Association of Thyroid-Stimulating Hormone Levels with Microvascular Complications in Type 2 Diabetes Patients

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Background: Subclinical hypothyroidism (SCH) is typically featured by elevated serum concentration of thyroid-stimulating hormone (TSH). This study aimed to determine the relationship between TSH levels and microvascular complications in type 2 diabetes patients.

Material/Methods: A total of 860 type 2 diabetes patients were enrolled in this cross-sectional study. Subjects were evaluated for anthropometric measurements, thyroid function, diabetic retinopathy, and diabetic kidney disease. TSH was divided into 3 levels: 0.27–2.49 mU/l, 2.5–4.2 mU/l, and >4.2 mU/l.

Results: Among the participants, 76 subjects (8.8%) were diagnosed with subclinical hypothyroidism (SCH) (male: 6.6% and female: 11.8%). The prevalence of diabetic retinopathy did not differ among the groups (P=0.259). Of the 860 type 2 diabetic subjects, we further excluded invalid or missing data. Therefore, 800 and 860 subjects were included in our study of diabetic retinopathy (DR) and diabetic kidney disease (DKD), respectively. The frequencies of microalbuminuria and macroalbuminuria differed significantly among the different groups. The frequency of DKD was significantly different among the 3 groups (P=0.001) and was higher in subjects with higher TSH levels. After an adjustment for confounding variables, TSH levels were significantly associated with DKD (P<0.001). When compared with subjects with TSH 0.27–2.49 mU/l, the frequency of DKD was higher in subjects with TSH >4.20 mU/l (OR 1.531, 95% CI 1.174–1.997) and with TSH 2.50–4.20 mU/l (OR 1.579, 95% CI 1.098–2.270). However, TSH levels was not significantly correlated with DR (P=0.126).

Conclusions: Type 2 diabetic patients with higher TSH values had a higher prevalence of DKD.

MeSH Keywords: Diabetes Mellitus, Type 2 • Diabetic Nephropathies • Diabetic Retinopathy

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Background

Subclinical hypothyroidism (SCH) is typically featured by elevated serum concentration of thyroid-stimulating hormone (TSH) but with normal serum thyroxin levels [1,2]. It is not a rare endocrine disorder, as its prevalence has been reported to vary between 4% and 10% in large general population-screening surveys [3]. Although SCH usually shows an asymptomatic state, it indeed affects almost every organ in the body. The pathogenesis of SCH is related to endothelial dysfunction [4,5], hyperlipidemia [3,6,7], and atherosclerosis [8], which increase the risk of cardiovascular disease. A close interrelationship between SCH and chronic kidney disease (CKD) has also been repeatedly observed [9–11]. Moreover, the association between SCH and type 2 diabetes mellitus (T2DM) is well known, and the reported SCH levels in diabetes ranged from 2.2% to 17% [12–15]. However, how SCH is related to diabetes-related microvascular complications remains unclear.

SCH is independently linked with the occurrence of albuminuria in type 2 diabetes patients [15]. Furukawa et al. [16] considered that SCH was a determinant factor for diabetic nephropathy (DN). Further, 2 reports have shown SCH as a potential factor for increased risk of diabetic retinopathy (DR) [17,18]. However, this relationship between SCH and DR was not found by Ramis et al. [19]. Individuals with type 2 diabetes mellitus and SCH were associated with an increased risk of DN, but not with DR [20]. However, Kim et al. [21] took the opposite view.

The guidelines from the National Academy of Clinical Biochemistry (NACB) state that more than 95% of healthy individuals have a serum TSH concentration lower than 2.5 mU/l [22]. Thus, the suggestion has been made to lower the TSH upper reference limit to 2.5 mU/l [23]. It is possible that upper-normal TSH levels may play a role in chronic complications of type 2 diabetes. To this end, we performed the present study to examine whether there is any relationship between microvascular complications and TSH levels in type 2 diabetic subjects.

