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ORIGINAL ARTICLE

The prevalence and determinants of hypothyroidism in hospitalized patients with type 2 diabetes mellitus

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Abstract The purpose of this study was to investigate the prevalence of hypothyroidism among hospitalized patients with type 2 diabetes mellitus and its related factors, and to assess the prevalence of macrovascular and microvascular diseases among type 2 diabetes mellitus inpatients with hypothyroidism and euthyroidism. A total of 1662 type 2 diabetes mellitus inpatients hospitalized at the Metabolic Diseases Hospital, Tianjin Medical University from 1 January 2008 to 1 March 2013 were included in this study. Information on demographic and anthropometric factors and additional variables related to hypothyroidism were collected from medical records. Prevalence rates were calculated and standardized using direct method based on the age-specific and sex-specific structure of all participants. Data were analyzed using binary logistic regression with adjustment for potential confounders. The prevalence of hypothyroidism among type 2 diabetes mellitus inpatients was 6.8 %, and 77.0 % of the patients with hypothyroidism had subclinical hypothyroidism. The prevalence of hypothyroidism increased with age, and was higher in women (10.8 %) than in men (3.4 %). Older age (odds ratio, 1.74; 95 % confidence interval, 1. 05 to 2.89), female gender (odds ratio, 2.02; 95 % confidence interval, 1.05 to 3.87), and positive thyroid peroxidase antibody (odds ratio, 4.99; 95 % confidence interval, 2.83 to 8.79) were associated with higher odds of hypothyroidism among type 2 diabetes mellitus inpatients. The type 2 diabetes mellitus inpatients with hypothyroidism had higher prevalence of cerebrovascular diseases than those with euthyroidism after adjustment for age and gender. The prevalence of hypothyroidism among type 2 diabetes mellitus inpatients was 6.8 %, and most patients had subclinical hypothyroidism. Older age, female gender, and positive thyroid peroxidase antibody could be indicators for detecting hypothyroidism in type 2 diabetes mellitus inpatients.

Keywords Hypothyroidism · Type 2 diabetes mellitus · Related factor · Cross-sectional study

Introduction

Diabetes mellitus and thyroid disease are the two most common endocrine disorders in clinical practice, as metabolic abnormalities of insulin and thyroid hormones might influence one another [1]. Co-existence of type 2 diabetes mellitus (T2DM) and hypothyroidism is an emerging trend observed in clinical practice. Many studies reported that hypothyroidism was more prevalent in patients with T2DM [2, 3]. The overall prevalence of hypothyroidism in general population-screening surveys ranged from 2.1 to 9.5 % [4–6], while it ranged from 5.7 to 25.3 % in T2DM patients[7–10]. These differences can be explained by different diagnostic criteria for hypothyroidism, the degree of iodine intake, and the large diversity of population surveyed [11]. About 2-5 % of patients with subclinical hypothyroidism could progress to overt hypothyroidism per year if not treated [12] and be induced with adverse clinical consequence.

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Hypothyroidism frequently results from autoimmune destruction of thyroid follicles by auto-antibodies. Chubb et al. [13] demonstrated that anti-thyroid peroxidase antibody (anti-TPO) was independently associated with subclinical hypothyroidism in T2DM patients. Ishay et al. [14] also found that positivity for anti-thyroid antibody was significantly higher in patients with subclinical hypothyroidism than in euthyroid subjects. In addition, age, gender, and family history of thyroid disease have been considered as related factors for hypothyroidism in T2DM patients [10, 15]. However, the associations between hypothyroidism and smoking, lipoprotein levels, and duration of diabetes are inconclusive and conflicting [13, 15]. Therefore, further investigations are needed.

In this study, we aimed to investigate the prevalence of hypothyroidism, including subclinical hypothyroidism, among T2DM hospitalized patients and to assess its related factors in order to provide scientific basis for promoting early prevention of hypothyroidism in T2DM patients which would increase life quality and decrease healthcare costs.

Subjects and methods

Participants

The medical records of all T2DM patients ($n = 2613$) hospitalized at the Metabolic Diseases Hospital, Tianjin Medical University from 1 January 2008 to 1 March 2013 were reviewed. Among the 2613 T2DM hospitalized patients, 951 patients were excluded due to the lack of information about their thyroid function. Consequently, 1662 T2DM inpatients, 903 males and 759 females, were included in the present study. Informed consent was received from all participants. The ethical committee at Tianjin Medical University approved the study.

