RESEARCH

A high TSH level is associated with diabetic macular edema: a cross-sectional study of patients with type 2 diabetes mellitus

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Abstract

Aims: In this study, we determined the association between thyroid-stimulating hormone (TSH) and diabetic macular edema (DME) by assessing the prevalence and risk factors for DME in type 2 diabetes mellitus (T2DM) patients with different thyroid dysfunctions.
Methods: This was a retrospective cross-sectional study including 1003 euthyroid and 92 subclinical hypothyroidism (SCH) T2DM patients. DME status was detected by optical coherence tomography (OCT). The association between TSH and DME and the impact of TSH on DME were analyzed.
Results: The DME prevalence was 28.3% in the SCH patients and 14.0% in the euthyroid population. The serum FT4 ($P = 0.001$) and FT3 ($P < 0.001$) levels were significantly higher in the non-DME group than in the DME group, and the TSH level ($P < 0.001$) was significantly lower. Four subgroups (G1–G4) were divided by TSH level, and the chi-square test indicated that even in the normal range, the TSH level was positively related to DME prevalence ($P = 0.001$). Subgroup data indicated that the association between TSH and DME detected by OCT ($P = 0.001$) was stronger than the correlation between TSH and diabetic retinopathy detected by digital retinal photographs ($P = 0.027$). The logistic regression model confirmed that elevated TSH was an independent risk factor for DME. The odds ratio was 1.53 ($P = 0.02$).
Conclusions: A high TSH level was an independent risk factor for DME. More attention should be given to the TSH level in T2DM patients due to its relationship with diabetic complications.

Key Words
- TSH
- diabetic macular edema
- subclinical hypothyroidism
- optical coherence tomography

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Introduction

The prevalence of type 2 diabetes mellitus (T2DM) is increasing globally, and diabetic complications affect millions of people worldwide (1, 2). Diabetic eye diseases, such as diabetic retinopathy (DR) and diabetic macular edema (DME), represent the leading causes of vision loss in adults (3). DME left untreated is one of the most common causes of vision loss in people with diabetic eye disease (4). An epidemiologic study indicated that 25% of patients with T2DM and 20% of patients with type 1 diabetes (T1DM) would suffer from DME after 10 years of follow-up (5).

Thyroid dysfunctions, including clinical and subclinical thyroid dysfunction, are common diseases with a prevalence of up to 10% in the general population (6). Subclinical hypothyroidism (SCH), which is characterized by elevated thyroid-stimulating hormone (TSH), has

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attracted increasing attention, as it interacts with many metabolic diseases (7, 8). Thyroid hormones, including TSH, have been shown to affect different kinds of visual functions (9, 10). SCH, or an increased TSH concentration, has been shown to be correlated with diabetic complications, such as diabetic nephropathy (11) or diabetic eye diseases (12). Our group has also reported that T2DM patients with SCH have an increased risk of DR (13) and that T2DM patients with DR are at an elevated risk of SCH (14). All these results indicate an association between TSH and DR.

DME, which is defined as retinal swelling approaching or involving the center of the macula, is the most common cause of vision loss in T2DM patients (15). Many diagnostic tools are useful for detecting and monitoring the features of DME. Among them, optical coherence tomography (OCT) is a non-invasive and convenient method that is always used by experts as a more objective and accurate assessment (16). It is an objective and useful tool for describing, classifying, and managing DME (17, 18). In recent years, the Rotterdam study showed that increased thyroid hormone levels were correlated with an elevated risk of age-related macular degeneration (AMD), another type of macular degeneration leading to blindness and visual impairment that, as its name implies, is closely related to age (19). Another large population-based cohort study in Australia indicated an association between the incidence of AMD and thyroid dysfunction (20).

Although the association between thyroid hormone levels and DR and AMD has been reported recently, by comparison, very little is known about the DME prevalence in T2DM patients with different thyroid functions. Similarly, although previous studies have examined the possible risk influence of TSH for DR, few clinical studies have assessed the risk influence of TSH for DME. In this study, we investigated the prevalence of DME, which was detected by OCT, in T2DM patients with different thyroid functions. We sought to determine whether the TSH level was an independent risk factor for DME in our large Chinese T2DM patient sample.