Material and Methods

Patients

The baseline data were collected from August 2011 to August 2015. In total, we enrolled 860 hospital-based subjects in this cross-sectional study. Inclusion criteria were: individuals with previously diagnosed T2DM. Exclusion criteria were: (a) type 1 diabetes mellitus; (b) personal history of thyroid diseases; (c) clinical hypothyroidism; (d) subclinical or overt hyperthyroidism; (e) treatment with levothyroxine or anti-thyroid drugs; (f) pregnancy; (g) acute or chronic infection; (h) malignancy;

and (i) kidney disease other than diabetic kidney disease. Our study was approved by the Ethics Committee of the Metabolic Diseases Hospital, Tianjin Medical University. Written informed consent was provided by all subjects.

Clinical examination and laboratory measurements

Demographic and clinical data, including age, sex, height and weight, blood pressure, smoking and drinking status, previous history of hypertension and dyslipidemia, and duration of diabetes, were collected. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Hypertension was defined by a systolic blood pressure (SBP) ≥140 mmHg or a diastolic blood pressure (DBP) ≥90 mmHg or taking antihypertensive drugs. We also obtained results of the following variables: glycated hemoglobin (HbA1c), high-sensitivity C-reactive protein (hs-CRP), serum creatinine (Cr), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), and triglyceride (TG) levels. The reference range of HbA1c was 4.0–6.0%. Dyslipidemia was defined by a serum TC concentration >5.7 mmol/L, TG concentration >1.71 mmol/L, LDL-c concentration >3.1 mmol/L or HDL-c concentration <1.1 mmol/L, or taking lipid-lowering agents.

The tests of thyroid function

Thyroid function was confirmed by chemiluminescent immunometric assay. The reference ranges of serum T3, T4, TSH were 1.3–3.1 nmol/L, 66.0–181.0 nmol/L, and 0.27–4.2 µIU/ml, respectively. Moreover, the reference range of anti-thyroid peroxidase antibody (TPO-Ab) was 0-34 IU/ml. As described in a previous publication [24], the subjects were divided into 3 groups according to the TSH levels: 0.27–2.49 mU/l; 2.5–4.2 mU/l; and > 4.2 mU/l.

Assessment of diabetic complications

Estimated glomerular filtration rate (eGFR) was calculated using the equation [25]: 186× serum Cr$^{-1.154}$ × age$^{-0.203}$ × 0.742 (if female) ×1.233.

Diabetic kidney disease (DKD) [26,27] was defined as urinary albumin excretion ≥30 mg/24 h or eGFR <60 mL/min/1.73 m^2.

All patients were examined by an ophthalmologist using fundus photographs (2 eyes ×2 fields). Diabetic retinopathy (DR) was defined on the basis of the international clinical DR severity scale [28]. In this analysis, only 800 subjects were available.

Statistical analysis

All statistical analyses were performed using SPSS 19.0 software. Continuous variables are presented as mean ± standard

Table 1. Clinical characteristics of type 2 diabetic patients according to TSH levels.

