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Association of subtle alterations in thyroid function with presarcopenia in patients with type 2 diabetes mellitus

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ABSTRACT

Aims/Introduction: To investigate the association of subtle alterations in thyroid function with presarcopenia among patients with type 2 diabetes mellitus.

Materials and Methods: A total of 1,865 adult patients with type 2 diabetes mellitus were enrolled in this cross-sectional study, excluding patients with overt thyroid dysfunction. Skeletal muscle mass measured by dual energy X-ray absorptiometry was used to assess presarcopenia. Logistic regression models were used to estimate the effects of thyroid hormones on presarcopenia, and subgroup analyses were carried out in different strata of age, sex and body mass index, respectively.

Results: Compared with the euthyroid group (Euthy), the subclinical hyperthyroidism group had an increased odds of presarcopenia (multivariate-adjusted odds ratio 1.99, 95% confidence interval 1.09–3.63), but the subclinical hypothyroidism group did not ($P > 0.05$). In the subclinical hyperthyroidism group, age and body mass index <24 kg/m^2 were independent risk factors for presarcopenia. In the overall Euthy group, an increased odds of presarcopenia was correlated with the elevated free thyroxine : free triiodothyronine ratio (all P for trend <0.05), whereas not with increment in free triiodothyronine level (P for trend >0.05). Additionally, in Euthy subgroup analyses stratified by middle-age, sex and body mass index, a similar association was noted (all P for trend <0.05), but not in the older-aged patients (P for trend >0.05).

Conclusions: Subclinical hyperthyroidism was an independent risk factor for presarcopenia in patients with type 2 diabetes mellitus, but subclinical hypothyroidism was not. In the Euthy group with type 2 diabetes mellitus, a high free thyroxine : free triiodothyronine ratio was a good index of presarcopenia in addition to older age.

INTRODUCTION

Sarcopenia is emerging as one of the leading geriatric diseases, affecting 50 million people worldwide, and this figure is expected to increase to 500 million people by 2050[1]. It is defined as a progressive loss of skeletal muscle mass, strength or function with aging. This geriatric disease is associated with adverse outcomes, including frailty, falls, fractures and vascular diseases[2–6]. Presarcopenia is a new definition proposed in 2010 by the European Working Group on Sarcopenia in Older People (EWGSOP, the Sarcopenia Working Group)[7]. It corresponds to the preliminary stage of sarcopenia and is characterized by low muscle mass without impact on muscle strength or physical performance.

The etiology and mechanisms of sarcopenia or presarcopenia are multifactorial. Type 2 diabetes mellitus is a common cause of sarcopenia, with the risk of sarcopenia being threefold higher compared with individuals without diabetes[8]. Certain features, including age, sex, body mass index (BMI), glycemic control and a high body fat percentage are risk factors for sarcopenia in diabetes patients[9–12]. Nevertheless, other causes of sarcopenia in patients with type 2 diabetes mellitus are not well established. As is known, overt thyroid dysfunction have been proposed as a predisposing factor for sarcopenia[13]. Whether subclinical thyroid dysfunction or variation in euthyroid condition is a contributing factor to sarcopenia remains controversial,

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and data regarding patients with type 2 diabetes mellitus are scarce. Previous studies had reported a decline in muscle cross-sectional area in patients with subclinical hyperthyroidism (SCHyper) compared with patients with euthyroidism (Euthy), and a favorable effect was found on skeletal muscle area or mass after anti-thyroid treatment, as it improved significantly after treatment[13,14]. However, skeletal muscle mass was comparable between individuals with SCHyper and those with euthyroidism in another cross-sectional analysis[15]. Another study in Korea reported that subclinical hypothyroidism (SCHypo) had little influence on muscle mass[16], and hormone replacement therapy in patients with SCHypo provided no apparent benefits in terms of muscle tissue mass[17].

Recently, increasing attention has also been paid to the effects of normal concentrations of thyroid hormones (THs) on skeletal muscle parameters. Several studies have shown that even subtle variations in the euthyroid range might contribute to sarcopenia. Sheng *et al.*[18] showed that a higher normal free triiodothyronine (T3) concentration was positively associated with skeletal muscle mass in older Chinese euthyroid individuals. However, in healthy male siblings with euthyroidism, there was an inverse association between muscle cross-sectional area and free T3 (FT3) and free thyroxine (FT4)[19]. Another cross-sectional study found that a low FT3 : FT4 ratio was a better index of sarcopenia compared with serum FT3 or FT4 alone in a community-dwelling older population[20]. As aforementioned, the potential role of subtle thyroid variations in presarcopenia or sarcopenia is not entirely clear in the aging population; in particular, few data are available in patients with type 2 diabetes mellitus. The aim of the present study was to verify the association between subtle variations in thyroid function and presarcopenia among adult patients with type 2 diabetes mellitus, and to determine the risk factors according to different demographic anthropometric parameters (age, sex, BMI).

MATERIALS AND METHODS

Study participants

The present cross-sectional study examined 5,875 patients with a diagnosis of type 2 diabetes mellitus at discharge from the Department of Endocrinology and Metabolic Diseases, Tianjin Medical University General Hospital, Tianjin, China, between January 2013 and July 2019. A flow diagram schematizing the selection strategy is presented in Figure 1. The study was approved by the institutional review board of Tianjin Medical University General Hospital, and carried out in accordance with the Helsinki Declaration in 1995 (as revised in Fortaleza, Brazil, October 2013). The requirement to obtain informed consent was waived (approval number: IRB2020-YX-027-01), because we used an electronic dataset compiled from medical records from the Department of Endocrinology and Metabolism. This dataset did not contain personally identifiable information, except for date of birth.

