

# Association of Thyroid Hormone Levels with Microvascular Complications in Euthyroid Type 2 Diabetes Mellitus Patients

Yonghui Hu<sup>1,2</sup>, Zhibo Hu<sup>1,2</sup>, Wangna Tang<sup>1,2</sup>, Wenjie Liu<sup>1,2</sup>, Xiaoming Wu<sup>1,2</sup>, Congqing Pan<sup>1,2</sup>

<sup>1</sup>NHC Key Laboratory of Hormones and Development, Tianjin Key Laboratory of Metabolic Diseases, Chu Hsien-I Memorial Hospital & Tianjin Institute of Endocrinology, Tianjin Medical University, Tianjin, People's Republic of China; <sup>2</sup>Tianjin Key Laboratory of Metabolic Diseases, Tianjin Medical University, Tianjin, People's Republic of China

Correspondence: Congqing Pan; Xiaoming Wu, NHC Key Laboratory of Hormones and Development, Tianjin Key Laboratory of Metabolic Diseases, Chu Hsien-I Memorial Hospital & Tianjin Institute of Endocrinology, Tianjin Medical University, Tianjin, People's Republic of China, Email profpancq@163.com; xiaomingwu2014@126.com

**Purpose:** To examine the prevalence of different microvascular complications and investigate the association between thyroid hormones (THs) and these complications in euthyroid patients with type 2 diabetes mellitus (T2DM).

**Methods:** A total of 248 T2DM patients were analyzed retrospectively for the study. All patients received a detailed and standard assessment to identify diabetic peripheral neuropathy (DPN), diabetic nephropathy (DN), and diabetic retinopathy (DR). Multivariate logistic regression was carried out to analyze the association between THs and diabetic microvascular complications.

**Results:** The study found the prevalence of any microangiopathy to be 72.18% (n = 179). At the same time, the prevalence of DPN was 54.84% (n=136), while that of DN was 31.85% (n=79). Likewise, the prevalence of DR was 35.48% (n=88). The odds ratios (ORs) for free triiodothyronine (FT3) developing any microangiopathy, DPN, DN and DR were 0.200, 0.361, 0.310, and 0.588 (P<0.05), respectively. Also, the ORs for free thyroxine (FT4) developing any microangiopathy, DPN, DN and DR were 0.643, 0.800, 0.702 and 0.726 (P<0.05), respectively. Lastly, the ORs for thyroid-stimulating hormone (TSH) developing DPN was 1.57 (95% CI: 1.148–2.137, P=0.005).

**Conclusion:** The study concludes that serum FT3 and FT4 levels are negatively associated with any microangiopathy, DPN, DN and DR in euthyroid patients with T2DM, independent of traditional risk factors. However, the TSH levels are positively associated with DPN. Future larger sample-size studies are needed to confirm the relationship between thyroid hormone levels and microvascular complications in euthyroid patients with T2DM.

**Keywords:** microvascular complications, thyroid hormone, type 2 diabetes mellitus, diabetic peripheral neuropathy, diabetic nephropathy, diabetic retinopathy

## Introduction

Diabetes is one of the most common and fastest-growing diseases in the world. It is a chronic metabolic disease caused by absolute or relative insulin deficiency in the context of  $\beta$ -cell dysfunction, insulin resistance (IR), or both. Research from International Diabetes Federation (IDF) showed that in 2021, diabetes affect more than 536 million adults worldwide.<sup>1</sup> In general, improper treatment or poor alimentary control for diabetic patients can lead to life-threatening chronic complications including macrovascular complications, such as cardiovascular disease (CVD), and the microvascular complications, such as diabetic nephropathy (DN), diabetic retinopathy (DR) and diabetic peripheral neuropathy (DPN). One of the causes of death in diabetic patients is damage to the macrovascular system induced by hyperglycemia, including coronary and cerebrovascular arteries.<sup>2</sup> However, hyperglycemia-induced damage to the microvascular network in the kidney, eyes and nerves is more common.<sup>3</sup> Besides, it also has a serious impact on mortality.

The specific pathophysiology of hyperglycemia-induced microvascular damage is complex and partially explicated. Many clinical studies have established some risks of diabetes microvascular complications. For instance, a cross-sectional study comprising a high-risk Middle East population<sup>4</sup> found that the family history, severity, and duration of diabetes and hypertension were the same risk factors for multiplicity and individual complications. However, some risk factors were specific to individual microvascular complications. A recent study conducted by Raman et al<sup>5</sup> reported the risks of microvascular complications in subjects with new-onset T2DM, including increasing age, increasing systolic blood pressure, and increasing hemoglobin. Meanwhile, a study by Zoungas et al<sup>6</sup> established that the effect of diabetes duration was more significant in the youngest patients. Other risks included the presence of DR, the range of (HbA1c), dyslipidemia, lifestyle,<sup>7</sup> smoking, vitamin D deficiency, and cystatin C,<sup>8</sup> among others.

Since thyroid hormone receptors exist in both myocardium and vascular endothelial tissues, the role of thyroid hormone in the deterioration of vascular diseases is confirmed. Therefore, changes in the concentration of circulating thyroid hormone can regulate organ activity.<sup>9</sup> Recently, more researchers have focused on the effects of thyroid hormones (THs) on the microvascular complications of diabetes. In addition, many clinical studies have confirmed that abnormal thyroid function is related to diabetic microvascular complications.<sup>10–12</sup> Although some studies have expanded the relationship to the euthyroid states, the results are not consistent. For example, Wu et al<sup>13</sup> reported that the serum-free triiodothyronine (FT3) level, but not free thyroxine (FT4) or thyroid-stimulating hormone (TSH), is negatively associated with the DN in euthyroid patients with T2DM. Nonetheless, other studies have demonstrated a significant association between low to normal FT3 and FT4 levels and high TSH levels with increased incidence of DN, especially in cases of macroalbuminuria.<sup>14</sup> By comparing the prevalence of DR, some studies have found significant differences in the lower FT3 level, while the differences between the FT4, TSH, and TPO-Ab groups were not statistically significant.<sup>15</sup> These findings are inconsistent with Kong et al inference that normal low FT4 and high TSH levels after adjusting for other risk factors are related to the prevalence of DR.<sup>16</sup>

There may be many reasons for this ambiguity due to the heterogeneity of the study population and design, unexplained residual confounding factors, or varying degrees of microvascular results. In addition, our previous study found that the low-normal FT3 and FT4 levels are associated with macrovascular complications in euthyroid type 2 diabetes mellitus patients.<sup>17</sup> However, the relationship between thyroid hormone and diabetic microvascular complications remains unclear. Therefore, to provide more comprehensive information for future research, we performed the present study to analyze the association of thyroid hormone with individual and any form of diabetic microvascular complications in euthyroid T2DM patients in the same population.