	TSH 0.27–2.49 (n=572)	TSH 2.50–4.20 (n=212)	TSH >4.20 (n=76)	Total (n=860)	P-value
Age (years)	53.6±12.5	54.0±14.0	58.5±14.6	54.1±13.2	0.009
Gender (male/female)	353/219	102/110	32/44	487/373	<0.001
T2DM duration (years)	7.9±6.7	7.9±6.7	9.0±7.1	8.0±6.7	0.416
BMI (kg/m^2)	26.4±4.1	27.0±4.6	27.0±4.2	26.6±4.2	0.157
SBP (mmHg)	130.7±18.7	133.5±18.3	130.2±16.3	131.3±18.4	0.147
DBP (mmHg)	79.9±10.5	80.2±10.6	78.8±10.9	79.9±10.5	0.621
HbA1c (%)	9.63±2.19	9.38±2.10	9.14±2.13	9.53±2.16	0.093
TC (mmol/l)	4.97±1.25	4.94±1.08	5.01±1.28	4.97±1.21	0.901
TG (mmol/l)	2.11±2.19	2.16±2.05	2.04±2.13	2.11±2.15	0.909
LDL-c (mmol/l)	3.13±1.02	3.07±0.87	3.16±1.10	3.12±0.99	0.692
HDL-c (mmol/l)	1.24±0.29	1.25±0.26	1.25±0.29	1.24±0.28	0.730
Smoking (n,%)	228 (39.9)	46 (21.7)	13 (17.1)	287 (33.4)	<0.001
Drinking (n,%)	120 (21.0)	35 (16.5)	8 (10.5)	163 (19.0)	0.053
Hypertension (n,%)	253 (44.2)	110 (51.9)	39 (51.3)	402 (46.7)	0.114
Dyslipidaemia (n,%)	435 (76.0)	154 (72.6)	60 (78.9)	649 (75.5)	0.469
hs-CRP (mg/l)	2.91±3.93	3.34±3.71	3.39±4.36	3.06±3.92	0.314
Positive rate of TPO-Ab (n/N,%)	33/476 (6.9)	16/198 (8.1)	15/71 (21.1)	64/745 (8.6)	<0.001
TSH (μIU/ml)	1.49 (0.27-2.49)	3.12 (2.51-4.20)	5.42 (4.21-21.93)	1.88 (0.27-21.93)	<0.001

Data are expressed as mean ±SD, median (range) or number (percentage). TSH – thyroid-stimulating hormone; T2DM – type 2 diabetes mellitus; BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; HbA1c – glycated hemoglobin; TC – total cholesterol; TG – triglyceride; LDL-c – low-density lipoprotein cholesterol; HDL-c – high-density lipoprotein cholesterol; hs-CRP – high sensitivity C-reactive protein; TPO-Ab – anti-thyroid peroxidase antibody.

deviations. Variables with a skewed distribution are expressed as median with range. The data are expressed as frequency and proportion for categorical data. Statistical differences among groups were compared using one-way ANOVA for continuous variables and Kruskal-Wallis test for skewed data. Categorical variables were analyzed using the chi-square test or Fisher exact test, as appropriate. We performed multivariate logistic regression analysis to analyze the association between the TSH category and diabetic retinopathy, as well as DKD. A P-value of <0.05 was deemed to be statistically significant.

Results

The general characteristics of the 860 type 2 diabetic patients are shown in Table 1. No significant differences among the 3 groups in T2DM duration, BMI, SBP, DBP, HbA1c, TC, TG, LDL-c, HDL-c, hs-CRP were found. Furthermore, the prevalence of drinking, hypertension and dyslipidemia did not differ among the groups. The proportion of men was significantly different among the groups (P<0.001). Moreover, the differences

in age, smoking status, and positive rate of TPO-Ab were significantly different among the groups (P=0.009, P<0.001, and P<0.001, respectively).

The overall prevalence of subclinical hypothyroidism (SCH) was 8.8% (76/860) in subjects with type 2 diabetes mellitus. The prevalence of SCH in women was significantly higher than in men among patients with T2DM (11.8% [44/373] *vs.* 6.6% [32/487]; P=0.007).

Of the 860 type 2 diabetic subjects, we further excluded the invalid or missing data. Therefore, 800 and 860 subjects were included in our study of DR and DKD, respectively. The prevalence of diabetic retinopathy was 39.5% (316/800) in this cohort for analysis. Microalbuminuria and macroalbuminuria were reported in 22.1% (190/860) and 7.8% (67/860) of the patients. No significant difference was observed in the prevalence of diabetic retinopathy among the 3 groups (P=0.259). The frequencies of microalbuminuria and macroalbuminuria differed significantly among the different groups (P=0.044 and P=0.026, respectively). Thirty-six patients had an eGFR

Table 2. Prevalence of chronic complications in type 2 diabetic patients according to TSH levels.