Materials and methods

Population and study design

This was a retrospective cross-sectional study analysis conducted at Beijing Tongren Hospital. Patients were recruited from June 2015 to January 2017 from the hospital inpatient database. A total of 1135 patients with T2DM were selected. Patients with known thyroid diseases, thyroidectomy, taking medications that might affect thyroid function, pregnancy, malignancy, any acute intercurrent illness, or data severely missing were excluded. According to FT4 and TSH concentrations, six subjects with clinical hyperthyroidism and six subjects with clinical hypothyroidism were later excluded. Finally, 1103 euthyroid and 92 SCH subjects were assessed.

This study was approved by the ethics committee of Beijing Tongren Hospital (No. TRECKY2021-143). All procedures were performed in compliance with the 1964 Helsinki Declaration and its later amendments. Informed consent was obtained from all participants in our study.

Clinical examination

All data were obtained from medical records. Subjects' height, weight, BMI, and blood pressure were measured or calculated as described in a previous study in detail (14). Fasting venous blood was collected for testing the biochemical indicators, such as glucose, HbA1c, lipid profile, and renal and liver function, which were tested by enzymatic methods on a Hitachi 7600 analyzer using an enzymatic assay. The urine albumin excretion rate (UAER) was measured in an overnight urine specimen using chemiluminescence (Immulite 1000, DPC, USA). Thyroid function was measured using chemiluminescent methods (Cobas E601, Roche). Information on the measurement instruments was also referred to in previous articles (14).

Thyroid function definition

The reference range of TSH concentration was 0.4–4.0 mIU/L, the reference range of free triiodothyronine (FT3) was 2.3–6.3 pmol/L, and the reference range of free thyroxine (FT4) was 10–23 pmol/L. Euthyroidism was defined as both free thyroxine and TSH levels within the above laboratory reference ranges. SCH was defined as holding TSH levels ≥4.0 mIU/L within normal free thyroxine levels. We divided the euthyroid patients into four subgroups according to TSH levels (21, 22): G1 (TSH, 0.4–0.99 mIU/L), G2 (TSH, 1.0–1.99 mIU/L), G3 (TSH, 2.0–2.99 mIU/L), and G4 (TSH, 3.0–3.99 mIU/L).

OCT and DR measurements and definitions

OCT macular scans (6.0 mm OCT scans) were performed by a trained ophthalmologist. All patients were given tropicamide eye drops to dilate their pupils and then underwent the examination. The OCT measurements and calculations and the definition and classification of DME

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were performed according to a previous protocol (23). Digital retinal photographs were captured independently by two qualified retinal photography graders. DR and DMR were both classified according to international criteria (24). Eyes with more severe than moderate non-proliferative DR were graded as sight-threatening DR (STDR). Other DR conditions were graded as non-sight-threatening DR (NSTDR).

Statistical analysis

Statistical analysis was performed with SPSS 26.0 software (SPSS Inc.). The clinical characteristics are presented as the mean ± standard deviation for quantitative variables and as percentages for categorical variables. Student's *t* tests were performed to compare the means of continuous variables. Chi-square (χ^2) tests were run to compare proportions. The Mann–Whitney *U* test was performed as a non-parametric test when the data were non-normally distributed. Logistic regression (LR) analysis and the forward LR method were performed to determine the risk factors for DME. For all statistical analyses, *P* values of less than 0.05 were considered statistically significant.

Results

Characteristics and DME prevalence in euthyroid and SCH populations

The participants' basic clinical characteristics are summarized in Table 1 following the flowchart of the study shown in Fig. 1. Ultimately, there were 92 SCH patients and 1003 euthyroid subjects included. The basic clinical characteristics data, including duration of diabetes, blood pressure, history of hypertension, renal and liver function indicator levels, lipid profiles, glucose and HbA1c levels, uric acid level, thyroid function, etc., were collected. Among them, the female ratio was higher in the SCH group (52.17% vs 40.98%, *P* = 0.036), which indicated

Table 1 The characteristics of the included subjects stratified according to serum TSH level.

