Association between thyroid hormones and diabetic complications in patients with newly diagnosed type 2 diabetes: A cross-sectional study

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Research

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Abstract

Background

Diabetes mellitus (DM) and thyroid dysfunction (TD) are two closely associated disorders. The coexistence of TD could adversely influence metabolic control and even increase the long-term mortality in patients with DM. The objective of the present study was to investigate the thyroid status and the relationship between thyroid hormones, diabetic complications and metabolic parameters in patients with newly diagnosed type 2 DM (T2DM).

Methods

This is an observational cross-sectional study, conducting on 340 patients with newly diagnosed T2DM who were admitted to ward of endocrinology department and 120 matched nondiabetic subjects. Clinical characteristics were collected and laboratory measurements were conducted.

Results

Levels of free T3 (FT3), free T4 (FT4) and TSH were significantly lower in patients with T2DM as compared to nondiabetic subjects. The prevalence of TD was 21.2% in patients with diabetes, higher than that of controls (4.2%). The low T3 syndrome was the most frequent TD, shown in 14.7% of patients. The presence of diabetic complications (diabetic nephropathy (DN), diabetic ketosis), metabolic and demographic factors, including age, glycemic control and insulin resistance were factors associated with levels of thyroid hormones. FT3 level was inversely correlated with the level of urinary total protein (mg/24h) and the presence of DN. Multivariate analysis indicated low FT3 level as a strong independent risk factor (OR = 0.364, $P < 0.001$) for DN.

Conclusions

TD is not rarely seen in patients with newly diagnosed T2DM. Diabetic complications and diabetes-related metabolic and demographic factors are related to TD. Decreased FT3 is strongly correlated with the presence of DN.

Background

Diabetes mellitus (DM) and thyroid dysfunction (TD) are two closely associated disorders. TD is more common in patients with type 2 DM (T2DM) than in those without diabetes and can adversely influence metabolic control [1, 2]. In the long-term, the onset of TD can further increase the morbidity and mortality associated with diabetes [2]. Low levels of thyroid hormones, even in the normal range, were associated with diabetic complications including acute complications such as diabetic ketosis (DK) or diabetic ketoacidosis (DKA) [3] and chronic complications such as diabetic nephropathy (DN) [4] and diabetic retinopathy (DR) [5]. Hypothyroidism, as a main form of TD in diabetic patients, was indicated to be related to increased risks of DR and chronic kidney disease [6]. The relationship between T2DM and TD is complex and the underlying mechanisms have not been fully elucidated. Several studies have investigated the prevalence and risk factors of TD in patients with T2DM. But the population varied among these studies and researches in newly diabetic patients were relatively rare. Considering the addictive impact of

diabetes progression on thyroid function, we suppose it necessary to focus on patients with newly diagnosed diabetes on this issue. Therefore, we designed this study, to investigate the prevalence of TD and to determine the risk factors of TD in patients with newly diagnosed T2DM.

Methods

1. **Study population and design**

We studied patients with newly diagnosed T2DM who were admitted to ward of the Department of Endocrinology, The Second Affiliated Hospital of Guangzhou Medical University, from January 2014 to June 2019. The inclusion criteria were adults with newly diagnosed and treated T2DM based on the diagnostic criteria recommended by the Chinese Diabetes Society [7]. The exclusion criteria included: A. with history of thyroid disease or thyroid surgery; B. severe primary liver and kidney dysfunctions; C. using drugs potentially altering thyroid hormone concentrations such as amiodarone, beta-blockers and corticosteroids. These patients were newly diagnosed with T2DM when seeking medical service due to diabetes-related symptoms, or undergoing routine physical examination in community hospitals. Patients were admitted due to high glycemic level (HbA1c ≥ 9%) or diabetic complications including acute complications (diabetic ketosis (DK), DKA) and chronic complications (diabetic peripheral neuropathy). Nondiabetic mellitus subjects were selected from a population undergoing an annual physical examination at the Health Management Department, The Second Affiliated Hospital of Guangzhou Medical University, during the same period. Exclusion criteria were the same as the ones for patients with diabetes. Finally, a total of 340 patients with newly diagnosed T2DM and 120 subjects without T2DM were enrolled. The study was approved by the Ethics Committee of The Second Affiliated Hospital of Guangzhou Medical University. Written informed consent was waived due to the retrospective nature of the study.