	TSH 0.27–2.49	TSH 2.50–4.20	TSH >4.20	P-value
Retinopathy, n/N (%)	201/535 (37.6)	84/197 (42.6)	31/68 (45.6)	0.259
Microalbuminuria, n/N (%)	114/572 (19.9)	52/212 (24.5)	24/76 (31.6)	0.044
Macroalbuminuria, n/N (%)	36/572 (6.3)	20/212 (9.4)	11/76 (14.5)	0.026
eGFR (mL/min/1.73 m^2)	138.3±41.7	134.3±42.7	124.2±47.4	0.020
eGFR <60 mL/min/1.73 m^2, n/N (%)	12/572 (2.1)	11/212 (5.2)	13/76 (17.1)	<0.001
Diabetic kidney disease, n/N (%)	155/572 (27.1)	77/212 (36.3)	35/76 (46.1)	0.001

Data are expressed as mean ±SD or number (percentage). TSH – thyroid-stimulating hormone; eGFR – estimated glomerular filtration rate.

Table 3. Multivariate analysis of the relationship between TSH categories and diabetic retinopathy, diabetic nephropathy or chronic kidney disease in type 2 diabetic patients.

	OR (95% CI)	P-value
Diabetic retinopathy		0.126
TSH 0.27–2.49 mU/l	1.000	
TSH 2.50–4.20 mU/l	1.205 (0.856–1.695)	
TSH >4.20 mU/l	1.188 (0.914–1.545)	
Diabetic kidney disease		<0.001
TSH 0.27–2.49 mU/l	1.000	
TSH 2.50–4.20 mU/l	1.579 (1.098–2.270)	
TSH >4.20 mU/l	1.531 (1.174–1.997)	

Adjusted for age, gender, duration of T2DM, BMI, HbA1c, smoking, drinking, hypertension and dyslipidaemia. OR – odds ratio; CI – confidence interval; TSH – thyroid-stimulating hormone; T2DM – type 2 diabetes mellitus; BMI – body mass index; HbA1c – glycated hemoglobin.

<60 (mL/min)/1.73 m^2. eGFR <60 mL/min/1.73 m^2 was found in 4.2% (36/860) of the subjects. The frequency of eGFR <60 (mL/min)/1.73 m^2 differed significantly among the different groups (P<0.001). Moreover, DKD occurred in 31.0% (267/860) of the subjects. The frequency of DKD differed significantly among the 3 groups (P=0.001). The higher frequency of DKD in subjects was related to the higher TSH levels (Table 2).

We also performed multivariate logistic regression analysis. After an adjustment for potential explanatory factors, including age, sex, duration of T2DM, BMI, HbA1c, smoking, drinking, hypertension, and dyslipidemia, TSH level was significantly associated with DKD (P<0.001; Table 3). When compared with subjects with TSH 0.27–2.49 mU/l, the frequency of DKD was higher in subjects with TSH >4.20 mU/l (OR 1.531, 95% CI 1.174–1.997) and with TSH 2.50–4.20 mU/l (OR 1.579, 95% CI 1.098-2.270). However, TSH level was not significantly correlated with diabetic retinopathy (P=0.126; Table 3).

Discussion

Several studies have assessed the relationship between thyroid function and microvascular complications in patients with T2DM, but the results were controversial. Previous studies showed that SCH was associated with DR [17,18], while 2 other studies could not find any relationship between SCH and DR [19,20]. Moreover, it was reported that SCH was an independent risk factor for DN [16,20]. However, Kim et al. failed to show a relationship between SCH and DN [21].

Previous studies have demonstrated an association between TSH and eGFR in the general population [9,10]. However, studies in patients with diabetes mellitus are still lacking. Rodacki et al. reported that there was a significant interrelationship between thyroid function and a lower GFR in subjects with type 1 diabetes [24]. Furukawa et al. found that eGFR was higher in the euthyroid group than that in the SCH group among

patients with T2DM [16]. However, the study failed to confirm the relationship between SCH and CKD [16].