Characteristic	Total	SCH	Euthyroid	*P*-value
Serum TSH (mIU/L)		TSH ≥ 4	0.4 ≤ TSH < 4.0	
Subjects	1095	92	1003	
Sex, female (%)	41.92	52.17	40.98	**0.036**
Age (year)	56.56 (12.53)	58.85 (9.84)	56.47 (12.73)	0.069
DM duration (year)	11.97 (8.11)	12.08 (7.78)	11.96 (8.14)	0.893
History of HP (%)	57.99	58.54	58.05	0.886
Systolic BP (mmHg)	129 (16.37)	128 (16.74)	129.28 (16.35)	0.773
Diastolic BP (mmHg)	74.58 (10.89)	72.76 (10.71)	74.75 (10.90)	0.110
Height (cm)	167.07 (8.56)	165.32 (8.89)	167.23 (8.52)	0.055
Weight (cm)	72.44 (13.53)	70.51 (12.29)	72.61 (13.55)	0.181
BMI (kg/m^2)	25.88 (3.93)	25.67 (3.29)	25.90 (3.98)	0.632
BUN (mmol/L)	5.36 (1.76)	6.01 (2.30)	5.30 (1.69)	**<0.001**
CREA (μmol/L)	67.14 (23.47)	74.92 (27.85)	66.43 (22.91)	**0.001**
ALT (U/L)	25.91 (24.70)	27.26 (23.95)	25.78 (24.77)	0.584
AST (U/L)	23.65 (16.78)	27.71 (24.07)	23.28 (15.91)	**0.016**
Total cholesterol (mmol/L)	4.51 (1.05)	4.51 (1.05)	4.51 (1.05)	0.995
Triglycerides (mmol/L)	1.95 (1.78)	1.83 (1.57)	1.96 (1.79)	0.512
LDL cholesterol (mmol/L)	2.69 (0.88)	2.67 (0.89)	2.69 (0.88)	0.874
HDL cholesterol (mmol/L)	1.08 (0.31)	1.11 (0.34)	1.07 (0.31)	0.223
Uric acid (μmol/L)	339.54 (87.73)	355.39 (91.10)	338.10 (87.32)	0.072
FPG (mmol/L)	7.26 (1.71)	7.15 (1.54)	7.27 (1.72)	0.571
HbA1c (%)	8.82 (1.91)	8.60 (1.80)	8.84 (1.92)	0.245
UAER (μg/min)	135.95 (815.33)	128.79 (570.28)	136.60 (834.49)	0.931
C-Peptide (uU/mL)	1.98 (1.10)	2.24 (1.28)	1.96 (1.08)	**0.027**
FT3 (pmol/L)	4.43 (0.53)	4.18 (0.53)	4.46 (0.53)	**<0.001**
FT4 (pmol/L)	14.80 (2.00)	13.68 (1.98)	14.90 (1.97)	**<0.001**
TSH (mIU/L)	2.19 (2.04)	6.65 (4.46)	1.78 (0.85)	**<0.001**
Anti-TPOAB (IU/L)	25.14 (61.17)	65.42 (115.77)	21.48 (52.12)	**<0.001**
Anti-TGAB (IU/L)	65.81 (176.65)	197.61 (403.18)	53.76 (132.96)	**<0.001**

Intergroup comparisons were done using Student's *t*-test; Data are expressed as the mean (S.D.). Bold indicates statistical significance, $P < 0.05$. ALT/AST, alanine/aspartate aminotransferase; anti-TGAB, anti-thyroglobulin antibody; anti-TPOAB, anti-thyroid peroxidase antibody; BUN, blood urea nitrogen; CREA, creatinine; FPG, fasting plasma glucose; HbA1c, hemoglobin A1C; HDL/LDL, high/Low-density lipoprotein; UAER, urinary albumin excretion rates.

