diabetes mellitus (T2DM).

Patients and Methods: Patients with T2DM admitted to our hospital between January 2023 and June 2023 were retrospectively analyzed. The patients were divided into DR and non-diabetic retinopathy (NDR) groups according to whether DR occurred. Thyroid function-related hormones (TSH, FT3, and FT4), blood glucose indices (FBG and HbA1c), and blood lipid indices (HDL-C, LDL-C, TC, and TG) of the two groups were analyzed by univariate and multivariate logistic regression to explore the risk factors for DR. Pearson correlation analysis and multiple stepwise regression analysis were used to investigate the correlation of TSH or FT3 with FBG, HbA1c, and TG in DR patients.

Results: Of the 286 patients with T2DM included in this study, 101 (35.31%) developed DR and 185 (64.69%) did not. High TG, FBG, HbA1c, and TSH and low FT3 levels were independent risk factors for DR in T2DM patients. TSH positively correlated with TG, whereas FT3 negatively correlated with TG and HbA1c in T2DM patients with DR.

Conclusion: Higher TSH and lower FT3 in T2DM patients with normal thyroid function may affect glucose and lipid metabolism, thereby increasing the risk of DR.

Keywords: type 2 diabetes mellitus, diabetic retinopathy, thyroid-stimulating hormone, free triiodothyronine, glucose and lipid metabolism

Introduction

Type 2 diabetes mellitus (T2DM), the most common metabolic disease, is characterized by abnormally high blood glucose levels and is often accompanied by disorders of glucose and lipid metabolism.[1] With the development of the disease, T2DM can cause chronic progressive lesions in many tissues and organs, such as eyes, kidneys, nerves, heart, and blood vessels, and eventually lead to their functional decline and even failure. Diabetic retinopathy (DR) is a common microvascular complication of T2DM. DR can be classified into proliferative diabetic retinopathy (PDR) and non-proliferative diabetic retinopathy (NPDR). DR is the primary cause of visual impairment in middle-aged and elderly people.[2] A meta-analysis of 22,896 diabetic patients from 35 studies worldwide showed that the prevalence of DR was 34.6%.[3] DR seriously threatens the life quality of patients with diabetes and places a heavy economic burden on society. Patients with DR exhibit no obvious symptoms during the early stages of the disease. However, with continuous disease progression, blurred vision, decreased vision, and even blindness can occur.[4] Therefore, it is of great significance

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to actively explore relevant indicators to predict the risk of visual impairment in T2DM patients for the evaluation of patient condition and the formulation of treatment plans.

Although the pathogenesis and etiology of DR have not been fully clarified, a long duration of diabetes, poor control of blood sugar, hypertension, hyperlipidemia, obesity, and genetics are considered risk factors for DR.[5,6] However, some individuals with well-controlled blood sugar levels and no hypertension also develop severe DR, indicating that other risk factors also contribute to the occurrence of DR.[7] The role of thyroid hormones (THs) in diabetic microangiopathy has recently attracted increasing attention. Several studies have confirmed that THs metabolism plays a key role in retinal development and increases retinal blood vessel density.[8,9] It was found that low FT3 level was positively correlated with the risk of diabetic nephropathy in patients with type 2 diabetes or type 1 diabetes with normal thyroid function.[10,11] In addition, high thyroid-stimulating hormone (TSH) levels have been shown to be an independent risk factor for DR.[12] Subclinical hypothyroidism is closely associated with a high incidence of DR.[13] It was reported that the fluctuation of thyroid hormone level significantly affected glucose and lipid metabolism in T2DM patients.[14] However, few studies have investigated the relationship between thyroid-related hormone levels and glycolipid metabolism in patients with DR. Therefore, this study aimed to investigate the levels of thyroid-related hormones and glycolipid metabolism in DR patients with normal thyroid function and to analyze the potential correlation between thyroid-related hormones and DR.