Clinical data collection and measurement

Clinical data, including sociodemographic characteristics (age, sex, smoking status, alcohol consumption), anthropometric measurements (bodyweight, height) and clinical profile (type 2 diabetes mellitus duration, complications, hypertension, hyperlipidemia and medication [e.g., glucose-lowering drugs, lipid-lowering drugs]), were collected using a standardized electronic inpatient medical record data collection form. All blood samples were drawn on the morning after admission after at least 10 h of fasting. Plasma glucose, glycated hemoglobin, triglyceride, total cholesterol, low-density lipoprotein and high-density lipoprotein were assessed. Hyperlipidemia was defined as a total cholesterol concentration of ≥5.17 mmol/L, a triglyceride concentration of ≥1.7 mmol/L, a low-density lipoprotein concentration of >3.37 mmol/L or a history of hyperlipidemia[21]. Serum FT3 and FT4, and serum thyroid-stimulating hormone (TSH) concentrations were measured using chemiluminescence immunoassay and expressed as pmol/L, pmol/L and mIU/L, respectively. The normal concentration ranges of FT3, FT4 and TSH were 3.5–6.5 pmol/L, 11.5–22.7 pmol/L and 0.55–4.78 mIU/L, respectively. Participants were stratified into three categories as follows: SCHypo (TSH concentration of >4.78 mIU/L, normal FT4, normal FT3); SCHyper (TSH concentration of <0.55 mIU/L, normal FT4, normal FT3); or euthyroidism (normal TSH, FT4, FT3). Skeletal muscle mass was estimated by dual energy X-ray absorptiometry using a Prodigy-GE densitometer (GE Healthcare, Chicago, IL, USA). Measurements were carried out by trained technicians using standardized procedures recommended by GE Healthcare.

Diagnostic criteria

Skeletal muscle mass was estimated by the skeletal muscle mass index (SMI) using appendicular lean mass divided by the square of height (kg/m^2), measured by dual energy X-ray absorptiometry using a Prodigy-GE densitometer (GE Healthcare, Chicago, IL, USA). Presarcopenia was defined as SMI <7.0 kg/m^2 in men and <5.4 kg/m^2 in women according to cut-off values from the Asian Working Group for Sarcopenia[22]. BMI was calculated as weight divided by the square of height (kg/m^2). Overweight/obesity was determined by BMI according to the Working Group on Obesity in China 2003[23]. Obesity was defined as a BMI of ≥28 kg/m^2, and overweight was defined as 24.0 $kg/m^2 \leq$ BMI < 28 kg/m^2. Participants were classified into middle-aged (40–64 years) and older-aged (≥65 years) subgroups.

Statistical analysis

Population characteristics are expressed as the mean ± standard deviation or median (interquartile range) for continuous variables, and number (percentage) for categorical variables. Frequencies of presarcopenia in different thyroid function states are presented based on age, sex and BMI, respectively. Characteristics of participants in groups (SCHypo/SCHyper vs Euthy) were compared using Dunnett's *t*-test ($P < 0.05$ was significant)