2. **Measurement and data collection**

Demographic information including family history and habit of smoking was collected through the review of medical records. Body mass index (BMI) was calculated as weight (kg) divided by squared height (m). Blood pressure (BP) was detected twice in a sitting position after a 10-minute rest period and recorded as a mean of the two successive measurements. Hypertension was defined as systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg, or with positive histories of hypertension. Venous blood samples were collected in the morning after an overnight fast for laboratory measurement. Serum free triiodothyronine (FT3), free thyroxine (FT4) and thyroid stimulating hormone (TSH) were measured using electrochemiluminescence immunoassays. Normal ranges were as follows: TSH 0.4-5.0 mIU/L, FT3 2.63-5.70 pmol/L, and FT4 9.01-19.05 pmol/L. Euthyroid was considered if thyroid hormone levels fall within reference range and thyroid dysfunction was considered if thyroid hormones fall outside the reference range. Subclinical hypothyroidism was defined as a serum TSH of more than 5.0 mIU/L, in combination with a normal FT4. Overt hypothyroidism was defined as a serum TSH of more than 5.0 mIU/L, in combination with a subnormal FT4. Subclinical hyperthyroidism was defined as a TSH of less than 0.4 mIU/L with normal FT4. Overt hyperthyroidism was defined as a TSH of less than 0.4 mIU/L with elevated FT4. Low T3 syndrome was defined as a FT3 level of less than 2.63 pmol/L and/or a FT4 level of less than 9.01 pmol/L, combined with a normal or subnormal TSH. Routine biochemical parameters (including fasting plasma glucose, 2-h postprandial plasma glucose, C-Peptide, glycated hemoglobin (HbA1c), serum high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol, triglyceride, uric acid, serum creatinine) were measured by routine laboratory methods. The estimated glomerular filtration rate (eGFR) was calculated according to Modification of Diet in Renal Disease equation: eGFR (mL/min/1.73 m^2) = 186 × $(SCr/88.4)^{-1.154}$×$(age)^{-0.203}$ ×

(0.742 if female) [8]. Urine samples of 24 hours were collected to measure urine albumin levels using a chemiluminescence assay. Spot urinary samples of patients were collected at 7:00-8:00 am. Urinary albumin concentration was measured by nephelometry immunoassay and urinary creatinine concentration was measured by velocity method. The average value of the urinary albumin-to-creatinine ratio (UACR) was calculated. Diabetic nephropathy (DN) was defined as an increased UACR of ≥ 30 mg/g or albumin excretion rate (AER) ≥ 30 mg/24h in the absence of urinary tract infection or other renal abnormalities. Homeostatic model assessment of insulin resistance (HOMA-IR) and β cell function (HOMA-β) was calculated using well-established methods: HOMA-IR = 1.5 + fasting blood glucose (mmol/L) × fasting C-peptide (pmol/L) / 2800, HOMA-β = 0.27 × fasting C-peptide (pmol/L) / (fasting blood glucose (mmol/L) – 3.5) [9].

3. **Statistical analysis**

For continuous variables like thyroid hormones, student's t-test or one-way analysis of variance (ANOVA) were used. Chi-square test was used for categorical variables. Numeric values were presented as mean ± standard deviation (SD) and categorical values were presented as number (%). For evaluation of correlation between FT3, FT4, FT3/FT4 ratio or TSH and other variables, Pearson correlation coefficient was calculated. Factors associated with DN was analyzed with multivariate logistic regression. A two-sided *P* value < 0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS statistical software version 22 for Windows (IBM Corp., Armonk, New York, USA).