Materials and Methods

Patient Selection

Patients with T2DM admitted to our hospital between January 2023 and June 2023 were retrospectively analyzed. The inclusion criteria were in accordance with the diagnostic criteria of T2DM: having a history of T2DM, or fasting blood glucose (FPG) level $\geq$ 7.0 mmol/L or postprandial blood glucose $\geq$ 11.1 mmol/L or glycosylated hemoglobin (HbA1c) $\geq$ 7.0%.[15] The exclusion criteria were as follows: (1) abnormal thyroid function or thyroid malignant diseases; (2) acute complications of diabetes mellitus; (3) previous history of hypothalamic or pituitary diseases; (4) malignant tumors; (5) acute infection state; (6) using lipid-regulating drugs or drugs affecting blood lipids in the near future; (7) taking drugs that may affect thyroid function, such as iodine, glucocorticoids, and amiodarone; and (8) incomplete clinical data, such as personal history, relevant examinations, and medication records. Based on the occurrence of DR, patients were divided into DR group and non-diabetic retinopathy (NDR) group. Diabetic retinopathy was screened by professional ophthalmologists using non-mydriatic fundus photography. This study was approved by the Ethics Committee of Affiliated Jinhua Hospital, Zhejiang University School of Medicine. The requirement for informed consent was waived due to the retrospective nature of this study. The Declaration of Helsinki was strictly followed, and all patients' data were kept confidential.

Data Collection

Demographic and clinical data including age, sex, height, weight, diabetes duration, hypertension history, coronary heart disease history, smoking status, and drinking status were collected from the Haitai Electronic Medical Record System. Body mass index (BMI) was calculated by dividing weight by the square of height (kg/m^2). The blood biochemical indexes of all patients are also obtained from this system, including high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), triglyceride (TG), FBG, HbA1c, TSH, free triiodothyronine (FT3), and free thyroxine (FT4). Venous blood was collected from all patients with an empty stomach for more than 12 h for clinical analysis on the day after admission. Blood sugar and lipid levels were measured using an automatic biochemical analyzer. HPLC was used to determine HbA1c levels. FT3, FT4, and TSH levels were detected using an electrochemiluminescence immunoassay.

Statistical Analysis

Data were analyzed using SPSS 23.0. The measurement data conforming to the normal distribution are expressed by $\bar{x} \pm s$, and the comparison between groups is made by independent sample t-test or one-way ANOVA test. The LSD test was used for post-event pairwise comparisons. Measurement data that did not conform to the normal distribution are represented by M (P25–P75), and the Mann–Whitney U-test was used for comparison between groups. The counting data

were expressed as [n (%)], and the comparison between groups was performed using χ^2 test. Univariate and multivariate logistic regression analyses were used to explore risk factors for DR in T2DM patients. Pearson correlation analysis and multiple stepwise regression analysis were conducted to explore the correlation between TSH or FT3 and FBG, HbA1c, or TG levels in patients with DR. All tests were two-tailed, and a P value <0.05 was considered statistically significant.

Results
Clinical Characteristics of Included Patients
A total of 286 patients with T2DM were included in this study, with 101 and 185 patients in the DR and NDR groups, respectively (Figure 1). The average age of DR group was (62.52±11.89) years, and the average BMI was (21.51 ±3.73) kg/m^2, including 68 males and 33 females. The average age of NDR group was (58.98±12.05) years, and the average BMI was (21.22±3.98) kg/m,^{2} including 110 males and 75 females. There were no significant differences in sex, BMI,coronary heart disease history, drinking history, or smoking history between the two groups (P > 0.05) (Table 1). However, age, diabetes duration, and the proportion of hypertensive patients were higher in the DR group than in the NDR group.

Comparison of Thyroid-Related Hormones, Blood Sugar and Blood Lipid
Compared with NDR group, LDL-C, TG, FBG, HbA1c, and TSH levels were higher in the DR group (P < 0.05), while FT3 level was lower (P < 0.05) (Table 2). HDL-C, TC, and FT4 levels were not significantly different between the two groups (P > 0.05).