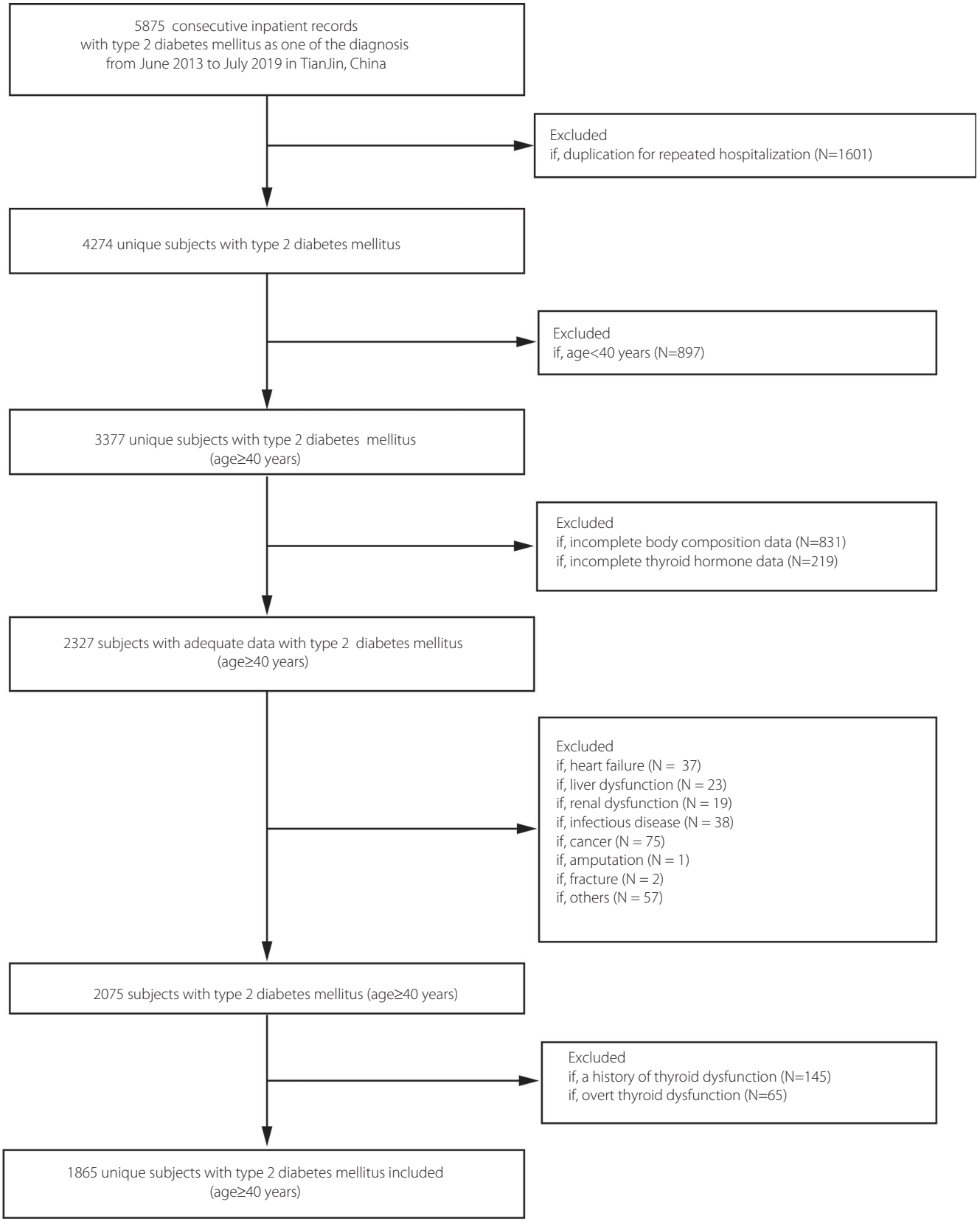

Figure 1 | A flow diagram schematizing the selection strategy.

when appropriate, otherwise, using the χ^2-test and Wilcoxon rank-sum test with Bonferroni correction ($P < 0.025$ was significant). Differences in SMI between quartile 2–4 and quartile 1 of normal THs were analyzed using ANOVA and Dunnett's *t*-test ($P < 0.05$ was significant). Multivariate logistic regression models were used to estimate the effects of subclinical thyroid dysfunction on the odds of presarcopenia, identify independent risk factors, and subgroup analyses stratified by age, sex and BMI, respectively. To further investigate the correlation between euthyroidism and presarcopenia, we divided serum FT3, FT4 and TSH into quartiles, and carried out logistic regression analyses in subgroups stratified by age, sex and BMI, respectively. All analyses were adjusted for potential (covariates were significantly different between the subclinical thyroid dysfunction group and euthyroid group, and were also significantly associated with presarcopenia [$P < 0.1$]) and plausible confounders (such as age, sex, BMI and so on). These analyses were carried out using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 3.6.2 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

In the present study, we enrolled 1,865 Chinese patients with type 2 diabetes mellitus with a mean age of 61.13 ± 9.41 years (50.2% women; 64.7% middle-aged). The prevalence of presarcopenia in the general, middle-aged and older-aged patients was 11.0%, 8.7% and 15.2%, respectively. The characteristics of participants in the three groups are shown in Table 1. Compared with the Euthy group, participants with SCHypo were significantly older, predominantly women, and had lower rates of current smoking and alcohol consumption. However, there were no differences observed in the prevalence of presarcopenia. In contrast, SCHyper individuals had a higher prevalence of presarcopenia with younger age and a lower BMI value, but less use of sulfonylurea than the Euthy group.

The presarcopenia distributions in the three thyroid subgroups (age, sex and BMI) are presented in Table 2. The SCHyper group had the highest prevalence of presarcopenia, with 19.5% of the middle-aged participants, 22.6% of men and 43.2% of patients with BMI <24 kg/m^2, respectively. Logistic regression models were used to clarify the association between SCHyper/SCHypo and presarcopenia (Table 3). SCHyper was positively correlated with presarcopenia (crude odds ratio [OR] 1.96, 95% confidence interval [CI] 1.19–3.22, $P < 0.01$). After adjusting for confounders (age, sex, smoking, alcohol, duration, obesity subgroup, hypertension, hyperlipemia, glycated hemoglobin, insulin, metformin, sulfonylureas, dipeptidyl peptidase inhibitors, antihyperlipidemia drugs), this positive association remained significant (adjusted OR 1.99, 95% CI 1.09–3.63, $P = 0.03$). However, the SCHypo group was not observed to have a correlation (adjusted OR 1.16, 95% CI 0.58–2.29, $P = 0.68$).

Multivariate logistic regression was carried out to identify the independent risk factors for presarcopenia in patients with SCHyper (Table S1). As shown in Table S1, the first three demographic parameters with statistical significance were age, sex and BMI in the SCHyper group. Age was an independent risk factor for presarcopenia (adjusted OR 1.06, 95% CI 1.04–1.09, $P < 0.01$), whereas BMI was an independent protective factor for presarcopenia (adjusted OR 0.07, 95% CI 0.05–0.10, $P < 0.01$), as well as female sex (adjusted OR 0.27, 95% CI 0.18–0.41, $P < 0.01$). In the further subgroup analyses stratified by age, sex and BMI, respectively (Figure 2), middle-age was positively associated with higher odds of presarcopenia (adjusted OR 2.37, 95% CI 1.14–4.91), as well as BMI <24 kg/m^2 (adjusted OR 2.10, 95% CI 1.05–4.22). However, sex difference was not observed ($P > 0.05$).