Results

1. **Baseline characteristics**

Detailed baseline demographic and clinical characteristics of included subjects were presented in Table 1. The two groups were age- and sex-matched. The mean (±SD) age of the patients with T2DM was 54.85 (± 14.1) years old, ranging from 18 to 90 years. Male patients constituted the majority (n = 221, 65.0%). The mean (±SD) BMI of the patients was 24.6 (± 3.8) kg/m^2. About 30% of the study population had a family history of diabetes. Social history of smoking was reported by 28.5% of the patients. Mean (±SD) HbA1c level was 11.9 (± 2.5) %. Levels of FT3, FT4 and TSH were significantly lower in patients with T2DM (FT3 3.53 ± 0.81 pmol/L, FT4 14.54 ± 2.78, TSH 1.66 ± 1.80 μIU/ml) as compared to controls (FT3 5.07 ± 0.68 pmol/L, FT4 17.16 ± 3.07, TSH 2.49 ± 2.13 μIU/ml) (*P* < 0.001). TD was found in 72 (21.2%) patients with T2DM and 5 (4.3%) in nondiabetic subjects (*P* < 0.001). To avoid the impact of acute condition on thyroid function, we exclude the patients with DK or DKA. Levels of thyroid hormones (FT3 3.71 ± 0.69 pmol/L, FT4 14.63 ± 2.63, TSH 1.59 ± 1.44 μIU/ml) remained to be lower and the prevalence of TD (n = 31, 13.0%) remained to be higher in patients with diabetes than in controls (*P* < 0.001).

Table 1 Demographic and clinical characteristics of subjects.

Characteristic	Newly diagnosed T2DM	Non-T2DM	*P*
	n = 340	n = 120	
Demographic data			
Age, years	54.9 ± 14.1	54.1 ± 10.2	0.532
Male, n (%)	221 (65.0)	74 (61.7)	0.513
Hypertension, n (%)	124 (36.5)	15 (12.5)	< 0.001*
Clinical parameters			
BMI, kg/m^2	24.6 ± 3.8	24.4 ± 2.8	0.501
Systolic BP, mmHg	134 ± 19	130 ± 22	0.073
Diastolic BP, mmHg	85 ± 12	83 ± 15	0.073
HbA1c, %	11.9 ± 2.5	5.8 ± 0.7	< 0.001*
FPG, mmol/L	13.3 ± 5.0	5.0 ± 0.7	< 0.001*
eGFR, ml/min/1.73m^2	91.4 ± 26.0	90.0 ± 17.4	0.519
TG, mmol/L	2.65 ± 3.86	1.73 ± 1.24	< 0.001*
TC, mmol/L	5.26 ± 1.49	4.89 ± 0.90	< 0.001*
LDL-C, mmol/L	3.40 ± 1.10	3.15 ± 0.91	0.015*
HDL-C, mmol/L	1.02 ± 0.29	1.22 ± 0.29	< 0.001*
Uric acid, μmol/L	344 ± 205	379 ± 95	0.074
Thyroid function			
FT3, pmol/L	3.53 ± 0.81	5.07 ± 0.68	< 0.001*
FT4, pmol/L	14.54 ± 2.78	17.16 ± 3.07	< 0.001*
FT3/FT4 ratio	0.30 ± 0.06	0.25 ± 0.06	< 0.001*
TSH, μIU/ml	1.66 ± 1.80	2.49 ± 2.13	< 0.001*
Thyroid dysfunction, n (%)	72 (21.2)	5 (4.2)	< 0.001*

Continuous data are expressed as means ± standard deviation, categorical data as n (%). BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; FT3, free triiodothyronine; FT4, free thyroxine; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein cholesterol; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglycerides; TSH, thyroid stimulating hormone; *P-value < 0.05.