Logistics Regression Analysis for Risk Factors of DR
Univariate and multivariate logistic regression analyses revealed that TG, FBG, HbA1c, TSH, and FT3 levels were risk factors for DR (P < 0.05) (Table 3). TG, FBG, HbA1c, and TSH levels in patients with T2DM were positively correlated
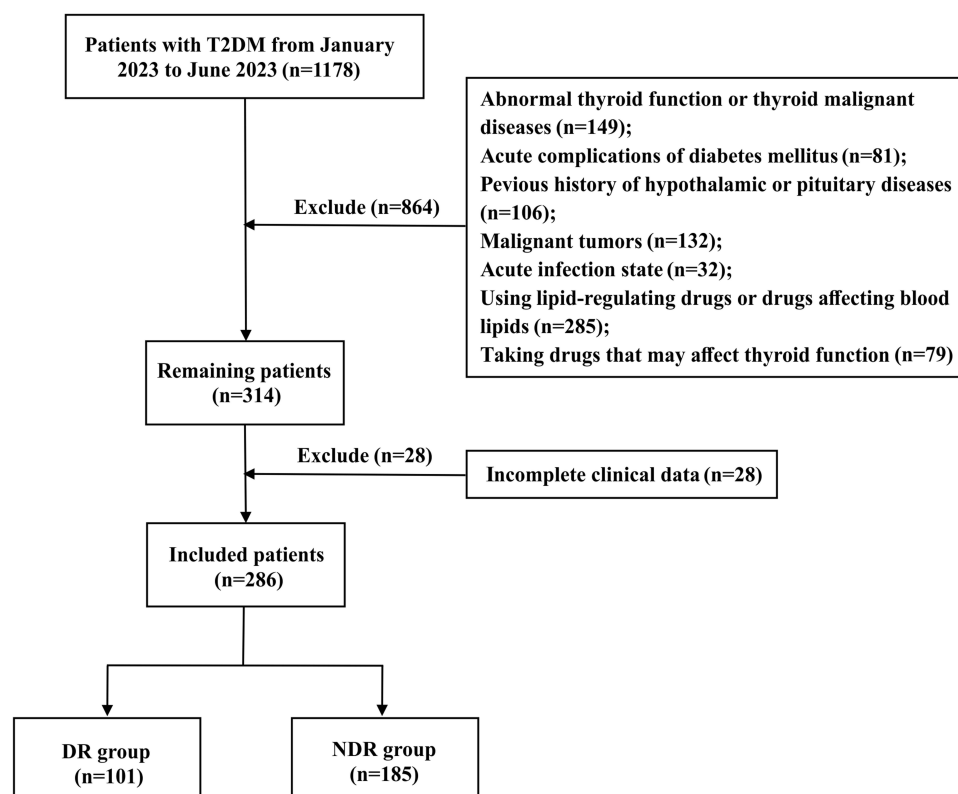

Figure 1 Flow chart of case screening.
Abbreviations: T2DM, type 2 diabetes mellitus; DR, diabetic retinopathy; NDR, non-diabetic retinopathy.

Table 1 Clinical Characteristics of Included Patients

Variables		DR Group (n=101)	NDR Group (n=185)	χ^2/t/Z	P-value
Sex	Male	68(23.78%)	110(38.46%)	1.721	0.19
	Female	33(11.54%)	75(26.22%)		
Age (years)		62.52±11.89	58.98±12.05	2.386	0.018
BMI (kg/m^2)		21.51±3.73	21.22±3.98	0.593	0.554
Duration of diabetes (years)		8.30(4.00–12.00)	5.43(3.00–8.00)	−5.256	<0.001
Hypertension (case, %)	Yes	64(22.38%)	72(24.67%)	15.657	<0.001
	No	37(25.17%)	113(39.51%)		
Coronary heart disease (case, %)	Yes	31(10.84%)	69(24.48%)	1.253	0.263
	No	70(24.13%)	116(40.56%)		
Drinking (case, %)	Yes	41(14.34%)	70(24.48%)	0.209	0.648
	No	60(20.98%)	115(40.21%)		
Smoking (case, %)	Yes	45(15.73%)	77(26.92%)	0.23	0.632
	No	56(34.15%)	108(37.76%)		

Note: Data are expressed as mean ± standard deviation, median (quartile 25, quartile 75) or numbers (%).
Abbreviations: BMI, body mass index; DR, diabetic retinopathy; NDR, non-diabetic retinopathy.