To investigate the association of thyroid hormones with presarcopenia, we carried out logistic regression models with thyroid hormones as quartiles in the Euthy group, but not in the SCHypo and SCHyper groups due to their small sample sizes. The data of SMI in the euthyroid group were divided into four groups according to quartiles of thyroid hormones (Table S2). The results showed that there were significant differences in SMI among quartiles of FT3 or FT4 : FT3 ratios in the euthyroid patients with type 2 diabetes mellitus (both $P < 0.01$), but no differences were observed across quartiles of FT4 and TSH. Furthermore, SMI seemed to have an increasing tendency across quartiles of FT3, whereas a declining trend across quartiles of FT4 : FT3 ratios. Consistently, in adjusted logistic regression models, an elevated FT4 : FT3 ratio was correlated with increased odds of presarcopenia (P for trend <0.05), whereas the correlation was not in FT3 level increment (P for trend >0.05; Table 4).

The adjusted correlations between normal thyroid hormones and presarcopenia in euthyroid patients with type 2 diabetes mellitus are shown in Table 4. There was no association between normal thyroid hormones and presarcopenia noted in the older-aged patients (P for trend >0.05). However, in the overall euthyroid group, an increased odds of presarcopenia was correlated with an elevated FT4 : FT3 ratio (all P for trend<0.05), whereas not with an increment in the FT3 level (P for trend >0.05). Additionally, in the euthyroid subgroup analyses stratified by middle-age, sex and BMI, a similar association was noted (all P for trend <0.05), but not in the older-aged patients (P for trend >0.05). Notably, women had a pronounced association in the highest quartile of FT4 : FT3 ratios with the odds for presarcopenia 4.9-fold higher than that in the first quartile 1 (adjusted OR 4.90, 95% CI 1.28–17.76). In addition, patients with BMI <24 kg/m^2 also had an inverse correlation between TSH level and odds of presarcopenia (P).

DISCUSSION

In the present study, we first evaluated the association between subtle variation in thyroid function and presarcopenia among patients with type 2 diabetes mellitus. The major finding was that the SCHyper group had a higher prevalence of presarcopenia than the Euthy group, and it was correlated with

Table 1 | Patient characteristics according to thyroid function

	SCHypo (n = 126)	Euthy (n = 1,626)	SCHyper (n = 113)	$P^{‡}$	$P^{§}$
Age, years (mean ± SD)	64.21 ± 9.80	60.97 ± 9.39	59.99 ± 8.60	**<0.01***	**0.48**
Female, *n* (%)	82 (65.1)	795 (48.9)	60 (53.1)	<0.01†	0.39
Presarcopenia, *n* (%)	14 (11.1)	170 (10.5)	21 (18.6)	0.82	<0.01†
SMI, kg/m^2 (mean ± SD)	7.06 ± 1.05	7.29 ± 1.11	7.02 ± 1.27	**0.05**	0.02†
BMI, kg/m^2 (mean ± SD)	26.76 ± 4.16	26.68 ± 3.94	25.30 ± 3.93	**0.97**	<0.01†
Median duration, months (IQR)	120 (48–216)	120 (60–204)	120 (48–189)	**0.80**	**0.80**
Smoking status, *n* (%)	27 (21.4)	557 (34.3)	35 (31.0)	<0.01†	0.48
Alcohol consumption, *n* (%)	16 (12.7)	401 (24.7)	22 (19.5)	<0.01†	0.21
FT3, pmol/L (mean ± SD)	4.28 ± 0.64	4.45 ± 0.52	4.66 ± 1.25	<0.01†	<0.01†
FT4, pmol/L (median ± SD)	14.18 ± 1.79	15.20 ± 2.07	16.27 ± 2.81	<0.01†	<0.01†
TSH, mIU/mL (median ± SD)	7.37 ± 3.03	2.03 ± 0.94	0.27 ± 0.19	<0.01†	<0.01†
Fasting glucose (mmol/L)	8.11 ± 3.61	8.33 ± 3.40	8.01 ± 3.35	**0.73**	**0.56**
HbA1c, % (median ± SD)	8.09 ± 1.74	8.31 ± 1.88	8.23 ± 1.83	**0.39**	**0.89**
Hyperlipidemia, *n* (%)	113 (89.7)	1392 (85.6)	91 (80.5)	0.21	0.14
Hypertension, *n* (%)	72 (57.1)	1009 (62.1)	58 (51.3)	0.27	**0.03***
Overweight/obesity, *n* (%)	94 (74.6)	1235 (76.0)	69 (61.1)	0.73	<0.01†
Drug therapy					
Insulin, *n* (%)	87 (69.1)	1156 (92.5)	80 (73.5)	0.63	0.59
OADs, *n* (%)	112 (88.9)	1504 (92.5)	103 (91.2)	0.15	0.60
MET, *n* (%)	57 (45.2)	879 (54.1)	52 (46.0)	0.06	0.10
SUD, *n* (%)	28 (22.2)	436 (26.8)	19 (16.8)	0.26	0.01†
GLIN, *n* (%)	16 (12.7)	203 (12.5)	16 (14.2)	0.94	0.60
GSD, *n* (%)	92 (73.0)	1216 (74.8)	84 (74.3)	0.66	0.92
TZD, *n* (%)	3 (2.4)	72 (4.4)	3 (2.7)	0.27	0.40
DPP4I, *n* (%)	1 (0.8)	64 (3.9)	1 (0.9)	0.08	0.12
SGLT2I, *n* (%)	–	2 (0.1)	1 (0.9)	0.69	0.18
GLP1AD, *n* (%)	–	38 (2.3)	3 (2.7)	0.10	0.75
LIPD, *n* (%)	57 (45.2)	765 (47.1)	30 (26.6)	0.70	<0.01†