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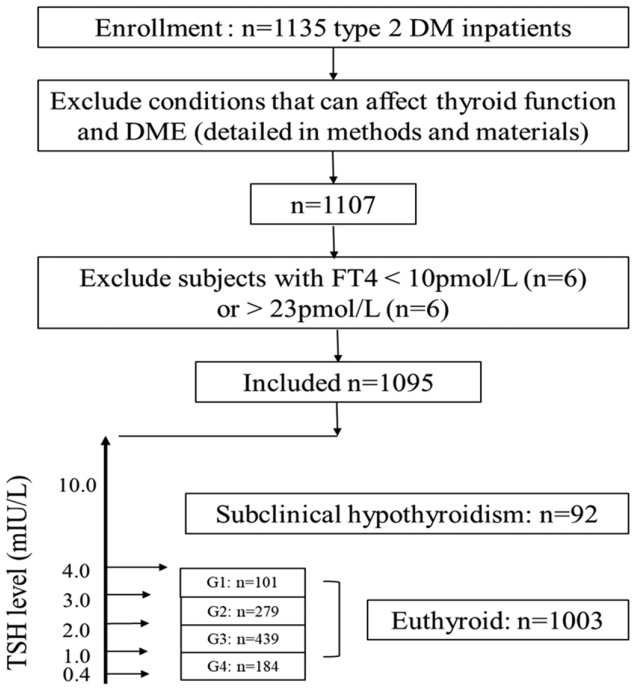

Figure 1
Flowchart of the study.

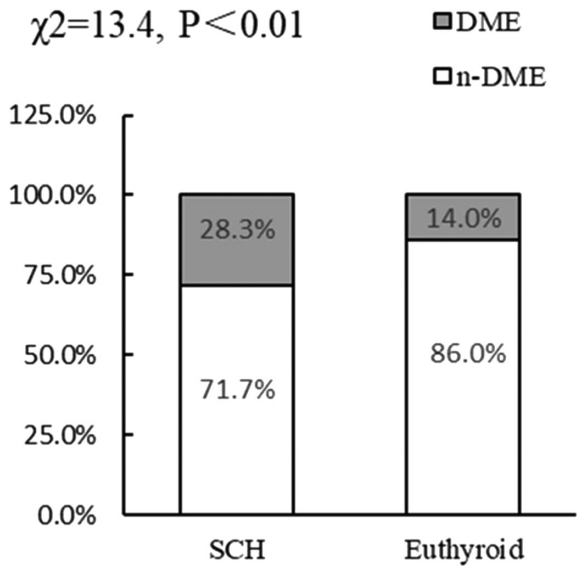

Figure 2
DME prevalence in SCH and euthyroid populations. Number and ratios of DME or n-DME cases in euthyroid and SCH populations. The chi-square (χ^2) test indicated that SCH patients were more susceptible to DME. DME, diabetic macular edema; n-DME, non-diabetic macular edema.

that females might be more susceptible to subclinical thyroid disease. The renal functional indicators, namely, the blood urea nitrogen (BUN) and creatinine (CREA) levels, were significantly different between the SCH and euthyroid populations (P < 0.001, P=0.001, P=0.005). Higher BUN and CREA levels were seen in the SCH group than in the euthyroid population. The liver indicator AST showed the same trend (P=0.016). The FT3, FT4, and TSH concentrations are shown in Table 1.

The DME prevalence in the euthyroid and SCH groups is shown in Fig. 2. Among the SCH patients, 26 (28.3%) subjects had DME, and 66 (71.7%) subjects had non-DME. In the euthyroid population, 140 (14.0%) subjects had DME, and 863 (86.0%) subjects had non-DME. The DME prevalence of the two groups was significantly different (28.3% vs 14.0%, χ^2 = 13.4, P < 0. 01).