Data collection

Data information retrieved from the medical records included age, gender, lifestyle, medical histories, height, weight, blood pressure, and laboratory data. Age was classified into six categories, which were <30, 30–39, 40–49, 50–59, 60–69, and ≥70 years. Diabetic duration was categorized as <10, 10–19, and ≥20 years. Cigarette smoking (current smokers vs. former or nonsmokers) was dichotomized. Height and weight were measured in light clothes without shoes, and recorded to the nearest 0.1 cm or 100 g respectively. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Blood pressure was measured twice by using a mercury sphygmomanometer on the right brachial artery after a 5-min rest period and the mean value of the two readings was used as the final measure. Glycosylated hemoglobin (HbA1c) was measured using an ion-exchange high performance liquid chromatography. Serum total cholesterol (TC), triglyceride (TG) and low-density lipoprotein cholesterol (LDL-C) were measured by enzymatic method. High-density lipoprotein cholesterol (HDL-C) was calculated using the Friedwald's equation [16]. TC was categorized as ≤5.7 mmol/L and >5.7 mmol/L. TG was categorized as ≤1.71 mmol/L and >1.71 mmol/L. LDL-C was categorized as ≤3.1 mmol/L and >3.1 mmol/L. HDL-C was categorized as ≥1.1 mmol/L in males or ≥1.2 mmol/L in females, and <1.1 mmol/L in males or <1.2 mmol/L in females. Serum thyroid stimulating hormone (TSH), free thyroxine (FT4) and free triiodothyronine (FT3) were measured by electrochemiluminescence immunoassay and their normal references were defined as 0.27–4.2 μIU/mL, 12.0–22.0 pmol/L, and 3.25–6.80 pmol/L, respectively.

Definitions of hypothyroidism and T2DM

Subclinical hypothyroidism was defined as serum TSH > 4.2 μIU/mL and normal FT4 level (12.0–22.0 pmol/L). Overt hypothyroidism was defined as serum TSH > 4.2 μIU/mL and a low FT4 level (<12.0 pmol/L) [17].

T2DM was assessed as having previously been diagnosed with diabetes mellitus, or fasting plasma glucose ≥7.0 mmol/L or postprandial 2-h plasma glucose ≥11.1 mmol/L according to the WHO criteria (1999) [18].

Statistical analysis

Results were expressed as mean ± standard deviation for normal distributive variables or median (interquartile range) for skewed distributive variables. The characteristics of the participants among three groups were compared using Chi-square tests for categorical variables and one-way analysis of variance for continuous variables. Binary logistic regression analyses were performed to estimate the odds ratios (ORs) and 95 % confidence intervals (CIs) for hypothyroidism. Standardized estimates of prevalence were calculated by the direct method based on the age-specific and sex-specific structure of all participants. All statistical analyses were performed using IBM SPSS Statistics 20.0 (IBM Corp, New York, NY). $P < 0.05$ was considered statistically significant.

Results

Among the 1662 T2DM hospitalized patients, 113 had hypothyroidism, including 26 (23 %) with overt hypothyroidism and 87 (77 %) with subclinical hypothyroidism.

The total prevalence of hypothyroidism among the T2DM inpatients was 6.8 % and the prevalence in females (10.8 %) was much higher than that in males (3.4 %). The prevalence of overt hypothyroidism and subclinical hypothyroidism were 1.6 and 5.2 %, respectively. The prevalence of hypothyroidism increased with age in both men and women, but the patterns were different. In females, the prevalence of hypothyroidism increased rapidly till the age of 50–59 and increased tardily thereafter, while it increased tardily till the age of 60–69 and increased rapidly thereafter in males (Fig. 1).

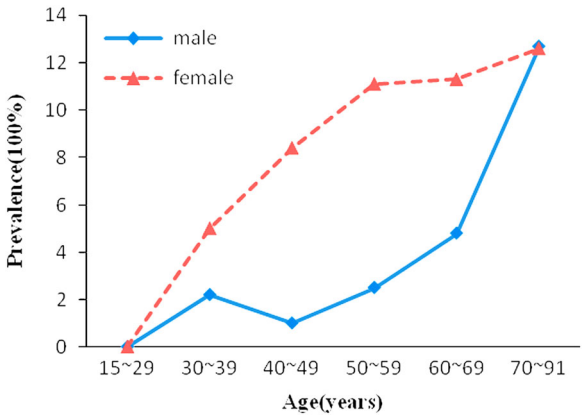

Fig. 1 Prevalence of hypothyroidism among inpatients with Type 2 diabetes mellitus by age and gender

The basic characteristics of the T2DM inpatients with hypothyroidism and euthyroidism are shown in Table 1. Compared to the euthyroid group, the inpatients in the overt hypothyroid group and subclinical hypothyroidism group were older, females were more represented, had a longer duration of diabetes, more patients were treated with insulin and were positive TPO-Ab, had higher serum TC, LDL-C, HDL-C and TSH levels, but less were smokers, had lower serum FT3 and FT4 levels (all $p < 0.01$). There was no significant difference among the three groups in terms of metformin treatment, serum HbA1c and TG levels, systolic blood pressure, diastolic blood pressure, and BMI (all $p > 0.05$).