BMI, body mass index; DPP4I, dipeptidyl peptidase-4 inhibitor; FT3, free triiodothyronine; FT4, free thyroxine; GLIN, glinides; GLP1RA, glucagon-like peptide-1 receptor agonist; GSD, α-glycosidase inhibitors; HbA1c, glycated hemoglobin; IQR, interquartile range; LIPD, antihyperlipidemic drug; MET, metformin; OAD, oral antidiabetic drug; SD, standard deviation; SMI, skeletal muscle mass index; SUD, sulfonylureas; TSH, thyroid-stimulating hormone; TZD, thiazolidinone. *$P < 0.05$ was significant (P values in bold font calculated by Dunnett t-test). †$P < 0.025$ was significant (P-value in regular font calculated by χ^2-test or Wilcoxon rank-sum test). ‡Comparison between patients with subclinical hypothyroidism and patients with euthyroidism. §Comparison between patients with subclinical hyperthyroidism and patients with euthyroidism.

Table 2 | Frequencies (%) of presarcopenia in different thyroid subgroups

	SCHypo (%)	Euthy (%)	SCHyper (%)
Age			
<65 years	5/64 (7.8)	85/1066 (8.0)	15/77 (19.5)
≥65 years	9/62 (14.5)	85/560 (15.2)	6/36 (16.7)
Sex			
Male	8/44 (18.2)	125/831 (15.0)	12/53 (22.6)
Female	6/82 (7.3)	45/795 (5.7)	9/60 (15.0)
BMI			
<24 kg/m^2	11/32 (34.4)	124/391 (31.7)	19/44 (43.2)
≥24 kg/m^2	3/94 (3.2)	46/1235 (3.7)	2/69 (2.9)

BMI, body mass index; Euthy, euthyroidism; SCHyper, subclinical hyperthyroidism; SCHypo, subclinical hypothyroidism.

Table 3 | Association between subclinical thyroid dysfunction and presarcopenia

	Crude		Adjusted†	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Euthy	Ref	–	Ref	–
SCHypo	1.07 (0.60–1.91)	0.82	1.16 (0.58–2.29)	0.68
SCHyper	1.96 (1.19–3.22)	<0.01*	1.99 (1.09–3.63)	0.03*

CI, confidence interval; Euthy, euthyroidism; OR, odds ratio; Ref, reference; SCHyper, subclinical hyperthyroidism; SCHypo, subclinical hypothyroidism. *$P < 0.05$. †Adjusted for age, sex, smoking, alcohol, duration, glycated hemoglobin (HbA1c), obesity subgroup, hypertension, hyperlipemia, insulin, metformin, sulfonylureas, dipeptidyl peptidase-4 inhibitor and antihyperlipidemic drug.