2. **Analyses of associated factors of thyroid status**

Among the categories of thyroid disorders, low T3 syndrome (n = 50, 14.7%) was the most common form, followed by subclinical hyperthyroidism (n = 14, 4.1%), hypothyroidism (n = 6, 1.8%) and subclinical hypothyroidism (n = 2, 0.6%). Distribution of thyroid status and the corresponding thyroid hormone levels were shown in Table 2. Higher prevalence of TD was found in patients over 60 years old (n = 32, 27.4%) than in younger patients (n = 40, 17.2%) (P = 0.044). We found a lower level of FT3 (3.21 ± 0.74 pmol/L) in patients with diabetic ketosis (DK) or diabetic ketoacidosis (DKA) than patients without DK or DKA (3.71 ± 0.69 pmol/L)(P < 0.001). Moreover, the level of FT3 further decreased with the deterioration of DK (2.60 ± 1.23 pmol/L) (P = 0.005). The level of FT4 (12.54 ± 3.64 pmol/L) was also significantly lower in patients with DKA (P = 0.004). But no difference was shown between patients with DK (14.75 ± 2.80 pmol/L) and patients without DK (14.63 ± 2.63 pmol/L) in FT4 level. Lower level of FT3 (3.12 ± 0.86 pmol/L) was also found in patients with DN (P < 0.001), accompanied with lower levels of FT4 and TSH, compared with patients with normoalbuminuria. The levels of FT3 and FT4 were lower in patients over 60 years old (FT3 3.32 ± 0.77 pmol/L, FT4 14.08 ± 2.80 pmol/L) than in patients with younger age (FT3 3.64 ± 0.81 pmol/L, FT4 14.78 ± 2.74 pmol/L) (P < 0.001, P = 0.027, respectively). Pearson correlation analysis revealed negative factors of FT3 level including DK or DKA, DN, age and HbA1c. Positive correlated factors of FT3 level included eGFR, diastolic blood pressure (DBP), fasting C-peptide, 2-h C-peptide, fasting insulin, 2-h insulin and HOMA-IR. DK or DKA and age remained to be negative correlated factors of FT4. DK or DKA, DN and HbA1c remained to be negative correlated factors of FT3/FT4 ratio. None of the metabolic or demographic parameters was strongly associated with TSH level (Table 3).

Table 2 Distribution of thyroid status in patients with newly diagnosed T2DM

Thyroid status	N (%)	FT3, pmol/L	P_1	FT4, pmol/L	P_2	TSH, μIU/ml	P_3	Positive thyroid antibodies	P_4
Total	340 (100)	3.52 (0.81)	-	14.54 (2.78)	-	1.66 (1.80)	-	28 (8.5)	-
Euthyroid	268 (78.8)	3.78 (0.64)	-	14.77 (2.64)	-	1.61 (1.00)	-	16 (6.6)	-
Low T3 syndrome	50 (14.7)	2.32 (0.47)	< 0.001*	13.46 (2.92)	0.002*	1.04 (0.68)	< 0.001*	5 (10.4)	0.444
Subclinical hyperthyroidism	14 (4.1)	3.34 (0.52)	0.011*	15.12 (2.88)	0.625	0.27 (0.10)	< 0.001*	4 (30.8)	0.005*
Hypothyroidism	6 (1.8)	2.72 (0.70)	0.013*	11.80 (4.10)	0.007*	11.15 (6.26)	0.013*	3 (50.0)	0.001*
Subclinical hypothyroidism	2 (0.6)	3.32 (0.42)	0.305	14.77 (4.55)	1.000	5.08 (0.71)	< 0.001*	0 (0.0)	1.000

FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone; P, group with thyroid dysfunction versus group in euthyroid status; P_1, comparison of FT3 level; P_2, comparison of FT4 level; P_3, comparison of TSH level; P_4, comparison of proportion of positive thyroid antibodies; *P-value < 0.05.

Table 3 Correlation between thyroid hormones and demographic and metabolic parameters