Table 2 Comparison of Thyroid-Related Hormones, Blood Sugar and Blood Lipid Levels

Variables	DR Group (n=101)	NDR Group (n=185)	χ^2/t	P-value
HDL-C (mmol/L)	1.11±0.32	1.04±0.33	1.857	0.064
LDL-C (mmol/L)	3.33(1.69–4.51)	2.84(1.71–4.02)	−2.082	0.037
TC (mmol/L)	5.51±1.52	5.73±1.62	−1.139	0.256
TG(mmol/L)	3.03(2.15–3.94)	1.96(0.98–2.74)	−6.384	<0.001
FBG (mmol/L)	9.91±2.26	8.92±2.28	3.502	0.001
HbA1c (%)	12.72(9.26–16.06)	10.08(7.77–12.54)	−5.883	<0.001
TSH (mIU/L)	2.90±1.41	1.96±0.97	6.625	<0.001
FT3 (pmol/L)	4.60(3.74–5.30)	5.29(4.15–6.39)	−4.681	<0.001
FT4 (pmol/L)	11.76±2.30	12.02±2.42	−0.878	0.38

Note: Data are expressed as mean ± standard deviation, median (quartile 25, quartile 75) or numbers (%).
Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; TSH, thyroid stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; DR, diabetic retinopathy; NDR, non-diabetic retinopathy.

with the risk of DR, with TSH being the risk factor with the strongest correlation (OR = 1.493, 95% CI 1.142–1.951, P = 0.003) among these risk factors. However, FT3 levels were negatively correlated with DR risk (OR = 0.752, 95% CI 0.582–0.972, P = 0.030).

Table 3 Logistics Regression Analysis for the Risk Factors of Diabetic Retinopathy

Variables	Univariate			Multivariate		
	OR	95% CI	P-value	OR	95% CI	P-value
HDL-C	2.026	0.957–4.289	0.065	—	—	—
LDL-C	1.222	1.043–1.431	0.013	1.099	0.916–1.319	0.309
TC	0.914	0.784–1.067	0.255	—	—	—
TG	1.979	1.592–2.461	<0.001	1.435	1.119–1.840	0.004
FBG	1.202	1.077–1.342	0.001	1.14	1.005–1.293	0.042
HbA1c	1.289	1.187–1.400	<0.001	1.187	1.084–1.301	<0.001
TSH	1.948	1.557–2.436	<0.001	1.493	1.142–1.951	0.003
FT3	0.582	0.465–0.729	<0.001	0.752	0.582–0.972	0.03
FT4	0.955	0.863–1.058	0.955	—	—	—

Abbreviations: OR, Odds ratio; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; TSH, thyroid stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine.

Comparison of FBG, HbA1c or TG at Different TSH Levels in DR Patients

According to the TSH concentration, the T2DM patients with DR divided into low-level group (≤2 mIU/L), middle-level group (2 mIU/L ~ 3.5 mIU/L) and high-level group (≥3.5 mIU/L). The differences in TG levels among the three groups were statistically significant (P < 0.05). With an increase in TSH levels, TG levels gradually increased. HbA1c levels in the high TSH-level group were significantly higher than those in the low and middle TSH-level group (P < 0.05). There were no significant differences in the FBG levels among the three groups (Figure 2).