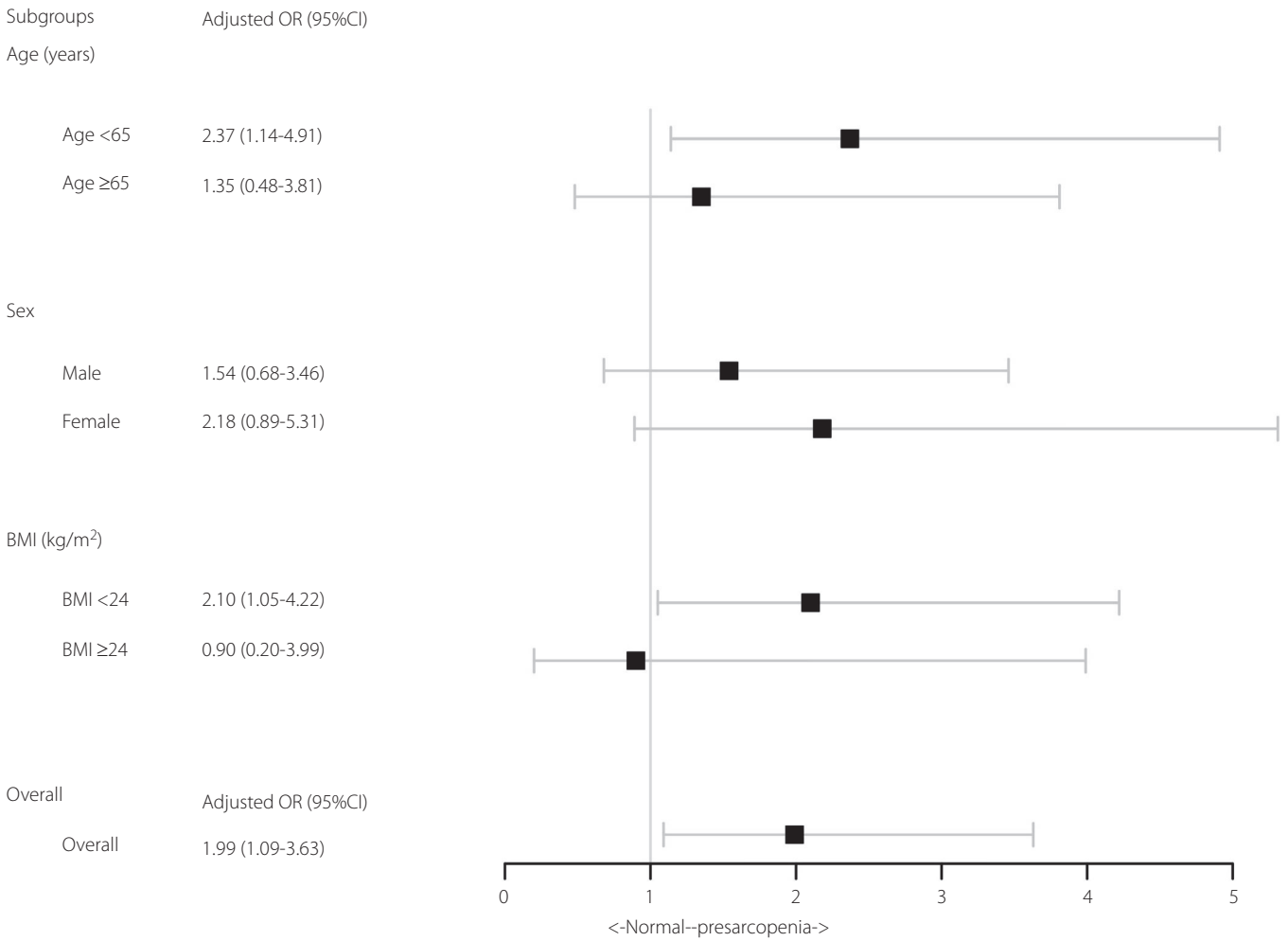

Figure 2 | Adjusted odds ratios (ORs) for subclinical hyperthyroidism associated with presarcopenia in type 2 diabetes mellitus patients across subgroups. BMI, body mass index; CI, confidence interval.

presarcopenia. In the SCHyper group, age and BMI <24 kg/m^2 were independent high-risk factors for presarcopenia.

THs play a critical role for sarcopenia with aging[24]. Overt hyperthyroidism has been proposed as a risk factor for sarcopenia[13]; however, whether the association likewise exists in subclinical thyroid dysfunction is not well illustrated. Several population-based studies have been carried out,[16,25,26] and they are likely applicable for the general population or community-dwelling older adults. In one large prospective cohort study of >1,000 community-dwelling older men, the authors found an increased risk of sarcopenia at baseline among individuals with SCHyper (65–74 years), but not in the prospective analyses[25]. In contrast, Ceresini *et al.*[15] showed that the skeletal muscle mass (calf muscle cross-sectional area) was comparable between SCHyper and Euthy participants among the elderly men and women. Another study from the Korean Longitudinal Study on Health and Aging (KLoSHA) showed that SCHypo was not related with presarcopenia in the elderly[16]. Recently, a large-scale cohort study of 6,974 participants from Brazil reported that neither SCHyper and SCHypo were associated with presarcopenia[26]. These conflicting results can be explained by the diverse study designs, populations and clinical settings, as well as varying diagnostic criteria. In the present analyses, SCHyper had a positive correlation with high odds of presarcopenia. Middle-age was considered as one impressive risk factor for presarcopenia in the SCHyper group. In addition, a low BMI was another risk factor. These appeared to be in line with the characteristics of relative hyperthyroid status.

Another important finding was that among euthyroid patients with type 2 diabetes mellitus, a high FT4 : FT3 ratio was associated with an increased risk of presarcopenia in addition to the older-aged participants, and the odds ratio was more pronounced in women. This was in contradiction with previous studies in aged populations. Roef *et al.*[19] found that free and total T3 and T4 were all inversely associated with muscle mass in young euthyroid men. Other studies showed

Table 4 | Adjusted relationships of thyroid hormone concentration quartiles with presarcopenia among type 2 diabetes mellitus patients with euthyroidism