Variables	FT3		FT4		FT3/FT4 ratio		TSH	
	r	*P*	r	*P*	r	*P*	r	*P*
Age	-0.168	0.002*	-0.141	0.009*	-0.101	0.063	0.063	0.247
BMI	0.079	0.159	0.002	0.971	0.073	0.195	0.080	0.156
DK or DKA	-0.388	< 0.001*	-0.113	0.038*	-0.348	< 0.001*	0.092	0.089
Diabetic nephropathy	-0.302	< 0.001*	-0.072	0.187	-0.272	< 0.001*	-0.057	0.299
Urinary total protein (mg/24h)	-0.292	< 0.001*	-0.192	0.001*	-0.168	0.004*	0.027	0.644
Albumin excretion rate (mg/24h)	-0.263	< 0.001*	-0.191	0.004*	-0.130	0.054	0.094	0.165
eGFR	0.150	0.006*	0.179	0.001*	0.044	0.417	-0.046	0.396
Diabetic peripheral neuropathy	0.009	0.873	0.126	0.020*	-0.068	0.212	0.031	0.564
HbA1c	-0.224	< 0.001*	0.111	0.041*	-0.273	< 0.001*	0.016	0.765
FPG	0.030	0.586	0.173	0.001*	-0.042	0.442	-0.019	0.733
LDL-C	0.065	0.230	-0.001	0.985	0.113	0.039*	-0.070	0.199
HDL-C	0.065	0.230	0.020	0.710	0.042	0.439	-0.006	0.909
Triglyceride	-0.060	0.270	-0.117	0.031*	0.033	0.547	0.012	0.827
Total cholesterol	0.002	0.968	-0.067	0.218	0.090	0.097	-0.075	0.169
Fasting C-Peptide	0.241	< 0.001*	0.017	0.764	0.195	0.001*	0.065	0.262
2-h C-Peptide	0.372	< 0.001*	0.025	0.670	0.347	< 0.001*	0.041	0.490
Fasting insulin	0.173	0.020*	-0.139	0.062	0.282	< 0.001*	0.010	0.892
2-h insulin	0.167	0.020*	-0.194	0.011*	0.337	0.001*	-0.002	0.976
HOMA-IR	0.178	0.002*	0.070	0.225	0.112	0.053	0.105	0.071
HOMA-β	0.042	0.470	-0.080	0.168	0.051	0.381	0.071	0.905
Systolic BP	0.043	0.434	-0.067	0.216	0.035	0.521	-0.045	0.413
Diastolic BP	0.176	0.001*	0.069	0.203	0.096	0.077	-0.088	0.105

BMI, body mass index; BP, blood pressure; DK, diabetic ketosis; DKA, diabetic ketoacidosis; eGFR, estimated glomerular filtration rate; FPG, free plasma glucose; FT3, free triiodothyronine; FT4, free thyroxine; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β cell function; LDL-C, low-density lipoprotein cholesterol; TSH, thyroid stimulating hormone; *P-vale < 0.05.

3. **Analyses of associated factors of DN**

Comparisons between patients with DN and patients with normoalbuminuria was shown in Additional file 1. FT3 level (3.07 ± 0.89 vs 3.67 ± 0.72, P < 0.001) and FT3/FT4 ratio (0.26 ± 0.05 vs 0.22 ± 0.06, P < 0.001) was significantly lower in patients with DN . Furthermore, there was a decline of FT3 level with progressing albuminuria. FT3 level was inversely correlated with the level of urinary total protein (mg/24h) and the presence of DN (Table 3, Figure 1). After adjusting various confounding factors, multivariate analysis indicated low FT3 level as a strong independent risk factor (OR = 0.364, P < 0.001) for DN. (Table 4).

Table 4 Multivariate analysis of associated factors of diabetic nephropathy in patients with newly diagnosed T2DM

Variable	OR	β	Wald χ^2	P
Age	1.011	0.011	0.525	0.469
Hypertension	1.212	0.193	0.607	0.607
BMI	1.095	0.092	3.825	0.049*
HOMA-IR	1.021	0.021	7.286	0.007*
HOMA-β	1.001	0.001	1.862	0.172
DK or DKA	2.043	0.715	4.082	0.043*
eGFR	1.000	0.000	0.001	0.980
FT3	0.364	-1.011	11.856	0.001*
FT4	1.102	0.097	2.279	0.131

BMI, body mass index; DK, diabetic ketosis; DKA, diabetic ketoacidosis; eGFR, estimated glomerular filtration rate; FT3, free triiodothyronine; FT4, free thyroxine; HOMA-β, homeostasis model assessment of β cell function; HOMA-IR, homeostasis model assessment of insulin resistance; *P-value < 0.05.