The results of binary logistic regression analysis demonstrated that older age (OR, 1.74; 95 % CI, 1.05 to 2.89), female gender (OR, 2.02; 95 % CI, 1.05 to 3.87), and positive TPO-Ab (OR, 4.99; 95 % CI, 2.83 to 8.79) were

Table 1 Characteristics of type 2 diabetic inpatients with hypothyroidism and euthyroidism

Variables	Overt hypothyroidism ($n = 26$)	Subclinical hypothyroidism ($n = 87$)	Euthyroidism ($n = 1522$)	p value
Age (years)	61.6 ± 12.1	60.9 ± 9.4	55.6 ± 11.3	<0.001
Female (n, %)	19(73.1)	63(72.4)	663(43.6)	<0.001
Smoker (n, %)	8(30.8)	19(21.8)	693(45.5)	<0.001
Duration of diabetes (years)	8.5(2.0,13.5)	9.0(4.0,16.0)	6.0(2.0,12.0)	0.001
Insulin treatment (n, %)	15(57.7)	51(58.6)	698(45.9)	0.036
Metformin treatment (n, %)	15(57.7)	54(62.1)	853(56.0)	0.540
BMI (kg/m^2)	26.1 ± 2.8	26.5 ± 4.3	26.6 ± 4.0	0.816
SBP (mmHg)	134.1 ± 20.8	140.7 ± 20.6	136.0 ± 20.0	0.089
DBP (mmHg)	81.2 ± 10.0	78.9 ± 11.0	81.4 ± 11.1	0.105
HbA1c (mmol/L)	8.6 ± 1.9	8.4 ± 2.2	8.7 ± 2.1	0.490
TC (mmol/L)	5.7 ± 1.6	5.8 ± 1.8	5.2 ± 1.2	0.001
TG (mmol/L)	1.7 ± 0.9	2.5 ± 3.7	2.1 ± 1.7	0.093
HDL-C (mmol/L)	1.6 ± 0.4	1.5 ± 0.3	1.4 ± 0.4	0.013
LDL-C (mmol/L)	3.5 ± 1.2	3.6 ± 1.2	3.3 ± 1.0	0.005
TSH (μIU/mL)	12.7(8.0,53.2)	5.6(4.8,7.5)	1.4(1.0,2.0)	<0.001
FT3 (pmol/L)	3.2 ± 0.8	4.0 ± 0.6	4.4 ± 1.0	<0.001
FT4 (pmol/L)	9.2 ± 2.5	15.3 ± 2.1	17.1 ± 3.2	<0.001
Positive TPO-Ab (n, %)	14(53.8)	23(26.4)	108(7.1)	<0.001

Values are mean ± SD or, M(IQR) or n (%)

Abbreviations: *BMI* body mass index, *SBP* systolic blood pressures, *DBP* diastolic blood pressures, *HbA1c* glycosylated hemoglobin, *TC* total cholesterol, *TG* triglyceride, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *TSH* thyroid stimulating hormone, *FT3* free triiodothyronine, *FT4* free thyroxine

related to higher odds of hypothyroidism, but smoking, duration of diabetes, insulin treatment, metformin treatment, BMI, serum TC, and LDL-C levels were not associated with hypothyroidism among the T2DM inpatients after adjusting for possible confounding factors (Table 2).

Compared to the euthyroid group, the hypothyroid group had a higher prevalence of cardiovascular diseases (62.8 vs. 52.6 %) and cerebrovascular diseases (39.8 vs. 29.8 %). The differences in the prevalence of cardiovascular and cerebrovascular diseases between those two groups were statistically significant in females, but not in males. No significant difference in the prevalence of nephropathy and retinopathy were found between those two groups in both males and females (Table 3). The age- and gender-standardized prevalence of cerebrovascular diseases in hypothyroid group (40.9 %) was higher than in the euthyroid group (34.8 %) ($p < 0.05$), while the difference in the standardized prevalence of cardiovascular diseases between the two groups (51.0 vs. 53.5 %) was not statistically significant ($p > 0.05$).