The present study revealed that serum TSH levels were associated with diabetic kidney disease, but not with diabetic retinopathy. The multivariate analysis demonstrated the higher frequency of DKD with higher TSH levels. Thyroid function was an independent factor for DKD in subjects with T2DM after adjustment for several other factors. Our results were consistent with those of Chen et al. [20], showing that SCH was associated with DN, but differed from those of Kim et al. [21], who reported an association between SCH and an increased risk of severe diabetic retinopathy, but not with diabetic nephropathy.

Currently, the reasons for this discrepancy remain unanswered. They may be related to differences in demographic and clinical characteristics, ethnicity, and research design. The duration of diabetes and poor glycemic control are risk factor for microvascular complications in type 2 diabetes. Our study had younger participants (the mean age 54.1±13.2 years) with poorer glycemic control (HbA1c 9.53±2.16%) than did that of Kim et al. [21]. Furthermore, 56.6% of the sample were men in the present study. Besides, in our and other studies [21], the duration of T2DM was shorter than those other previous studies [17,21]. Moreover, the sample size of other previous studies [17,21] was smaller than the present study. In addition, our hospital is a specialized hospital for the prevention and treatment of diabetes and its complications. Thus, the number of subjects with severe diabetic retinopathy was small in this study, which was different from the studies conducted in Beijing Tongren Hospital [17,18].

Several mechanisms may be involved in the relationship between thyroid dysfunction and microvascular complications in diabetes. Firstly, it has been demonstrated that insulin resistance is associated with clinical and subclinical hypothyroidism [29]. A correlation between insulin resistance and microalbuminuria has been reported [30]. A possible mechanism could be defective fibrinolysis [31] or impaired vasodilation [32] associated with insulin resistance, and SCH decreased paraoxonase and arylesterase activities [33], meaning that the antioxidative capacity of SCH decreased significantly. However, oxidative stress plays an important role in the pathogenesis

of diabetes-related complications; lipid levels may be responsible for the association. Disordered lipid metabolism was observed in patients with subclinical hypothyroidism [6,7]. As is well known, dyslipidemia plays an important role in the pathogenesis of diabetic complications [34]. SCH is often complicated with endothelial dysfunction, manifested by thickening of the capillary basement membrane [35,36]. It has been reported that endothelial dysfunction can affect the pathogenesis of diabetic complications [17]. Lastly, thyroid hormone influences kidney growth, kidney structure, and many of its functions [37]. Overt and subclinical hypothyroidism affects kidney function as a result of cardiac dysfunction, peripheral vascular resistance, endothelial dysfunction, and renal hemodynamics.

Our study has several limitations. Firstly, this hospital-based study was a cross-sectional analysis. Thus, we could not establish a causal relationship between serum TSH levels and macrovascular complications in patients with T2DM. Secondly, thyroid function was evaluated at a single time point. Thirdly, the definition of DKD was based on 1-point measurement. Nevertheless, albuminuria measurement was measured in 24-h urine samples for all the participants. Fourthly, our hospital is a specialized hospital for the prevention and treatment of diabetes and its complications. The number of patients in poor condition was relatively small. Lastly, all the subjects were from a single center.

Conclusions

In conclusion, although we could not demonstrate the interrelationship between thyroid function and DR in type 2 diabetes patients, our findings suggest that type 2 diabetic patients with higher TSH values had a higher prevalence of DKD. A large randomized controlled clinical trial should be performed to determine whether there is a true association between TSH values and the risk of microvascular complications in patients with T2DM. Further prospective investigation is also warranted to assess whether appropriate thyroid replacement therapy is necessary for type 2 diabetes patients with high TSH levels.

Conflict of interest

No conflict of interest exists.

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