Discussion

In this study, lower levels of thyroid hormones and a higher prevalence of TD were found in patients with diabetes as compared to the control group, which is in accordance with previous studies [10, 11]. The prevalence of TD varied in patients with DM in different regions, ranging from 4% to over 20% [2]. The differences can be explained by the large population diversity, the varied degree of iodine intake, different diagnostic criteria of TD and different sensitivities of laboratory assays [12]. Subclinical hypothyroidism or hypothyroidism was reported to be the most common form of TD in several studies [12-15]. No significant differences were found in the prevalence or incidence of TD by diabetes type in community-based study or study recruiting outpatients [16-18]. Compared with T2DM, the

association between type 1 DM (T1DM) and autoimmune thyroid diseases was stronger [16, 17]. Studies recruiting T1DM patients with DKA showed higher prevalence of low T3 syndrome and hypothyroidism [3; 16-18]. In this study, hospitalized patients with newly diagnosed T2DM were included and a relatively high prevalence of TD was found, among which low T3 syndrome constituted the majority.

Low T3 syndrome, also known as euthyroid sick syndrome (ESS) or nonthyroidal illness syndrome (NTIS), was initially described in the 1970s. It represents a state of alterations in thyroid hormone economy, which usually present in critically ill patients [19]. Low T3 syndrome is characterized by decreased serum T3 and T4 concentrations, increased serum reverse T3 (rT3) concentrations and unaltered or inappropriately low serum TSH [20]. Complicated mechanisms were involved in its pathogenesis, including downregulation of TRH and TSH production, changes in thyroid hormone metabolism and inhibitory effect of cytokines on the thyroid gland [21]. The presence of low T3 syndrome is a predictor of poor prognosis of acute or chronic illnesses.

DK or DKA was found to be closely related to low T3 syndrome in this study. Previous studies in DKA mainly focused on T1DM, especially on pediatric patients with T1DM. Similar results were shown. The high prevalence of low T3 syndrome, which is comparable to previous studies in T1DM, may be explained by the relatively high proportions of patients with DK or DKA (29.7%) in this study. TD including low T3 syndrome and hypothyroidism was more common in patients with DKA [3, 22-24]. The presence of low T3 syndrome was associated with poor glycemic control [3, 22] and free thyroid hormones were correlated with the severity of DKA [22], which was in accordance with our findings. The decreased thyroid hormones could increase to normal soon after correction of DKA [3, 23].

The relationship between thyroid hormones and DN is becoming a concern these years. A study in euthyroid subjects with T2DM showed that low levels of thyroid hormones (FT3 and FT4) were associated with DN [4]. The prevalence of kidney disorders in patients with T2DM increased with decreasing FT3 level [25]. DN was a risk factor of TD in patients with T2DM [12, 13]. High levels of TSH and low levels of FT3 were observed in T2DM patients with DN [26]. Moreover, high levels of TSH and/or low levels of FT3 were associated with more severe proteinuria, renal insufficiency and glomerular lesions in patients with DN [25, 27]. We also observed that FT3 and FT4 were positively associated with eGFR levels. Patients with DN demonstrated lower FT3 level and FT3/FT4 ratio. The presence of DN was significantly associated with decreased FT3. A prior study in adult euthyroid patients with T1DM showed that higher FT3 level was related to lower prevalence of microangiopathy and better metabolic control [28], which further supported our findings. The exact mechanisms are not fully elucidated. Thyroid hormones play important roles in the growth, development and physiology of kidneys, and also, in maintaining vascular and endothelial functions [29, 30]. TD including subclinical clinical hypothyroidism and low T3 syndrome is involved in the impairment of vascular function and damage of endothelial dilatation function, which may be associated with the pathogenesis of DN [31].