Comparison of thyroid function levels between the DME and non-DME groups

The thyroid function (FT3, FT4, TSH) levels between the DME and non-DME groups were compared. The FT3 and FT4 levels were compared by Student's t test, while the TSH level was compared by the Mann–Whitney U test, as TSH was non-normally distributed. As shown in Fig. 3, the median TSH level was significantly higher in the DME group than in the non-DME group (2.20 (3.1, 1.5) vs 1.70 (2.5, 1.1) mIU/L, P < 0.001). The FT3 (4.47 ± 0.53 vs 4.25 ± 0.52 pmol/L, P < 0.001) and FT4 (14.89 ± 2.00 vs 14.33 ± 1.90 pmol/L, P=0.001) levels are also displayed in Fig. 3 and were significantly different. The FT3, FT4, and TSH levels were significantly different between the DME and non-DME groups.

DME prevalence in the four subgroups of the euthyroid population

The euthyroid population was divided into four subgroups according to the TSH level. Table 2 shows the association between TSH in the normal range and the prevalence of DME. The chi-square (χ^2) test was performed in comparison to the DME prevalence in the G1–G4 subgroups. In the G1–G4 subgroups, the DME prevalence was 17 (9.24%), 49 (11.16%), 52 (18.64%), and 22 (21.78%), respectively (P = 0.001). There was a consistent and significant decline in prevalence with decreasing TSH levels, even within the normal range.

Comparison of DR and DME in subjects with different thyroid dysfunction

To compare the DR and DME status in different thyroid function groups, the DR prevalence in the SCH and euthyroid subjects is shown in Fig. 4. In the SCH patients,

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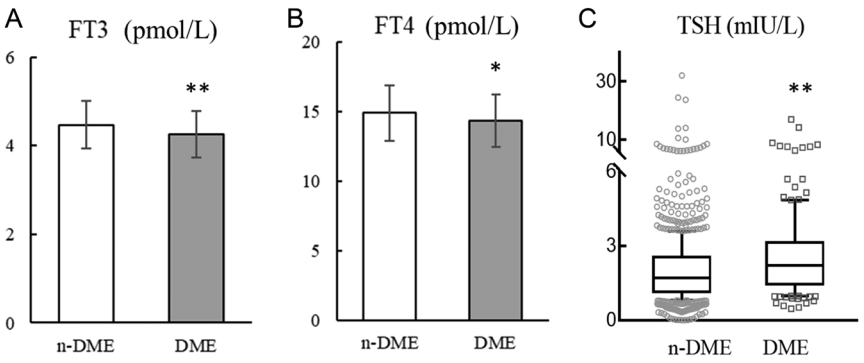

Figure 3
Thyroid function in DME or non-DME populations. Student's *t* test was performed to compare FT3 and FT4 levels in the non-DME and DME populations. Data are expressed as the mean (S.D.) for FT3 and FT4. As TSH was non-normally distributed, the median was expressed for the TSH level. A Mann–Whitney *U* test was run to determine the differences in TSH levels. Comparisons of FT3 (A), FT4 (B), and TSH (C) are shown. $^{*}P = 0.001$, $^{**}P < 0.001$.

29 (31.5%) subjects had DR, and 63 (58.5%) subjects had non-DR. In the euthyroid population, 226 (22.5%) subjects had DR, and 777 (77.5%) subjects had non-DR. The DR prevalence of the two groups was significantly different (31.5% vs 22.5%, $\chi^2 = 3.81$, $P = 0.037$).

DR, which is usually assessed by digital retinal photographs, was divided into different stages (24): normal, mild, moderate, severe non-proliferative (NPDR), and proliferative DR (PDR). STDR included severe NPDR and PDR. Thus, the status of DR and STDR in the subgroups was compared in Table 2. In the G1–G4 subgroups, the DR prevalence was 37 (20.11%), 87 (19.82%), 69 (24.73%), and 33 (32.67%), respectively ($P = 0.027$). There was a similarly significant difference in prevalence with DR in the subgroups within the normal range. This result indicated that the correlation between TSH and DME detected by OCT was stronger ($P = 0.001$) than the correlation between TSH and DR detected by digital retinal photographs ($P = 0.027$). There was no significant difference when comparing the STDR prevalence in those four subgroups ($P = 0.095$).