Comparison of FBG, HbA1c or TG at Different FT3 Levels in DR Patients

Similarly, based on FT3 level, the T2DM patients with DR were divided into low-level group (≤4.5 pmol/L), middle-level group (4.5 pmol/L ~ 6 pmol/L) and high-level group (≥6 pmol/L). The differences in TG levels among the three groups were statistically significant (P < 0.05). As FT3 levels increased, TG levels gradually decreased. There were no
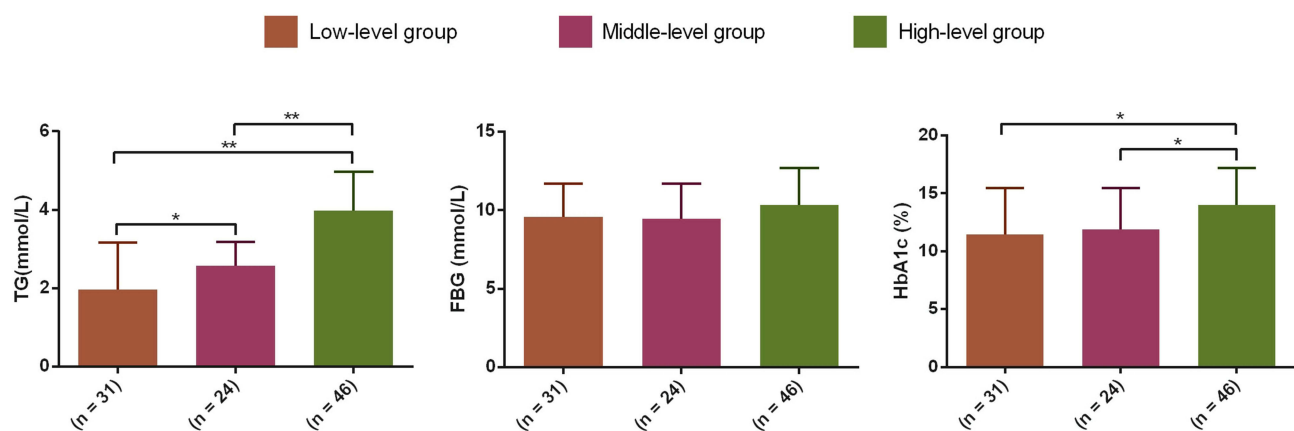

Figure 2 Comparison of FBG, HbA1c or TG at different TSH levels in diabetic retinopathy patients. *P < 0.05, **P < 0.01.
Abbreviations: TG, triglycerides; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; TSH, thyroid stimulating hormone.

significant differences in TG levels among the three groups (P < 0.05). Compared with the low and middle FT3-level groups, HbA1c level in the low FT3-level group was significantly higher (P < 0.05). However, there was no significant difference in HbA1c levels between the middle and high FT3-level group (Figure 3).

Correlation Analysis of TSH or FT3 with FBG, HbA1c or TG in DR Patients

Pearson correlation analysis (Figure 4) showed: (1) TSH was positively correlated with TG (r = 0.711, P < 0.001) and HbA1c (r = 0.321, P = 0.001), but not with FBG (P > 0.05); (2) FT3 was negatively correlated with TG (r = −0.537, P < 0.001), FBG (r = −0.241, P = 0.015) and HbA1c (r = −0.363, P < 0.001). Multiple stepwise regression analyses were performed with TSH or FT3 as dependent variables and FBG, HbA1c, and TG as independent variables. The results are as follows: (1) TSH is significantly correlated with TG (β = 0.711, P < 0.001), but not with FBG and HbA1c; (2) FT3 is closely related to TG (β = −0.468, P < 0.001) and HbA1c (β = −0.212, P = 0.017), but not to FBG (Table 4). Therefore, TSH negatively correlated with TG, whereas FT3 negatively correlated with TG and HbA1c levels in T2DM patients with DR.

Discussion

With improvements in living standards and lifestyle changes, the incidence of T2DM is increasing. Untimely T2DM treatment can induce microvascular injury and cause DR, significantly increasing the risk of visual impairment. The continuous increase in blood glucose level in T2DM patients could damage the function of the retinal microvascular barrier, leading to the occurrence of DR.[16] Therefore, it is important to identify clinically related indicators that can predict the risk of DR in T2DM patients for preventing and treating DR.