## Methods

### Study Subjects

The information in this study comes from patients at Tianjin Medical University Chu Hsien-I Memorial Hospital. In this cross-sectional study, the electronic hospitalization record system was used to collect data from February 2019 to December 2019, covering demographic and anthropometric parameters, including age, sex, duration of T2DM, medical treatments, family history of T2DM, hypertension history, and body mass index (BMI). After fasting overnight, the following venous blood laboratory parameters were collected: total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), very low-density lipoprotein cholesterol (VLDL), HbA1c, FT3, FT4 and TSH levels. This study was approved by the Ethics Committee of Tianjin Medical University Chu Hsien-I Memorial Hospital and was conducted following the Declaration of Helsinki. All patients provided written informed consent.

The inclusion criteria were aged  $\geq 18$  years old with normal thyroid function, and previously diagnosed with T2DM according to the criteria of the American Diabetes Association.<sup>18</sup> The exclusion criteria were patients who had any acute complications of diabetes, serious infection, a history of thyroid disease, serious connective tissue disease or myositis, hypothalamus or pituitary diseases, levothyroxine replacement treatment, and malignant tumors, liver or renal dysfunction, and lack of necessary relevant information.

## Definition of Normal Thyroid Function

Patients with THs in this range were considered normal thyroid function: TSH (0.56–5.91  $\mu$ IU/mL), FT3 (3.28–6.47 pmol/L) and FT4 (7.64–16.03 pmol/L).

## Definition of Any Microangiopathy

Patients with any kind of the following microvascular complications were classified into any microangiopathy group.

## Definition of Diabetic Peripheral Neuropathy

Symptoms of peripheral neuropathy and abnormal results on nerve conduction examinations were utilized to diagnose DPN. The diagnostic criteria were as follows:<sup>19</sup> (1) the presence of at least two positive findings among sensory symptoms, signs, and reflex abnormalities consistent with a distal symmetrical polyneuropathy; (2) at least one abnormal nerve characteristic of amplitude, latency, F-wave, or nerve conduction velocity in two or more nerves among the median, peroneal, and sural nerves.

## Definition of Diabetic Nephropathy

A 24-hour urine sample was used to assess the urine albumin-to-creatinine ratio (UACR). In the absence of urinary tract infection or other renal abnormalities, patients with a UACR increase of  $\geq 30$  mg/g and/or estimated glomerular filtration rate (eGFR)  $< 90$  mL/min/1.73m<sup>2</sup> were diagnosed with DN.

## Definition of Diabetic Retinopathy

All patients underwent ophthalmoscope and fundus photography using 45° four-field stereo digital photography. DR was defined by the classification of the American Academy of Ophthalmology.<sup>20</sup>

## Statistical Analysis

SPSS, version 26.0, Chicago IL, USA, was conducted for statistical analysis. All P values were on both sides. P values  $< 0.05$  were defined as statistically significant. Use the Student's *t*-test or Mann–Whitney *U*-test to compare the differences of continuous variables. And use the chi-square test for categorical variables. After adjusting for potential confounders, multivariate logistic regression was performed to evaluate the independent association between THs and diabetic microvascular complications. A receiver operating characteristic curve (ROC) has been made to find the cutoff point of THs to indicate different microvascular complications in euthyroid patients with T2DM.

## Results

### Comparison of Clinical Characteristics Among Microvascular Complications and Non-Microvascular Complications Groups

From February 2019 to December 2019, a total of 345 patients were diagnosed with T2DM according to the standards of the American Diabetes Association. Among them, 97 cases were excluded due to 22 cases of type I diabetes and gestational diabetes, 58 cases without basic relevant information, and 17 cases taking drugs that affect thyroid function. Finally, 248 patients were included in this study. Figures 1 and 2 provide information on the frequency of microvascular complications: DPN 136 (54.84%), DN 79 (31.85%), and DR 88 (35.48%). At the time of the investigation, 72.18% ( $n = 179$ ) of the patients had microvascular disease; 34.27% ( $n = 85$ ) had only one complication; 25.81% ( $n = 64$ ) had two types of microvascular complications and 12.10% ( $n = 30$ ) had three types of microvascular complications.

Table 1 shows the thyroid hormone levels for different complications. Compared with the group without microvascular complications, the FT3 and FT4 of the microvascular complications group were significantly reduced ( $P < 0.01$ ). There was no significant difference in TSH levels between the group without microvascular complications and with microvascular complications ( $P > 0.05$ ). Besides, there was no significant difference in the incidence of any microangiopathy, DPN, DN and DR between males and females ( $P > 0.05$ ). Table 1 also lists

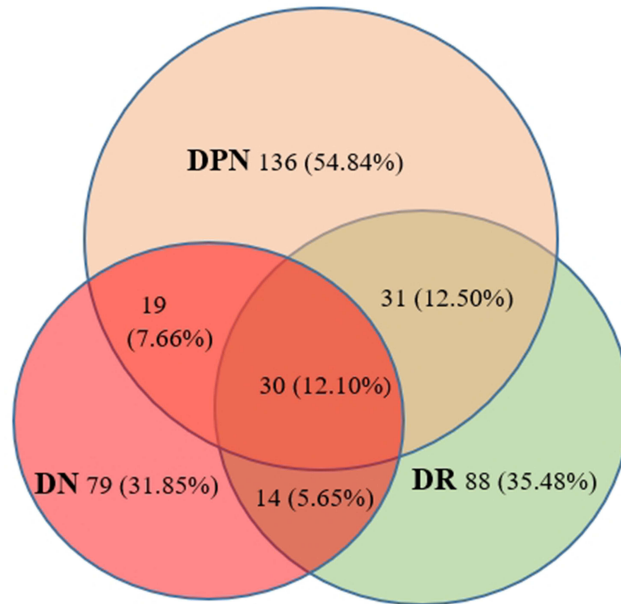


Figure 1 Prevalence of diabetic microvascular complications.