Influence of risk factors for DME in the euthyroid population

To explore the influence of risk factors for DME in the euthyroid subjects, logistic regression models were used. As Table 3 shows, forward LR method analysis confirmed that age ($P = 0.014$), DM duration ($P < 0.001$), BMI ($P < 0.001$), BUN level ($P = 0.029$), C-peptide level ($P < 0.001$), and UAER ($P = 0.012$) were risk factors for DME. After adjusting for traditional risk factors, TSH resisted being an independent risk factor for DME. The odds ratio of TSH to DME was 1.53 (95% CI, 1.07–2.20; $P = 0.02$). LR was performed in the euthyroid population, and the characteristics of TSH are shown in Table 2. The ROC curve was established using logistic prediction values for DME, including the clinical variables above. The AUC was 0.76 (95% CI, 0.72, 0.80; $P < 0.001$) (Fig. 5).

Discussion

In a retrospective cross-sectional study, we investigated the association between thyroid function and the prevalence of DME. TSH levels were associated with an elevated risk of developing DME, even in the normal range. To our knowledge, there have been a limited number of studies examining the relationship between thyroid disease and AMD. However, few studies have focused on the association between TSH and DME, and few studies have compared DR by digital retinal photographs and DME by OCT in T2DM patients with thyroid dysfunction.

Our study had the following characteristics that need to be clarified. First, as our hospital houses one of the

Table 2 DME and DR prevalence in different TSH subgroups in euthyroid population.

	G1 TSH (0.4–0.99 mIU/L)	**G2 TSH** (1.0–1.99 mIU/L)	**G3 TSH** (2.0–2.99 mIU/L)	**G4 TSH** (3.0–3.99 mIU/L)	***P*-value**
Subjects	184	439	279	101	
DME (%)	17 (9.24)	49 (11.16)	52 (18.64)	22 (21.78)	
n-DME (%)	167 (90.76)	390 (88.84)	227 (81.36)	79 (78.22)	**0.001**
DR (%)	37 (20.11)	87 (19.82)	69 (24.73)	33 (32.67)	
n-DR (%)	147 (79.89)	352 (80.18)	210 (75.27)	68 (67.33)	**0.027**
STDR (%)	14 (37.84)	17 (19.54)	21 (30.43)	4 (12.12)	
n-STDR (%)	23 (62.16)	70 (80.46)	48 (69.57)	29 (87.88)	0.095

Numbers and ratios of DME or DR cases in different groups in the euthyroid population. Chi-square (χ^2) test for trend indicated even in the euthyroid population, DME and DR prevalence were both significantly increased according to the TSH levels. Bold indicates statistical significance, $P < 0.05$.

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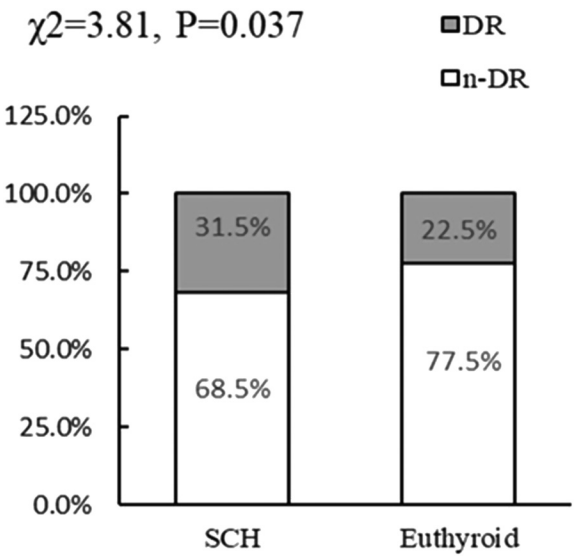

Figure 4
DR prevalence in SCH and euthyroid populations. Numbers and ratios of DR or n-DR cases in euthyroid and SCH populations. The chi-square (χ^2) test indicated that SCH patients were more susceptible to DR. DR, diabetic retinopathy; n-DR, and non-diabetic retinopathy.