This study found that high serum TSH and low serum FT3 levels are independent risk factors for DR in T2DM patients. TSH, a hormone secreted by the adenohypophysis, can regulate the proliferation of thyroid cells, promote the synthesis and secretion of THs, and improve the blood supply to the thyroid. Abnormally high TSH expression can accelerate oxidative stress, induce vascular endothelial cell damage, and alter local hemodynamics in T2DM patients.[17] These pathological changes can aggravate damage to endothelial cells in the fundus, thicken the basement membrane, and block capillaries, thereby causing visual impairment in T2DM patients. A cross-sectional study found that high TSH levels are an independent risk factor for diabetic macular edema in T2DM patients.[12] Both FT3 and FT4 are the main active forms of THs in the body and can accurately reflect the metabolic state of the thyroid. T3 has the strongest biological activity among THs and plays an important role in metabolic processes. Many important biochemical processes in the human body, including fat production and decomposition, glucose metabolism, and insulin resistance, are affected by THs.[18] Abnormal changes of THs are closely associated with the development of various diseases such as diabetes, coronary heart disease, and nonalcoholic fatty liver disease.[19] Notably, THs are essential for retinal
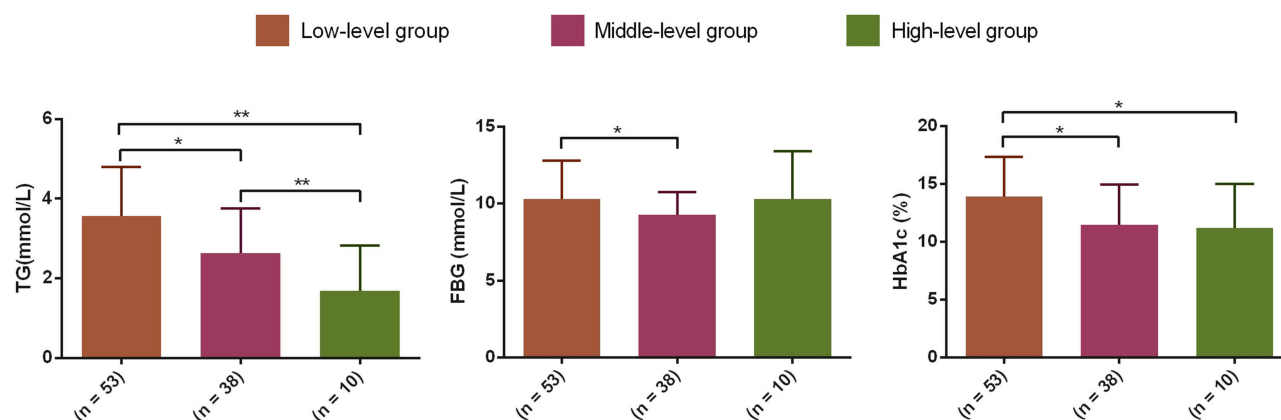