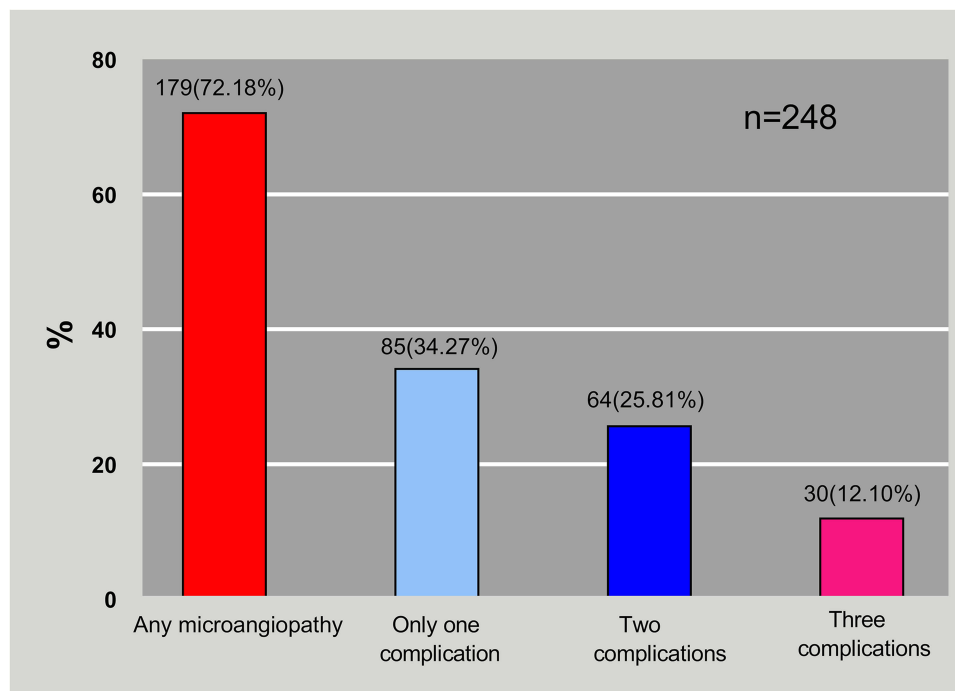


Figure 2 Frequency of diabetic microvascular complications.

some of the drugs commonly used in T2DM patients which are known to influence TSH levels and other diabetic complications. Patients with microvascular complications were more likely to be prescribed insulin, and less likely to use sulphonylureas. The information on other clinical and laboratory characteristics is given in Table 1 as well.

**Table 1** Baseline Characteristics of Study Participants in This Retrospective Study

Characteristics	Any Microangiopathy		DPN		DN		DR	
	No	Yes	No	Yes	No	Yes	No	Yes
Patients no. (n)	69	179	112	136	169	79	160	88
Age (years)	51.3±11.6	60.1±12.9**	52.0±12.3	62.3±11.8**	54.7±12.1	63.9±13.0**	55.4±11.7	61.6±14.6*
Sex, male (%)	68.1	58.7	67.9	55.9	60.9	62.0	62.5	59.1
Duration of T2DM (years)	4.0(9.3)	10.0(11.0) **	7.2(9.8)	12.0(13.0) **	8.0(11.0)	11.0(10.0) *	6.0(9.0)	14.0(9.0) **
Family history of T2DM (no/yes)	13/56	37/142	22/90	28/108	33/136	17/62	35/125	15/73
HBP (no/yes)	48/21	91/88*	68/44	71/65	104/65	35/44*	101/59	38/50*
BMI (Kg/m <sup>2</sup> )	25.28±3.95	27.01±4.01*	26.07±4.05	26.91±4.04	26.08±4.16	27.49±3.67*	26.24±4.24	27.04±3.69
HbA1C (%)	9.29±2.65	9.09±2.34	9.04±2.40	9.24±2.46	9.06±2.46	9.33±2.36	8.93±2.50	9.54±2.25
TG (mmol/L)	1.36(1.42)	2.50(1.81) *	1.49(1.71)	2.00(1.73)	1.59(1.63)	2.42(2.14)**	1.63(1.64)	2.13(1.90)
TC (mmol/L)	4.66±1.02	5.09±1.22*	4.75±1.13	5.15±1.20*	4.92±1.14	5.06±1.28	4.91±1.14	5.08±1.25
HDL (mmol/L)	1.16±0.27	1.15±0.30	1.14±0.29	1.16±0.30	1.17±0.31	1.12±0.27	1.15±0.30	1.16±0.28
LDL (mmol/L)	3.05±0.81	3.38±1.00*	3.07±0.90	3.47±0.97*	3.17±0.84	3.56±1.14*	3.16±0.86	3.52±1.09*
VLDL (mmol/L)	0.50(0.40)	0.61(0.39) *	0.56(0.45)	0.59(0.35)	0.56(0.39)	0.64(0.56)	0.57(0.40)	0.61(0.43)
TSH (mIU/L)	1.72(0.96)	1.70(1.04)	1.69(0.81)	1.71(1.26)	1.72(1.01)	1.66(0.85)	1.72(0.97)	1.70(1.44)
FT3 (pmol/L)	5.16±0.97	4.27±0.58 **	4.89±0.92	4.22±0.56 **	4.71±0.85	4.12±0.54 **	4.69±0.87	4.21±0.60 **
FT4(pmol/L)	13.89±2.24	11.36±2.38 **	12.96±2.54	11.33±2.62**	12.78±2.43	10.54±2.63 **	12.72±2.59	10.88±2.52 **
eGFR(mL/(min*1.73m <sup>2</sup> ))	128.15±4.37	111.53±22.64 **	118.65±18.63	114.09±22.19**	127.82±4.35	86.90±18.06**	120.90±15.97	107.52±25.27**
Insulin (no/yes)	42/27	84/95*	70/42	56/80**	103/66	23/56**	97/63	29/59**
Sulphonylureas (no/yes)	28/41	110/69**	59/53	79/57	72/97	62/17**	72/88	66/22**
Thiazolidinediones (no/yes)	45/24	121/58	76/36	90/46	123/46	43/36**	117/43	49/39**
Metformin (no/yes)	24/45	85/94	53/59	56/80	58/111	51/28**	52/108	57/31**
Others (no/yes)	51/18	145/34	89/23	107/29	131/38	65/14	138/28	64/24

Notes: \* P<0.05; \*\* P<0.01.