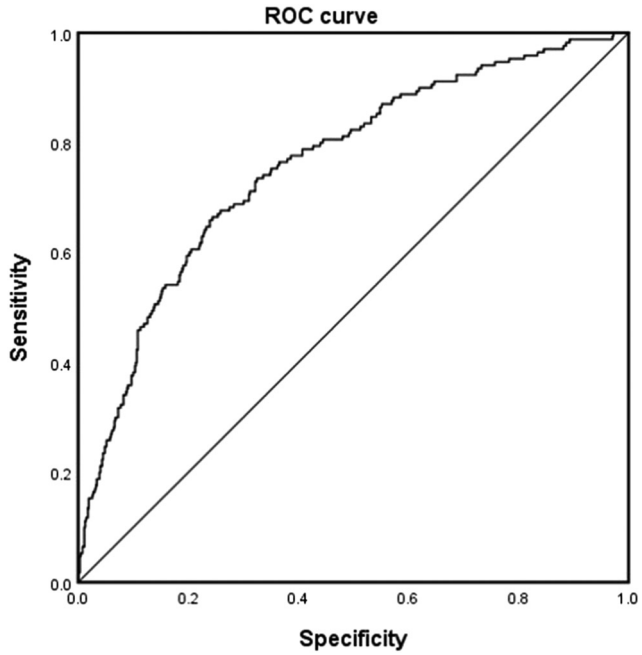

Figure 5
ROC curve. ROC curve analysis showed that the AUC of the clinical prediction model based on logistic regression analysis to predict in DME is 0.76. ROC curve, receiver operating characteristic curve; AUC, area under the curve.

most prestigious ophthalmology departments in China, some of our T2DM inpatients were recommended by ophthalmology and had already suffered from diabetic eye diseases, such as DR or DME. Therefore, the DR and DME prevalence in our study might be slightly higher than that in other published studies (25-27). This also offers relatively sufficient resources for the study of eye diseases in patients with T2DM. Secondly, considering that inpatients are usually admitted to the hospital due to uncontrolled high glucose levels, fasting plasma glucose (FPG) and HbA1c levels were consistently higher in our population in both the DME and non-DME groups. This might explain why these two important factors were not included in Table 3

Table 3 Influence of risk factors on DME based on logistic regression in euthyroid population.

	β	S.E.	**OR** (95% CI)	***P*-value**
AGE	−0.40	0.02	0.96 (0.93–0.99)	0.014
DM duration	0.12	0.03	1.13 (1.07–1.19)	<0.001
BMI	0.18	0.05	1.19 (1.09–1.31)	<0.001
BUN	0.21	0.09	1.23 (1.02–1.48)	0.029
C-peptide	−0.83	0.22	0.44 (0.29–0.67)	<0.001
UAER	0.01	0.00	1.00 (1.00–1.00)	0.002
TSH	0.42	0.18	1.53 (1.07–2.20)	0.02

For binary logistic regression analysis, the forward LR method was run to test the possible risk factors for DME. All variables in Table 1 above were entered into the model before TSH was input with the stepwise method ($P < 0.10$ and $P > 0.05$ as thresholds for inclusion and exclusion, respectively). All the statistically significant factors were listed in Table 3.

as influential risk factors for DME, which was different from previous epidemiologic data for T2DM patients in the community (4). Thirdly, in our study, there were 92 SCH and 1003 euthyroid subjects, and the SCH prevalence was 8.4%, which was consistent with previous studies (28). DME occurred or not, which as categorical variable data, had a large dispersion in the SCH group (TSH ≥ 4.0, the highest value was 32.1 mIU/L). Therefore, we further divided subgroups in the euthyroid population and conducted LR analysis in these four subgroups. This could more reliably reflect the role and importance of TSH for DME.