Levels of thyroid hormones were also suggested to be associated with some metabolic and demographic parameters. A study in non-diabetic individuals demonstrated that low T3 levels were significantly associated with decreased HOMA-IR, which indicated an association of thyroid function with insulin resistance [32]. FT3 and FT4 positively and negatively correlated with HOMA-IR and atherogenic lipid profiles, respectively, in a euthyroid population with obesity [33]. In euthyroid subjects, serum FT4 was negatively associated with and TSH was positively associated with insulin resistance. Also, FT4 was associated with risk of metabolic syndrome [34]. TSH and thyroid hormones were found to correlated with multiple cardiometabolic risk factors, with age- and sex-independent effects on cholesterol and glucose metabolism, both in adults and in children with diabetes [35, 36].

We also found some relationships between thyroid hormones and metabolic parameters including HOMA-IR, HbA1c, serum insulin and C-peptide levels. In some studies, obesity was also a risk factor of TD [8, 9]. Both FT3 and FT4 levels were positively correlated with BMI in euthyroid subjects with obesity [34]. Higher FT3 concentration correlated positively with markers of obesity such as BMI in euthyroid T1DM patients [28]. However, we did not find significant difference in levels of thyroid hormones between patients with obesity (BMI $\geq$ 28 kg/m^2) and patients with relatively normal BMI values. A large population-based study demonstrated that elevated TSH level within the normal range was a risk marker associated with a series of cardiometabolic changes including central obesity, insulin resistance, elevated BP, dyslipidemia, hyperuricemia, inflammation and hypercoagulability [37]. But in this study, we did not find significant relationship between TSH and other metabolic parameters.

Advanced age, long duration of diabetes and poor glycemic control were commonly indicated to be risk factors of low levels of FT3 and presence of TD in patients with T2DM [8. 9]. And the abnormalities seemed to be reversed upon restoration of metabolic control [38]. We also discovered higher prevalence of TD or low T3 syndrome in patients over 60 years old and patients with higher glycemic levels. TD was reported to be more common in female as compared to male patients with T2DM in many studies [13. 39. 40]. However, no gender difference was indicated in our study. This may be partly attributed to the different inclusion criteria. Most studies did not include low T3 syndrome as a form of TD. This may also explain the relatively higher prevalence of TD (21.2%) in our study since low T3 syndrome contributed over 50% of the disorders. Furthermore, subjects in the present study were admitted in ward for treatment of diabetes. The conditions of patients, particularly glycemic control, were generally worse than the ones in outpatient clinics. Actually, most subjects in our study had a HbA1c level over 10%. This may also contribute to the high prevalence of TD.

There are several limitations of the present study. First, only limited number of patients in a single center were involved. The samples were derived from an inpatient setting and may not be representative of the true population. Second, since the patients were not followed up for thyroid tests after hospital discharge, whether the abnormalities of thyroid function could get resolved with remission of diabetic conditions remains undefined. Third, due to the cross-sectional nature of this study, definite cause-and-effect relationships between TD and other abnormalities or factors could not be established. Therefore, our results should be interpreted with caution.

Conclusions

TD was not rare in patients with newly diagnosed T2DM. Low T3 syndrome was the most common subtype. Low FT3 level was strongly associated with diabetic complications including presence of DK or DKA and DN. Metabolic and demographic factors, including age, glycemic control and insulin resistance also correlated with levels of thyroid hormones. In the future, large prospective studies are needed to further investigate the prevalence of TD and to determine the association between TD and other factors in patients with T2DM.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Guangzhou University, Guangzhou, China. All procedures performed in the study were in accordance with the approved ethical standards and regulations. Informed consent was waived by the local ethics committee due to the retrospective nature of the study with no impact on health outcome.

Consent to publish

Not applicable.

Availability of data and material

The data used for analysis are available from the corresponding author on reasonable request.

Competing interests

All authors have no competing interests.

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Authors' contributions

XZ designed the study. XZ, YL, MY, XD, and YC collected the data. XZ, YL, and MY analyzed the data. XZ and WL wrote the manuscript. All authors have read and approved the final manuscript.

Acknowledgements

None.