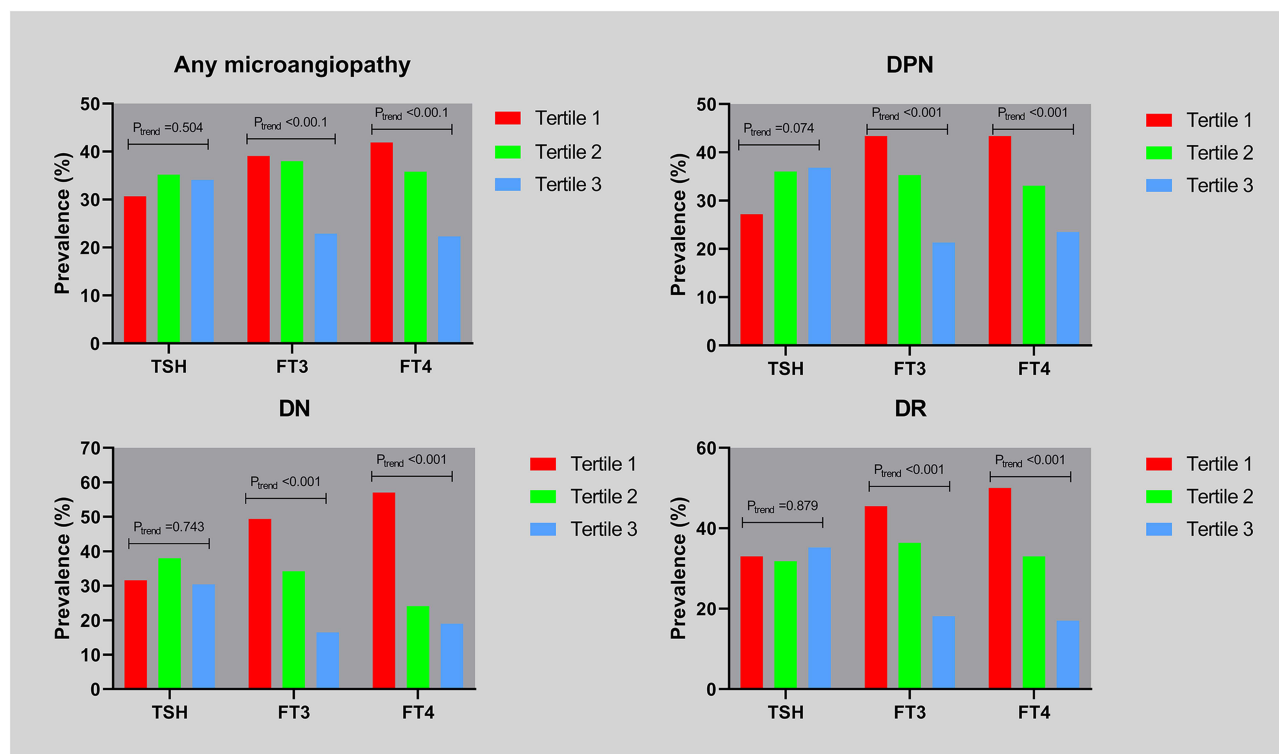
**Abbreviations:** DPN, diabetic peripheral neuropathy; DN, diabetic nephropathy; DR, diabetic retinopathy; T2DM, type 2 diabetes mellitus; HBP, hypertension; BMI, body mass index; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; VLDL, very low-density lipoprotein cholesterol; HbA1c, glycosylated hemoglobin; TSH, thyroid stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; eGFR, estimated glomerular filtration rate.

## The Prevalence of Microvascular Complications in Different Thyroid Hormone Tertiles

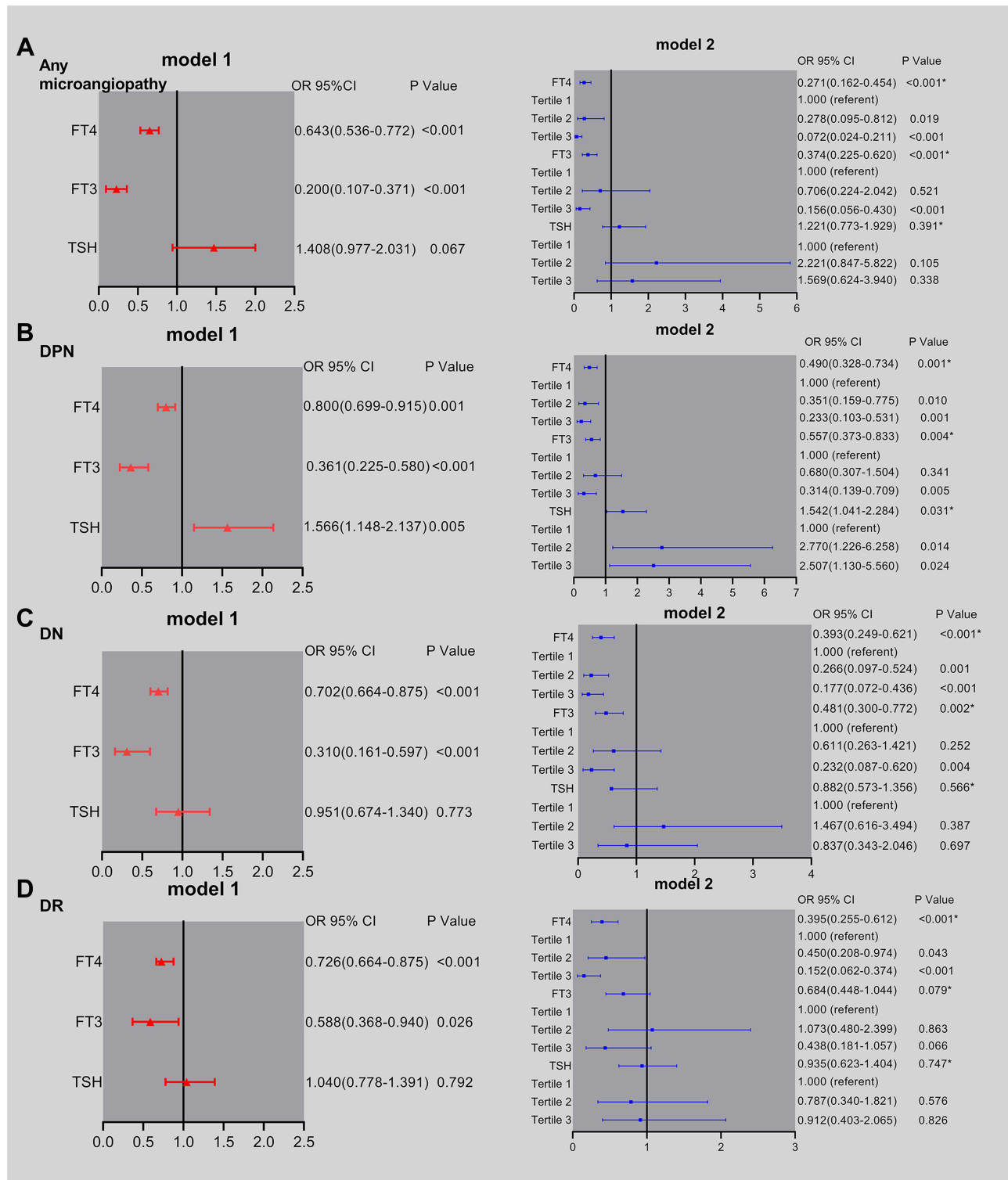
Figure 3 shows the prevalence of microvascular complications in different tertiles of thyroid hormone. The prevalence of individuals and any microangiopathy showed a significant downward trend in the three tertiles of FT3 and FT4 (FT3 tertiles: any microangiopathy: 39.1%, 38.0%, and 22.9%; DPN: 43.4%, 35.3% and 21.3%; DN: 49%, 34.2% and 16.5%; DR: 45.5%, 36.4% and 18.1% respectively; FT4 tertiles: any microangiopathy: 41.9%, 35.8% and 22.3%; DPN: 43.5%, 33.1%, and 23.5%; DN: 57.0%, 24.1%, and 19.0%; DR: 50.0%, 33.0%, and 17.0%, respectively.  $P_{\text{for trend}} < 0.001$  respectively. There was no significant difference in the prevalence of microvascular complications between the TSH tertiles.