Table 2 Factors and odds ratios (ORs) with 95 % confidence intervals (CIs) of prevalent hypothyroidism among inpatients with type 2diabetes mellitus

Factors	Unadjusted OR(95 % CI)	Adjusted[a] OR(95 % CI)
Age(years)	2.11(1.52,2.91)	1.74(1.05,2.89)
Female gender	3.43(2.24,5.25)	2.02(1.05,3.87)
Cigarette smoking	0.38(0.24,0.59)	0.46(0.19,1.12)
Duration of diabetes (years)	1.62(1.23,2.12)	0.93(0.60,1.46)
Insulin treatment	1.66(1.13,2.44)	1.15(0.65,2.03)
Metformin treatment	1.23(0.83,1.82)	1.22(0.69,2.16)
BMI (kg/m^2)	0.92(0.77,1.09)	1.03(0.81,1.30)
Serum TC > 5.7 mmol/L	1.67(1.11,2.51)	0.72(0.35,1.48)
Serum LDL-C > 3.1 mmol/L	1.76(1.16,2.68)	1.73(0.85,3.51)
Positive TPO-Ab	5.91(3.64,9.61)	4.99(2.83,8.79)

[a] Adjusting for other factors in this table

Discussion

In this study, we found that: (1) The prevalence of hypothyroidism was 6.8 % among hospitalized patients with T2DM, and that 77.0 % of these patients had subclinical hypothyroidism; (2) The prevalence of hypothyroidism increased with age, and was higher in women (10.8 %) than in men (3.4 %); (3) Older age, female gender, and positive TPO-Ab were associated with the higher odds of hypothyroidism among T2DM inpatients; (4) The T2DM patients with hypothyroidism had a higher prevalence of cerebrovascular diseases than those with euthyroidism after adjustment for age and gender.

Knudsen et al. found that the prevalence of hypothyroidism in the general population was 2.1 % [6]. A community-based study [4] in Nanjing, China reported that the prevalence of hypothyroidism in the general population was 4 %. However, thyroid dysfunction was more common in diabetic population than in the general population [2, 3, 19]. A study in South Africa reported that the prevalence of primary hypothyroidism in T2DM patients was 11.8 % (22.5 % in females and 5.4 % in males) [8]. A cross-sectional study in Taiwan, China reported that the prevalence of hypothyroidism among persons diagnosed with T2DM was 10.3 % [20]. Similarly, in Changsha, China, the prevalence of subclinical hypothyroidism in diabetic patients was 18.8 % [21]. A cross-sectional study demonstrated that the prevalence of hypothyroidism among the 411 T2DM patients was 25.3 % [10]. The present study showed that 6.8 % of the T2DM inpatients had hypothyroidism. Insulin resistance has been suggested as an essential

Table 3 The prevalence of macrovascular and microvascular diseases in hypothyroid and euthyroid groups in type 2 diabetic inpatients by gender

Gender	Groups	Macrovascular diseases				Microvascular diseases			
		Cardiovascular disease		Cerebrovascular disease		Nephropathy		Retinopathy	
		n (%)	*p* value	*n* (%)	*p* value	*n* (%)	*p* value	*n* (%)	*p* value
Male	Hypothyroidism	13(41.9)	0.53	10(32.3)	0.54	14(45.2)	0.11	5(16.1)	0.92
	Euthyroidism	406(47.3)		247(28.8)		278(32.4)		142(16.5)	
Female	Hypothyroidism	58(70.7)	0.04	35(42.7)	0.02	27(33.0)	0.13	15(18.3)	0.82
	Euthyroidism	394(59.4)		207(31.2)		170(25.6)		128(19.3)	
Total	Hypothyroidism	71(62.8)	0.03	45(39.8)	0.01	41(36.3)	0.09	20(17.7)	0.93
	Euthyroidism	800(52.6)		454(29.8)		448(29.4)		270(17.7)	

mechanism responsible for the deregulation of the thyroid hormones and the development of type 2 diabetes [22]. Thyroid hormones abnormalities described in patients with diabetes were related not only to glycemic control, but also to the increased inflammatory activity [23]. Some studies also suggested that high leptin level in diabetic patients might stimulate synthesis of TSH by affecting the hypothalamic-pituitary-thyroid axis via Janus activating kinase/signal transduction and activation of transcription (STAT) 3 factor in vitro and in vivo [24–26].