Figure 3 Comparison of FBG, HbA1c or TG at different FT3 levels in diabetic retinopathy patients. *P < 0.05, **P < 0.01.
Abbreviations: TG, triglycerides; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; FT3, free triiodothyronine.
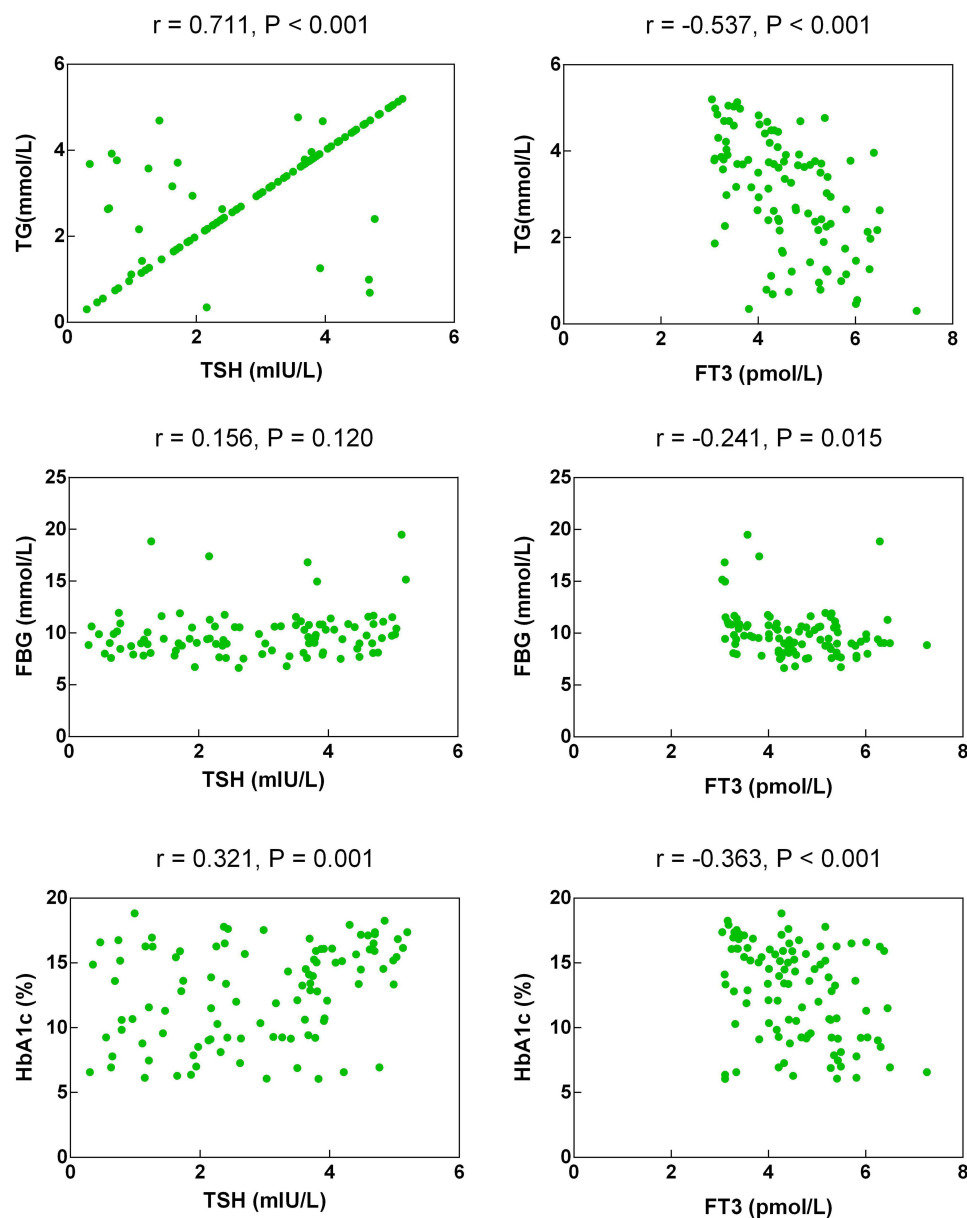
Figure 4 Correlation of TSH or FT3 with FBG, HbA1c or TG in diabetic retinopathy patients.
Abbreviations: TG, triglycerides; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; TSH, thyroid stimulating hormone; FT3, free triiodothyronine.

development and maturation of retina.[20] Glaschke et al[21] reported that THs deficiency affects the expression of retinal cone opsins and damages visual function in adult rodents. The decrease of T3 level can induce retinal cell dysfunction and death by aggravating the oxidative stress and inflammation in the eyes, thus promoting the onset of early diabetic

Table 4 Multivariate Linear Regression Analysis of TSH and FT3 Levels

Items	TSH			FT3		
	β	t	P-value	β	t	P-value
TG	0.711	10.051	<0.001	−0.468	−5.354	<0.001
FBG	0.019	0.258	0.797	−0.212	−1.399	0.017
HbA1c	0.102	1.369	0.174	−0.118	−2.419	0.165

Abbreviations: TG, triglycerides; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; TSH, thyroid stimulating hormone; FT3, free triiodothyronine.

retinopathy.[22] In addition, low T3 level may have a protective effect on retinal stress in the early stage of diabetic retinopathy.[23] Thus, timely correction of TSH and FT3 levels in T2DM patients may be helpful to prevent the occurrence or progress of DR.