## The Associations Between Thyroid Hormone Levels and Diabetic Microvascular Complications

Figure 4 shows the association between thyroid hormone levels and microvascular complications based on multivariate logistic regression. After adjusting for potential risk factors in Model 1, it was found that the levels of FT3 and FT4 were negatively associated with any microangiopathy, DPN, DN, and DR ( $P < 0.05$ , respectively). The TSH level was only positively associated with DPN ( $P = 0.005$ ). After the potential risk factors of Model 2 had been adjusted, the lower grade of FT3 was the independent risk of any microangiopathy, DPN and DN ( $P_{\text{for trend}} < 0.05$ ), and the lower grade of FT4 was the independent risk of any microangiopathy, DPN, DN and DR ( $P_{\text{for trend}} < 0.05$ ). A higher grade of TSH was an independent risk of DPN ( $P_{\text{for trend}} = 0.031$ ). Compared with patients with the lowest tertiles of FT3 and FT4, patients with higher tertiles of FT3 and FT4 were less likely to develop any microangiopathy, DPN, DN, and DR ( $P < 0.05$ , respectively). However, the higher tertile TSH was only associated with DPN compared with the lowest tertile (tertile 2: OR=2.770, 95% CI: 1.226–6.258,  $P = 0.014$ ; tertile 3: OR=2.507, 95% CI: 1.130–5.560,  $P = 0.024$ ).



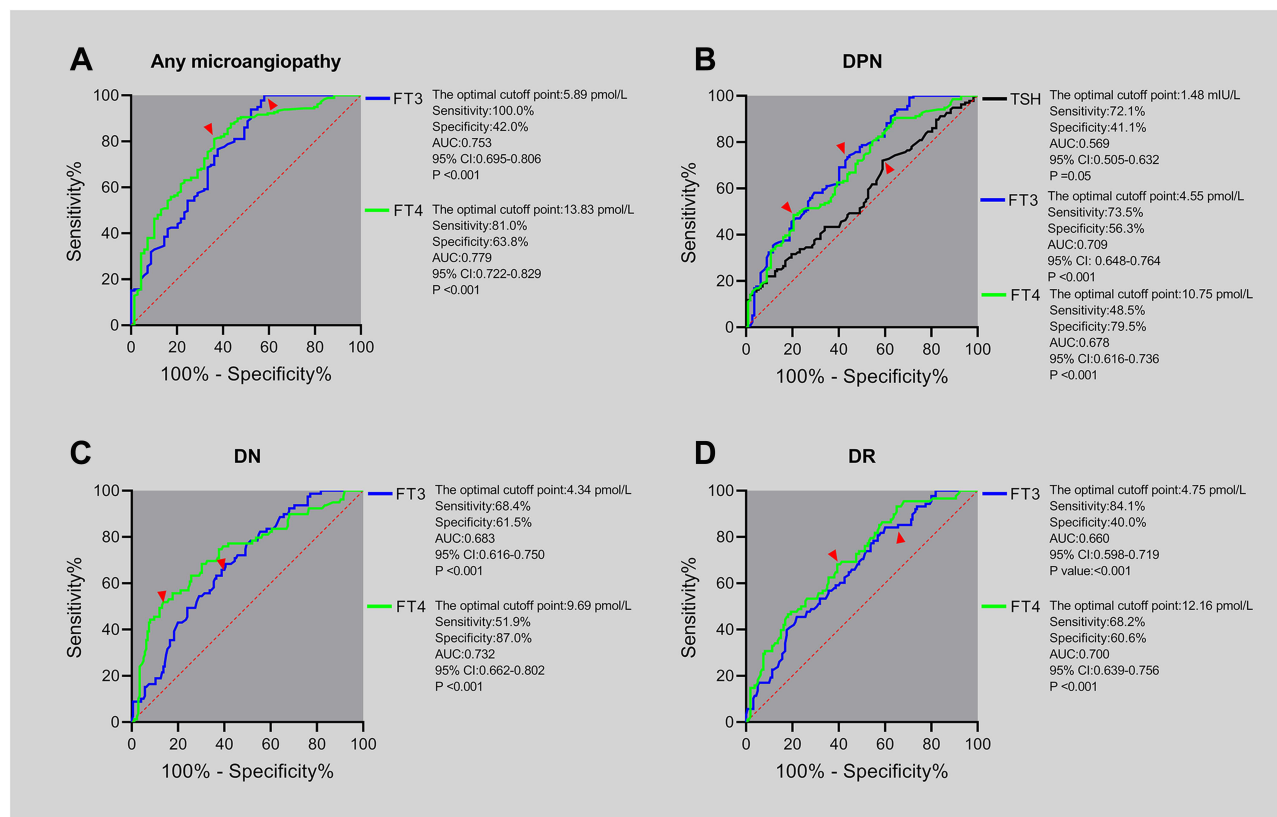
**Figure 3** Prevalence of microvascular complications among tertiles based on TSH, free FT3 and FT4 levels. TSH (tertile 1: 0.56–1.48  $\mu\text{IU/mL}$ , tertile 2: 1.48–2.03  $\mu\text{IU/mL}$ , tertile 3: 2.03–5.91  $\mu\text{IU/mL}$ ); FT3 (tertile 1: 3.28–4.06  $\text{pmol/L}$ , tertile 2: 4.06–4.73  $\text{pmol/L}$ , tertile 3: 4.73–6.47  $\text{pmol/L}$ ); FT4 (tertile 1: 7.64–10.59  $\text{pmol/L}$ , tertile 2: 10.59–13.72  $\text{pmol/L}$ , tertile 3: 13.72–16.03  $\text{pmol/L}$ ).