	Quartiles				*P* for trend
	1	2	3	4	
Total euthyroid population					
FT3, pmol/L (range)	<4.03	4.03–4.40	4.40–4.81	>4.81	–
Adjusted	1.00 (Reference)	0.97 (0.57–1.64)	0.71 (0.42–1.20)	0.67 (0.38–1.19)	0.1
FT4, pmol/L (range)	<13.53	13.53–15.00	15.00–16.55	>16.55	–
Adjusted	1.00 (Reference)	1.57 (0.88–2.80)	1.38 (0.77–2.49)	2.27 (1.29–3.98)*	<0.01
TSH, mIU/mL (range)	<1.25	1.25–1.85	1.85–2.78	>2.78	–
Adjusted	1.00 (Reference)	1.07 (0.65–1.78)	1.21 (0.72–2.01)	0.59 (0.32–1.10)	0.24
FT4 : FT3 ratios	<3.07	3.07–3.39	3.39–3.77	>3.77	–
Adjusted	1.00 (Reference)	1.88 (1.02–3.47)*	2.67 (1.49–4.77)*	2.65 (1.47–4.79)*	<0.01
Age					
Age <65 years					
FT3, pmol/L (range)	<4.03	4.03–4.40	4.40–4.81	>4.81	–
Adjusted	1.00 (Reference)	1.15 (0.51–2.60)	0.78 (0.36–1.70)	0.71 (0.32–1.58)	0.25
FT4, pmol (range)	<13.53	13.53–15.00	15.00–16.55	>16.55	–
Adjusted	1.00 (Reference)	0.85 (0.35–2.34)	1.07 (0.47–2.46)	1.89 (0.86–4.12)	0.05
TSH, mIU/mL (range)	<1.25	1.25–1.85	1.85–2.78	>2.78	–
Adjusted	1.00 (Reference)	1.14 (0.56–2.31)	1.47 (0.73–2.98)	0.48 (0.19–1.21)	0.42
FT4 : FT3 ratios	<3.07	3.07–3.39	3.39–3.77	>3.77	–
Adjusted	1.00 (Reference)	1.79 (0.76–4.24)	2.67 (1.18–6.02)*	3.26 (1.41–7.51)*	<0.01
Age ≥65 years					
FT3, pmol/L (range)	<4.03	4.03–4.40	4.40–4.81	>4.81	–
Adjusted	1.00 (Reference)	0.97 (0.57–1.64)	0.71 (0.42–1.20)	0.67 (0.38–1.19)	0.19
FT4, pmol/L (range)	<13.53	13.53–15.00	15.00–16.55	>16.55	–
Adjusted	1.00 (Reference)	2.79 (1.26–6.17)*	1.66 (0.71–3.86)	2.46 (1.08–5.59)*	0.11
TSH, mIU/mL (range)	<1.25	1.25–1.85	1.85–2.78	>2.78	–
Adjusted	1.00 (Reference)	0.84 (0.40–1.78)	0.95 (0.43–2.08)	0.67 (0.25–1.55)	0.44
FT4 : FT3 ratios	<3.07	3.07–3.39	3.39–3.77	>3.77	–
Adjusted	1.00 (Reference)	1.96 (0.79–4.87)	2.75 (1.18–6.45)*	2.20 (0.94–5.14)	0.08
Sex					
Male					
FT3, pmol/L (range)	<4.03	4.03–4.40	4.40–4.81	>4.81	–
Adjusted	1.00 (Reference)	1.17 (0.58–2.36)	0.80 (0.41–1.54)	0.69 (0.35–1.37)	0.16
FT4, pmol/L (range)	<13.53	13.53–15.00	15.00–16.55	>16.55	–
Adjusted	1.00 (Reference)	1.84 (0.91–3.77)	1.38 (0.67–2.88)	2.19 (1.10–4.36)*	0.06
TSH, mIU/mL (range)	<1.25	1.25–1.85	1.85–2.78	>2.78	–
Adjusted	1.00 (Reference)	1.12 (0.61–2.09)	1.60 (0.86–2.97)	0.58 (0.27–1.28)	0.62
FT4 : FT3 ratios	<3.07	3.07–3.39	3.39–3.77	>3.77	–
Adjusted	1.00 (Reference)	1.82 (0.90–3.65)	2.70 (1.39–5.27)*	2.11 (1.06–4.23)*	0.02
Female					
FT3, pmol/L (range)	<4.03	4.03–4.40	4.40–4.81	>4.81	–
Adjusted	1.00 (Reference)	0.76 (0.33–1.75)	0.59 (0.22–1.53)	0.92 (0.29–2.86)	0.51
FT4, pmol/L (range)	<13.53	13.53–15.00	15.00–16.55	>16.55	–
Adjusted	1.00 (Reference)	1.19 (0.41–3.40)	1.60 (0.58–4.45)	2.67 (0.96–7.43)	0.05
TSH, mIU/mL (range)	<1.25	1.25–1.85	1.85–2.78	>2.78	–
Adjusted	1.00 (Reference)	0.93 (0.38–2.29)	0.57 (0.21–1.52)	0.56 (0.20–1.54)	0.17
FT4 : FT3 ratios	<3.07	3.07–3.39	3.39–3.77	>3.77	–
Adjusted	1.00 (Reference)	2.40 (0.57–10.09)	3.13 (0.81–12.11)	4.90 (1.28–17.76)*	0.01
BMI					
BMI <24kg/m^2					
FT3, pmol/L (range)	<4.03	4.03–4.40	4.40–4.81	>4.81	–
Adjusted	1.00 (Reference)	1.25 (0.64–2.46)	0.79 (0.40–1.54)	0.84 (0.40–1.74)	0.17

Table 4 (*Continued*)