FBG only represents the blood glucose level at the time of blood drawing. In addition, FBG is greatly influenced by diet, exercise, and mood, which do not fully reflect blood glucose control over a period of time. As a clinically stable index of glucose metabolism, HbA1c reflects the average blood glucose level in the last three months before measurement. Therefore, HbA1c can be used to evaluate the control of long-term blood glucose levels in patients with diabetes more accurately than FBG. Long-term hyperglycemia leads to the non-enzymatic glycosylation of proteins in T2DM patients. Proteins combine with non-glycated molecules to form macromolecular glycated products such as crystallin and collagen, which cause pathological changes such as thickening of the blood vessel basement membrane and turbidity of the lens in the eyes.[24] A cross-sectional study of 13,473 patients with T2DM in China found that an elevated HbA1c level was an independent risk factor for early DR.[25] Abnormal lipid metabolism has also been proved to be an important risk factor for the occurrence and development of DR.[26] Kowluru et al[27] pointed out that hyperlipidemia could accelerate mitochondrial damage induced by hyperglycemia and promote the progression of DR. Several studies have reported that the blood lipid levels of patients with DR were significantly higher than those of patients without DR, and this has a significant correlation with the severity of DR.[28,29] TG is an important component of human blood lipids that regulates energy metabolism and maintains the balance of lipid metabolism. Notably, an increase in TG levels has been confirmed to be closely related to the occurrence of DR in T2DM patients.[30,31] Our study also found that T2DM patients with higher serum TG, FBG, and HbA1c levels were more likely to develop DR. These findings suggest that the disorder of glycolipid metabolism increases the risk of DR in T2DM patients.

Our Pearson correlation analysis and multiple stepwise regression analysis showed that TSH was negatively correlated with TG, whereas FT3 was negatively correlated with TG and HbA1c in T2DM patients complicated with DR. This suggests that T2DM patients with higher TSH and lower FT3 levels are prone to glucose and lipid metabolism disorders, thus increasing the risk of retinopathy. Glucose metabolism in T2DM patients with poor long-term blood glucose control is weakened, leading to a disorder in cellular energy utilization[32] Thus, the iodine pump function of the thyroid follicular cells is weakened, which reduces the iodine uptake ability of the thyroid gland and interferes with iodine organization. Thyroid follicular cells reduce the synthesis, eventually leading to a decline in serum FT3 level.[33] In addition, a study found that the expression of iodothyronine deiodinase 2 decreased significantly when mouse retinal cells were exposed to hyperglycemia. This reduced the conversion from thyroxine (T4) to triiodothyronine (T3), thereby resulting in reduced FT3 production.[22] Due to the insufficient synthesis and secretion of THs, the human body secretes a large amount of TSH to maintain the normal function of the thyroid gland, thus resulting in a significant increase in serum TSH levels. It was reported that the increase of TSH significantly increased the expression of interleukin-6 and anti-tumor necrosis factor-α in adipocytes, enhanced lipolysis and insulin resistance, and thus promoted the increase of TG level.[34,35] The increased TG level is also closely related to the decrease in THs levels, and the potential mechanism is that decreased THs weaken the activity of lipoprotein lipase and lower the clearance rate of TG.[36] The decrease of T3 level reduces the insulin synthesis of islet cells and weakens the sensitivity of peripheral tissues to insulin, leading to an increase in blood sugar.[37] A study reported that exogenous T3 treatment significantly reduced the blood sugar of T2DM mice model, which may be achieved by improving insulin synthesis and insulin sensitivity.[38] Therefore, abnormal levels of thyroid-related hormones have a significant effect on glucose and lipid metabolism, thereby accelerating the occurrence and development of DR.

There are still several limitations in this study. Firstly, it is a retrospective single-center study with small samples. Our findings need to be confirmed by a prospective multi-center and large-scale clinical study. In addition, all T2DM patients in our study chose oral metformin for hypoglycemic treatment. Some studies have reported that metformin may affect the serum levels of TSH, FT4, and FT3 in T2DM patients,[39,40] which interferes with our research results to some extent. Moreover, this study is actually a retrospective analysis of medical records, and it is unable to obtain a complete record of patients' diet, living habits and emotions. Because thyroid-related hormones, blood sugar and blood lipids are easily affected by these factors, our research results may have some deviations.

Conclusions

In conclusion, higher TSH and lower FT3 levels in euthyroid patients with DR may disturb the process of glucose and lipid metabolism, thus promoting the occurrence and development of DR. Therefore, closely monitoring the serum TSH, FT3, TG, FBG, and HbA1c levels in T2DM patients, and timely correcting TSH and FT3 levels and improving the disorder of glycolipid metabolism may be helpful to prevent DR.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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