**Figure 4** Association between thyroid hormone levels and microvascular complications (4A: any microangiopathy; 4B: DPN; 4C: DN; 4D: DR) based on multivariate logistic regression.

**Notes:** Model 1: Evaluating the risk of diabetic microvascular complications when the thyroid hormone is considered as a continuous variable; Model 2: Evaluating the risk of diabetic microvascular complications in different thyroid hormone tertiles. Adjusted confounders: age, sex, the duration of T2DM, family history of T2DM, the history of hypertension, BMI, TC, TG, HDL, LDL, VLDL and HbA1c. \*P values for trends across all tertiles.

**Abbreviations:** DPN, diabetic peripheral neuropathy; DN, diabetic nephropathy; DR, diabetic retinopathy.



**Figure 5** ROC analysis of thyroid hormones to diabetic microvascular complications (5A: any microangiopathy; 5B: DPN; 5C: DN; 5D: DR).

**Abbreviations:** DPN, diabetic peripheral neuropathy; DN, diabetic nephropathy; DR, diabetic retinopathy.

## The Predictive Value of Thyroid Hormone for Different Microvascular Complications

Figure 5 shows the results of the ROC curve analysis, which were used to determine the accuracy of THs in predicting different microvascular complications. The results indicated that the optimal cut-off points for FT3 for predicting any microangiopathy, DPN, DN, and DR were 5.89, 4.55, 4.34, and 4.75 pmol/L, respectively; the optimal cut-off points for FT4 were 13.83, 10.75, 9.69, and 12.16 pmol/L, respectively. The optimal cut-off point of TSH for DPN prediction was 1.48 mIU/L.

## Discussion

This study is dedicated to exploring the relationship between THs and different diabetic microvascular complications in Chinese euthyroid patients with T2DM. In summary, the analysis results showed that after adjusting for traditional confounding factors including age, sex, duration of T2DM, BMI, HBP, HbA1c, TG, TC, HDL-C, LDL-C and VLDL-C, the normal-low levels of free THs (FT3 and FT4) were associated with the increased risk of individual and any form of microvascular complications. With the exception of DPN, there was no association of TSH level with individual and any form of microvascular complications.

Our findings indicated that in euthyroid patients with T2DM, not only FT3 but also FT4 and TSH are associated with DPN. Several previous studies have indicated that thyroid hormone level was a risk factor for neuropathy in patients with subclinical hypothyroidism (SCH).<sup>21–23</sup> A cross-sectional study reported that after adjusting for potential confounding variables, TSH level was independently associated with DPN in T2DM patients (OR = 1.365, P < 0.01), which is consistent with our study.<sup>8</sup> Besides, Zhu et al<sup>24</sup> found that FT3 was closely related to abnormal nerve conduction study diagnosis in euthyroid T2DM patients.

Moreover, in the present study, the risk factors for developing DN and DR were lower free THs, not TSH levels in T2DM subjects with normal thyroid function. Several previous studies have reported the relationship between thyroid



function and DN in patients with diabetes, but these results are not consistent entirely.<sup>25–29</sup> Two cross-sectional studies of T2DM patients with normal thyroid function showed that only low FT3 levels were independently associated with a high risk of DN.<sup>13,27</sup> However, in another cross-sectional study of 1071 T2DM patients with normal thyroid function,<sup>14</sup> it was found that after adjusting for all covariates, TSH increased (OR 1.376, [95% CI, 0.894–0.998],  $P = 0.007$ ), FT3 level decreased (OR 0.413 [95% CI, 0.270–0.630],  $P < 0.001$ ) and FT4 level decreased (OR 0.856 [95% CI, 0.768–0.953],  $P = 0.005$ ) were associated with increased probability of macroalbuminuria. These conflicting results might be a result of differences in the characteristics of the study participants.

There are several reports on the influence of thyroid hormone levels on the development and duration of DR. A previous study showed that T2DM patients with subclinical hypothyroidism were associated with an increased risk of sight-threatening diabetic retinopathy.<sup>30</sup> Similarly, a meta-analysis indicated that exposure to subclinical hypothyroidism could increase the DR risk 2.13 times in patients with diabetes.<sup>31</sup> Besides, Zou et al<sup>15</sup> found that FT3 levels within the normal range were negatively correlated with the DR in euthyroid patients with T2DM. Compared with the low FT3 quartiles, the multivariate-adjusted ORs of DR in the highest FT3 quartiles was 0.368 (95% CI 0.201–0.673,  $P = 0.001$ ). In the study of Kong et al<sup>16</sup> after adjusting the traditional DR risk factors, it was found that low-normal FT4 levels were associated with the prevalence of DR in euthyroid patients with T2DM.