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Abbreviations

AER: Albumin excretion rate; ANOVA: one-way analysis of variance; BMI: Body mass index; BP: Blood pressure; DK: Diabetic ketosis; DKA: Diabetic ketoacidosis; DM: Diabetes mellitus; DN: Diabetic nephropathy; eGFR: Estimated glomerular filtration rate; FPG: Free plasma glucose; FT3: Free triiodothyronine; FT4: Free thyroxine; HbA1c: Glycated hemoglobin; HDL-C: High-density lipoprotein cholesterol; HOMA-β: Homeostasis model assessment of β cell function; HOMA-IR: Homeostasis model assessment of insulin resistance; LDL-C: Low-density lipoprotein cholesterol; PG: Plasma glucose; SD: Standard deviation; T2DM: Type 2 diabetes mellitus; T3: Triiodothyronine; TD: Thyroid dysfunction; TC: Total cholesterol; TG, Triglyceride; TSH: Thyroid stimulating hormone; UACR, Urinary albumin-to-creatinine ratio

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Figures

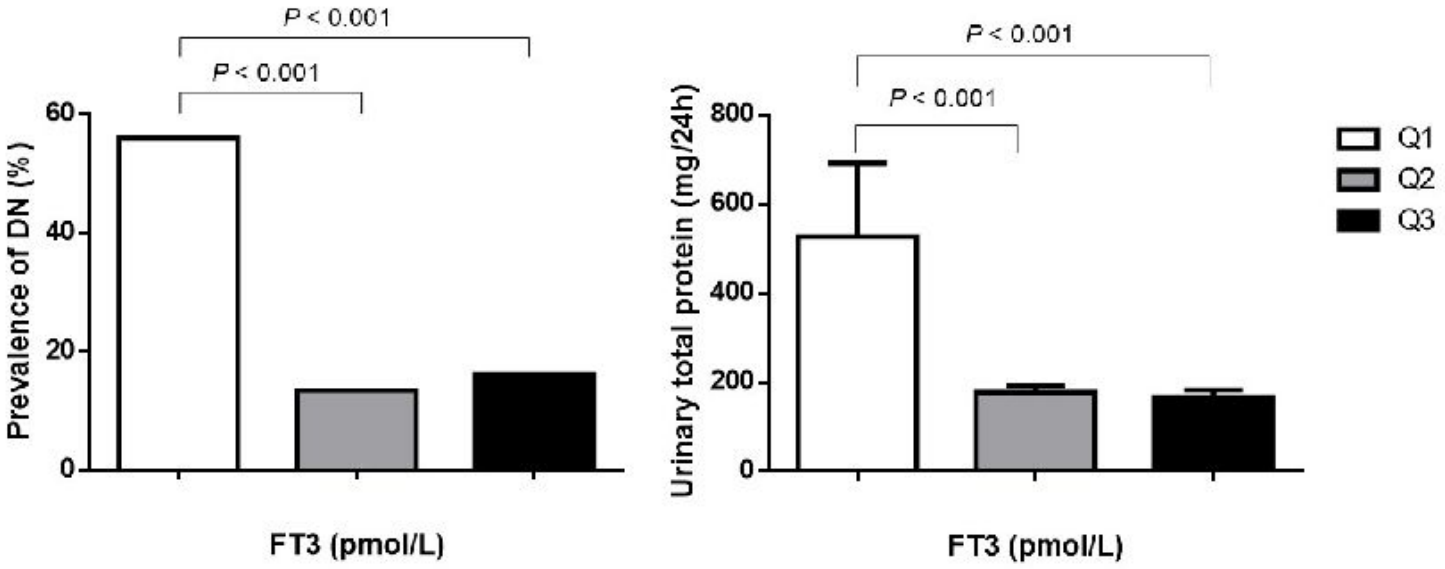

Figure 1

Prevalence of diabetic nephropathy and levels of urinary total protein in different FT3 quartiles. Quartile 1 (Q1, n = 109), 1.54 to < 3.26 pmol/L; Quartile 2 (Q2, n = 119), 3.26 to < 3.88 pmol/L; Quatile 3 (Q3, n = 112), 3.88 to ≤ 7.18 pmol/L.

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