In addition, subclinical hypothyroidism accounts for a large proportion of hypothyroid patients observed in our study. Perros et al. found that the prevalence of subclinical hypothyroidism was the highest in abnormal thyroid function [27]. Another cross-sectional study among Taiwanese T2DM patients also demonstrated that 61 % of the patients with hypothyroidism had subclinical hypothyroidism [20]. Subclinical hypothyroidism is often undiagnosed because of its unnoticeable symptoms. However, it represents mild thyroid failure and has adverse clinical consequence. Some studies suggested that T2DM patients with subclinical hypothyroidism had a high prevalence of cardiovascular, cerebrovascular diseases [20, 28–30] and nephropathy [20, 31]. Hence, screening subclinical hypothyroidism every 6 months among diabetic patients has an important role in improving their quality of life [32]. A study in Fremantle [13] has found that the patients with subclinical hypothyroidism did not have progressive thyroid disease if regular screening and active intervention are made available to them.

Aging is a risk factor for hypothyroidism in the general population as well as in T2DM patients [33]. A study [34] revealed that the prevalence of hypothyroidism was 5 and 21 % among American Indian females aged <60 and ≥60, respectively. A cross-sectional study has shown that female gender, family history of thyroid disease, and smoking can increased the odds of hypothyroidism in diabetic patients [1]. Giandalia et al. also found that diabetic women had lower FT4 and higher TSH serum levels as compared to diabetic men [35]. Autoimmunity against the thyroid gland is one of the most important causes for hypothyroidism. A retro-prospective cohort study [36] between September 1987 and January 1994 observed that 17 out of the 25 diabetic patients with positive TPO-Ab had developed hypothyroidism, while only 1 out of the 151 diabetic patients with negative TPO-Ab developed hypothyroidism. Diez et al. [37] also found that high positive rate of TPO-Ab was associated with hypothyroidism in T2DM patients. In the present study, we found that older age, female gender, and positive TPO-Ab could increase odds of hypothyroidism in T2DM patients. Therefore, we recommend that regular health check-ups and early intervention should be conducted among elderly female T2DM patients, especially the ones with positive TPO-Ab.

A 4-year longitudinal study in Taiwan, China demonstrated that T2DM patients with subclinical hypothyroidism had an increased risk of cardiovascular diseases and nephropathy, but not retinopathy [20]. However, a meta-analysis [38] showed that cardiovascular disease was not associated with subclinical hypothyroidism in T2DM patients. Furukawa et al. [39] found that subclinical hypothyroidism may be independently associated with diabetic nephropathy among Japanese T2DM patients. Our study observed that there was a higher prevalence of cerebrovascular diseases in the hypothyroid group compared to the euthyroid group, even after adjustment for age and gender. This finding could not be explained by the differences in age and gender between the two groups. It is not to be excluded that hypothyroidism and cerebrovascular diseases might share common risk factors. However, causal relationships of hypothyroidism and cerebrovascular diseases were unclear because of the cross-sectional design of our study.

The key strength of this study was the excellent possibility of comparison between the cases and controls as being from the same population. Furthermore, data on clinical examination for all participants was complete due to the use of the inpatient medical records. Some limitations in the present study need to be addressed. First, patients with diabetes were more likely to develop the low-T3 syndrome and the latter was more susceptible to hypothyroidism in severe illness [23, 40], so the association between hypothyroidism and some factors could have been underestimated in our study due to using T2DM hospitalized patients at a clinical setting. In addition, the participants of this study were T2DM patients, who hospitalized in one particular hospital and had the thyroid function evaluated, not entirely representative of the general T2DM patient population, so the selection bias could not be avoided. Second, iodine excess and deficiency were both found to be associated with thyroid dysfunction [41]; however, neither iodine intake nor urinary iodine level were available in our study. Thus, an insufficient iodine intake responsible for thyroid dysfunction in these patients cannot be excluded. Third, the temporality of the given associations was unclear because of the cross-sectional design of this study. Further studies are warranted.

In summary, the prevalence of hypothyroidism was 6.8 % among T2DM inpatients, and most had subclinical hypothyroidism. Older age, female gender, and positive TPO-Ab were associated with higher odds of hypothyroidism in T2DM inpatients, and patients with hypothyroidism had a higher prevalence of cerebrovascular diseases, especially among females. Therefore, regular testing of thyroid function and early intervention should be recommended in elderly female T2DM patients, especially among those who with positive TPO-Ab. Prospective cohort studies should be

carried out to determine the possible causal relationship between hypothyroidism and cerebrovascular diseases.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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