Given that thyroid hormone receptors are present in both myocardial and vascular endothelial tissues, thereby enabling changes in circulating thyroid hormone concentrations to modulate end-organ activity.<sup>9</sup> Supplementation with TH has been demonstrated to enhance glucose tolerance in wild-type mice<sup>32</sup> and to alleviate hyperglycemia in leptin receptor-deficient mice.<sup>33</sup> Several biological changes related to thyroid hormone levels have been found to confirm the impact of THs on microvascular complications, including the effect of THs on the body's metabolic functions (including glucose metabolism, insulin secretion, homocysteine and lipids), chronic inflammation caused by low levels of THs, and vascular endothelial function damage.<sup>34,35</sup> It has been demonstrated that decreased endothelial Nitric Oxide (NO) availability is related to endothelial dysfunction, which can further prompt the development of DPN in T2DM patients.<sup>36,37</sup> Vicinanza R et al reported that the process of endothelial NO production could be mediated by THs.<sup>38</sup> Hence, THs protect the endothelial cells of micro-vessels from degeneration, which may be reliable evidence for supporting our main results. Moreover, the impairment of vascular function characterized by a reduction in NO availability induced the alteration of renal hemodynamics and glomerular filtration, coupled with altered autoregulation, may be responsible for the relationship of low levels of free THs with DN.<sup>28,39</sup> A previous study showed that the glomerular expression of the TH-inactivating enzyme deiodinase 3 (DIO3) increased in diabetic rats. Human podocytes exposed to high glucose in vitro also exhibited obviously upregulated DIO3 expression.<sup>40</sup> Additionally, it has been demonstrated that subclinical hypothyroidism is often complicated with the thickening of the capillary basement membrane.<sup>41</sup> These changes lead to small vessel dysfunction,<sup>42</sup> increasing the risk of developing DR. Glaschke et al reported changes in the opsin expression pattern first at five to seven weeks after serum THs decreased to hypothyroid levels, concluding that the process may be influenced by the duration of hypothyroidism.<sup>43</sup> Furthermore, our previous study found that the low-normal FT3 and FT4 levels are also related to an elevated risk of macrovascular complications.<sup>17</sup> Therefore, it is necessary to effectively treat hypothyroidism in T2DM patients. Fortunately, treatment of hypothyroidism in adult patients with T2DM is simple and available because hypothyroidism is successfully treated with oral L-T4 monotherapy. This treatment is recommended when serum TSH levels are  $>10.0$  mU/L.<sup>44</sup>

This study has several limitations. First of all, because this study is cross-sectional and only one test of the subjects' thyroid function, there may be some statistical bias, and a high-quality prospective analysis is required. Second, we defined normal thyroid function as TSH, FT3, and FT4 within the normal reference range, and this study did not evaluate the levels of total thyroid hormone, reverse triiodothyronine (rT3) and thyroid autoantibodies. The relationship between thyroid hormone and diabetic microvascular complications may have been underestimated in the present research. Third, we did not check the level of urinary iodine concentration (UIC) in the study. Although the individuals we enrolled were T2DM patients with normal thyroid function, the TSH levels in the participants may be affected by iodine intake, which may affect the results of the study. Fourth, the sample size of the present study was relatively small which may lead to a certain deviation in the results of this study. Finally, all individuals were hospitalized Chinese adults at the same center, so the present results may not be applicable to all Chinese T2DM patients. Despite these limitations, this real-world study

can provide a roadmap to help diabetologists assess the possible development of microvascular complications in patients from a new perspective, and guide individual types of complications to prevent them.

## Conclusions

In conclusion, although we cannot prove the inter-relationship between thyroid hormone levels and microvascular complications in T2DM patients, our results show that low-level free thyroid hormone levels are significantly related to microvascular complications, and may be the independent risk factor for microvascular complications in euthyroid patients with T2DM. In addition, the level of TSH is significantly related to DPN, which may be an independent risk factor for DPN. Further prospective and larger sample size studies are needed to provide more reliable evidence to clarify this issue.

## Data Sharing Statement

The datasets generated for this study are available on request to the corresponding author.

## Funding

This study was supported by the following funding: the National Natural Science Foundation of China (No. 81873304).

## Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## References

1. Sun H, Saeedi P, Karuranga S, et al. IDF Diabetes Atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract.* 2022;183:109119. doi:10.1016/j.diabres.2021.109119
2. Morrish NJ, Wang SL, Stevens LK, Fuller JH, Keen H. Mortality and causes of death in the WHO Multinational Study of Vascular Disease in Diabetes. *Diabetologia.* 2001;44(Suppl 2):S14–21.
3. Harding JL, Pavkov ME, Magliano DJ, Shaw JE, Gregg EW. Global trends in diabetes complications: a review of current evidence. *Diabetologia.* 2019;62(1):3–16.
4. Cheema S, Maisonneuve P, Zirie M, et al. Risk factors for microvascular complications of diabetes in a high-risk middle east population. *J Diabetes Res.* 2018;2018:8964027.
5. Raman R, Gupta A, Krishna S, Kulothungan V, Sharma T. Prevalence and risk factors for diabetic microvascular complications in newly diagnosed type II diabetes mellitus. Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetic Study (SN-DREAMS, report 27). *J Diabetes Complications.* 2012;26(2):123–128.
6. Zoungas S, Woodward M, Li Q, et al. Impact of age, age at diagnosis and duration of diabetes on the risk of macrovascular and microvascular complications and death in type 2 diabetes. *Diabetologia.* 2014;57(12):2465–2474.
7. Yamazaki D, Hitomi H, Nishiyama A. Hypertension with diabetes mellitus complications. *Hypertens Res.* 2018;41(3):147–156.
8. Zhao W, Zeng H, Zhang X, et al. A high thyroid stimulating hormone level is associated with diabetic peripheral neuropathy in type 2 diabetes patients. *Diabetes Res Clin Pract.* 2016;115:122–129.
9. Jabbar A, Pingitore A, Pearce SH, Zaman A, Iervasi G, Razvi S. Thyroid hormones and cardiovascular disease. *Nat Rev Cardiol.* 2017;14(1):39–55.
10. Johnson L, Rayner B. A cross-sectional cohort study with microvascular complications in patients with type 2 diabetes with and without hypothyroidism. *Cardiovasc J Afr.* 2020;31(1):5–8. doi:10.5830/CVJA-2019-036
11. Mansournia N, Riyahi S, Tofangchiha S, et al. Subclinical hypothyroidism and diabetic nephropathy in Iranian patients with type 2 diabetes. *J Endocrinol Invest.* 2017;40(3):289–295.
12. Mehalingam V, Sahoo J, Bobby Z, Vinod KV. Thyroid dysfunction in patients with type 2 diabetes mellitus and its association with diabetic complications. *J Family Med Primary Care.* 2020;9(8):4277–4281.
13. 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.
14. Wang J, Li H, Tan M, et al. Association between thyroid function and diabetic nephropathy in euthyroid subjects with type 2 diabetes mellitus: a cross-sectional study in China. *Oncotarget.* 2019;10(2):88–97.
15. Zou J, Li Z, Tian F, et al. Association between normal thyroid hormones and diabetic retinopathy in patients with type 2 diabetes. *Biomed Res Int.* 2020;2020:8161797.
16. Kong X, Wang J, Gao G, et al. Association between free thyroxine levels and diabetic retinopathy in euthyroid patients with type 2 diabetes mellitus. *Endocr Res.* 2020;45(2):111–118.
17. Hu Y, Yan Z, Pan C. Associations of thyroid hormone levels and macrovascular complications in euthyroid type 2 diabetic patients. *Diabetes Metab Syndr Obes.* 2021;14:2683–2691.
18. American Diabetes Association. Standards of medical care in diabetes–2014. *Diabetes Care.* 2014;37(Suppl 1):S14–80.