Thyroid hormones, including TSH levels, are reported to be associated with diabetes and diabetic complications. Few studies have assessed the association between TSH and DME before. We addressed the association between them and the influential risks of TSH for DME. This study provides new data on the clinical characteristics of DME in the Chinese T2DM population. To prove the effect of TSH, the role of FT4 needed to be taken into account and excluded as they were interacting. On the one hand, we enrolled subjects with a normal FT4 level and excluded the clinical hypothyroidism and clinical hyperthyroidism populations. Only SCH and euthyroid subjects were eventually analyzed. On the other hand, to strengthen the effect of TSH on DME, we divided the euthyroid population

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into four subgroups and then compared the DME status and conducted LR analysis in the TSH subgroups in the normal range. Thus, we ruled out the possible effect of FT4 by the two procedures above.

The detailed mechanisms of TSH on DME remain unclear. The underlying mechanism may have the following aspects. First, some experimental and clinical studies have reported that TSH is associated with many metabolic diseases, including diabetes mellitus (29), alterations in lipid levels (22), atherosclerosis (30), and myocardial infarction (31). We also have performed some research on the mechanism of the effect of TSH on hyperlipidemia (32) and atherosclerosis (33). SCH can aggravate insulin resistance (IR) (34, 35), which affects retinal vascular destruction and the DR process. Thus, TSH might aggravate DME by affecting different metabolic diseases. Secondly, previous studies have shown that thyroid hormone receptors are expressed in human retinal pigment epithelial cells, which may be a direct target for thyroid hormones in the retinal vessel (36). The TSH receptor (TSHR) has also been reported to be expressed in human endothelial cells (37, 38) and might be a direct target of TSH in retinal diseases. Lastly, TSH, similar to growth hormone (GH) and vascular endothelial growth factor (VEGF), acts as a growth-promoting hormone in the body and has been reported to prompt thyroid tissue (39), vascular smooth muscle cell (40), and thyroid eye disease orbital fibroblast proliferation (41). Similarly, TSH might promote vascular or other layer proliferation in the retina. Moreover, there might be other possible mechanisms underlying the regulation of DME by TSH, which require further laboratory research.

DME is an important cause of vision loss so the treatment faces challenges. Laser photocoagulation treatment has been a valid treatment but has been inadequate in patients with chronic disease and has shown poor results in patients with diffuse DME (25). In recent years, laser photocoagulation has no longer been recommended as a consequence of recent clinical trials. In addition, anti-VEGF therapy has been substituted as the first-line therapy (5). Steroids play a role in the treatment of patients with chronically persistent DME. The introduction of new treatments will become a new research hotspot. Notably, one study has shown that inhibition of thyroid hormone signaling could result in the protection of cone photoreceptors from retinal degeneration in mouse models (42). As our study indicated that TSH levels were associated with DME, in the treatment of DME, thyroid function needs to be considered.

There are some limitations to our study. First, as it was a retrospective cross-sectional study at a single center, we could not determine whether TSH levels could be an actual risk factor for DME without follow-up data. In addition, the thyroid function status was classified based on one blood test in our participants. Thus, some subjects with transient TSH elevation might have been misclassified. Finally, in our study, we only used OCT to assess DME and did not perform invasive angiography as the definitive diagnostic tool for DME. In the future, large-scale and multicenter studies with longer follow-up times will be needed.

Conclusions

In conclusion, we demonstrated that in our study population, the level of TSH was associated with DME prevalence. TSH could be an independent risk factor for DME, even within the normal range. The OCT tests, as well as digital retinal photographs, were needed to assess the diabetes eye complications. Our study indicates that thyroid hormone levels need to be given more attention in patients with diabetes. In the treatment of T2DM, thyroid function should be monitored.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement
X Cao collected the data and edited the manuscript. M Lu analyzed the data and wrote the manuscript. R R Xie, L N Song, and W L Yang helped to collect the data. Z Xin and G R Yang gave suggestions. J K Yang designed the idea and gave the suggestions.

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