19. Martin CL, Albers JW, Pop-Busui R. Neuropathy and related findings in the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. *Diabetes Care*. 2014;37(1):31–38.
20. Fong DS, Aiello L, Gardner TW, et al. Retinopathy in diabetes. *Diabetes Care*. 2004;27(Suppl 1):S84–87.
21. Penza P, Lombardi R, Camozzi F, Ciano C, Lauria G. Painful neuropathy in subclinical hypothyroidism: clinical and neuropathological recovery after hormone replacement therapy. *Neurol Sci*. 2009;30(2):149–151.
22. Yerdelen D, Erteror E, Koç F. The effects of hypothyroidism on strength-duration properties of peripheral nerve. *J Neurol Sci*. 2010;294(1–2):89–91.
23. Han C, He X, Xia X, et al. Subclinical Hypothyroidism and Type 2 Diabetes: a Systematic Review and Meta-Analysis. *PLoS One*. 2015;10(8):e0135233.
24. Zhu FF, Yang LZ. The association between the levels of thyroid hormones and peripheral nerve conduction in patients with type 2 diabetes mellitus. *Exp Clin Endocrinol Diabetes*. 2018;126(8):493–504.
25. Han Q, Zhang J, Wang Y, et al. Thyroid hormones and diabetic nephropathy: an essential relationship to recognize. *Nephrology*. 2019;24(2):160–169.
26. Liu P, Liu R, Chen X, et al. Can levothyroxine treatment reduce urinary albumin excretion rate in patients with early type 2 diabetic nephropathy and subclinical hypothyroidism? A randomized double-blind and placebo-controlled study. *Curr Med Res Opin*. 2015;31(12):2233–2240.
27. Zou J, Tian F, Zhang Y, et al. Association between Thyroid Hormone Levels and Diabetic Kidney Disease in Euthyroid Patients with Type 2 Diabetes. *Sci Rep*. 2018;8(1):4728.
28. Zhao W, Li X, Liu X, Lu L, Gao Z. Thyroid Function in patients with type 2 diabetes mellitus and diabetic nephropathy: a single center study. *J Thyroid Res*. 2018;2018:9507028.
29. Lin Y, Sun Z. Thyroid hormone ameliorates diabetic nephropathy in a mouse model of type II diabetes. *J Endocrinol*. 2011;209(2):185–191.
30. 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):1018–1020.
31. Wu J, Yue S, Geng J, et al. Relationship between diabetic retinopathy and subclinical hypothyroidism: a meta-analysis. *Sci Rep*. 2015;5:12212.
32. López-Noriega L, Cobo-Vuilleumier N, Narbona-Pérez AJ, et al. Levothyroxine enhances glucose clearance and blunts the onset of experimental type 1 diabetes mellitus in mice. *Br J Pharmacol*. 2017;174(21):3795–3810.
33. Lin Y, Sun Z. Thyroid hormone potentiates insulin signaling and attenuates hyperglycemia and insulin resistance in a mouse model of type 2 diabetes. *Br J Pharmacol*. 2011;162(3):597–610.
34. Kim BY, Kim CH, Jung CH, Mok JO, Suh KI, Kang SK. Association between subclinical hypothyroidism and severe diabetic retinopathy in Korean patients with type 2 diabetes. *Endocr J*. 2011;58(12):1065–1070.
35. Stefanowicz-Rutkowska MM, Baranowska-Jurkun A, Matuszewski W, Bandurska-Stankiewicz EM. Thyroid dysfunction in patients with diabetic retinopathy. *Endokrynol Pol*. 2020;71(2):176–183.
36. Lu M, Yang CB, Gao L, Zhao JJ. Mechanism of subclinical hypothyroidism accelerating endothelial dysfunction (Review). *Exp Ther Med*. 2015;9(1):3–10.
37. Nukada H. Ischemia and diabetic neuropathy. *Handb Clin Neurol*. 2014;126:469–487.
38. Vicinanza R, Coppotelli G, Malacrinò C, et al. Oxidized low-density lipoproteins impair endothelial function by inhibiting non-genomic action of thyroid hormone-mediated nitric oxide production in human endothelial cells. *Thyroid*. 2013;23(2):231–238.
39. Taddei S, Caraccio N, Virdis A, et al. Impaired endothelium-dependent vasodilatation in subclinical hypothyroidism: beneficial effect of levothyroxine therapy. *J Clin Endocrinol Metab*. 2003;88(8):3731–3737.
40. Mantzouratou P, Lavecchia AM, Novelli R, Xinaris C. Thyroid Hormone Signalling Alteration in Diabetic Nephropathy and Cardiomyopathy: a “Switch” to the Foetal Gene Programme. *Curr Diab Rep*. 2020;20(11):58.
41. Cappola AR, Ladenson PW. Hypothyroidism and atherosclerosis. *J Clin Endocrinol Metab*. 2003;88(6):2438–2444.
42. Oflaz H, Kurt R, Cimen A, et al. Coronary flow reserve is also impaired in patients with subclinical hypothyroidism. *Int J Cardiol*. 2007;120(3):414–416.
43. Glaschke A, Weiland J, Del Turco D, Steiner M, Peichl L, Glösmann M. Thyroid hormone controls cone opsin expression in the retina of adult rodents. *J Neurosci*. 2011;31(13):4844–4851.
44. Biondi B, Kahaly GJ, Robertson RP. Thyroid Dysfunction and Diabetes Mellitus: two Closely Associated Disorders. *Endocr Rev*. 2019;40(3):789–824.

## Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy

Dovepress

### Publish your work in this journal

Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy is an international, peer-reviewed open-access journal committed to the rapid publication of the latest laboratory and clinical findings in the fields of diabetes, metabolic syndrome and obesity research. Original research, review, case reports, hypothesis formation, expert opinion and commentaries are all considered for publication. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/diabetes-metabolic-syndrome-and-obesity-targets-and-therapy-journal>