	Quartiles				*P* for trend
	1	2	3	4	
FT4, pmol/L (range)	<13.53	13.53–15.00	15.00–16.55	>16.55	–
Adjusted	1.00 (Reference)	1.49 (0.69–2.90)	1.97 (0.96–4.05)	2.55 (1.24–5.25)*	0.02
TSH, mIU/mL (range)	<1.25	1.25–1.85	1.85–2.78	>2.78	–
Adjusted	1.00 (Reference)	1.14 (0.62–2.09)	0.67 (0.35–1.27)	0.43 (0.20–0.90)*	0.02
FT4 : FT3 ratios	<3.07	3.07–3.39	3.39–3.77	>3.77	–
Adjusted	1.00 (Reference)	2.13 (1.00–4.56)*	2.64 (1.29–5.42)*	2.95(1.40–6.19)*	0.01
BMI ≥24kg/m^2					
FT3, pmol/L (range)	<4.03	4.03–4.40	4.40–4.81	>4.81	–
Adjusted	1.00 (reference)	0.74 (0.31–1.73)	0.62 (0.26–1.46)	0.55 (0.22–1.41)	0.18
FT4, pmol/L (range)	<13.53	13.53–15.00	15.00–16.55	>16.55	–
Adjusted	1.00 (Reference)	1.50 (0.63–3.56)	0.56 (0.18–1.72)	1.61 (0.68–3.82)	0.57
TSH, mIU/mL (range)	<1.25	1.25–1.85	1.85–2.78	>2.78	–
Adjusted	1.00 (Reference)	1.48 (0.54–4.09)	2.98 (1.15–7.69)	1.24 (0.40–3.86)	0.29
FT4 : FT3 ratios	<3.07	3.07–3.39	3.39–3.77	>3.77	–
Adjusted	1.00 (Reference)	1.39 (0.50–3.85)	2.86 (1.11–7.35)*	2.79 (1.08–7.13)*	0.01

Adjusted for age, sex, smoking, alcohol, duration, glycated hemoglobin, obesity subgroup, hypertension, hyperlipemia, insulin, metformin, sulfonylureas, dipeptidyl peptidase-4 inhibitor and antihyperlipidemic drug. CI, confidence interval; FT3, free triiodothyronine; FT4, free thyroxine; OR, odds ratio; TSH, thyroid-stimulating hormone. *$P < 0.05$.

that free T3 had a negative effect on muscle mass in both the middle- and older-aged individuals, whereas TSH had a U-shaped association with sarcopenia only in older participants[26]. Conversely, in another study, FT3 was positively correlated to skeletal muscle mass among older euthyroid individuals in China[18].

Recent data from the Ansung cohort study showed that an elevated FT4 : FT3 ratio, but not serum FT3 or FT4 alone, indicated low muscle mass in both sexes among the euthyroid population aged 40–69 years in Korea[20]. Furthermore, we found that the risk of presarcopenia increased with elevated FT4, but decreased with TSH in euthyroid patients with BMI <24 kg/m^2, which was not previously reported.

THs have a prominent role in skeletal muscle, especially in myogenesis, regeneration, contractility and metabolism[27]. Type 2 and 3 iodothyronine deiodinase have been identified in skeletal muscle cells. Type 2 iodothyronine deiodinase locally converts T4 to active T3[28]. By contrast, type 3 iodothyronine deiodinase inactivates T3 through inner-ring deiodination to produce rT3. This local control of T3 activity through suitable peripheral T4–T3 conversion is crucial in the target tissues, including skeletal muscle[29]. The FT3 : FT4 ratio is a surrogate marker of peripheral deiodination activity. A low FT3 : FT4 ratio or a high FT4 : FT3 ratio indicates a decline in peripheral T4–T3 conversion. As is well known, both aging and type 2 diabetes mellitus have adapative remodeling in the thyroid. In the elderly, a decreased thyroid volume and thyroid hormones occurs[30]. In the literature, most studies reported that FT3 level and FT3 : FT4 ratio decrease, whereas FT4 and TSH levels increase in an age-dependent manner among the older euthyroid individuals. These adaptive remodelings might help to establish a new homeostatic equilibria, and contribute to a longer lifespan and healthy aging through a reduction in basal metabolic rate, reactive oxygen species generation and oxidative deoxyribonucleic acid damage[31]. However the remodelings are not always adaptive, they might have detrimental effects. In one cluster analysis, long-lived individuals (age ≥105 years) characterized by a high FT4 level and low FT3 : FT4 ratio showed an impaired functional status and increased mortality[32]. It could be interpreted as a lack of preservation of 5′-deiodinase activity, and failing to preserve TH signaling and counteract the aging-associated metabolic disturbances.

Similarly, type 2 diabetes mellitus patients have a decline in T3 level and a slight drop in TSH level by reducing nocturnal TSH peak and TSH response to thyrotropin-releasing hormone, impairing the peripheral conversion of T4 to T3[33]. However, the changes also likely contribute to deleterious effects in skeletal muscle homeostasis. The concept of sarcopenia is not limited to aging, it is likely to occur at almost all age levels. In agreement with this line of thinking, we found that a high FT4 : FT3 ratio, but not FT3, was significantly correlated with presarcopenia in the euthyroid patients with type 2 diabetes mellitus. Interestingly, in the subgroup analysis, this relationship appeared to be pronounced only in the middle-aged group, but not in the older-aged group. It is suggested that other factors might be involved in presarcopenia in the older-aged patients with type 2 diabetes mellitus, such as nutrition and physical activity or sex hormones. Further studies are required to elucidate the roles of thyroid function by evaluating different target populations and identifying other potential mechanisms of sarcopenia.

One strength of the present study is that it is the first large-scale study that focused on patients with type 2 diabetes mellitus to investigate the association between subtle thyroid dysfunction and presarcopenia. Another strength was that we utilized the recommended device of dual energy X-ray absorptiometry for its affordability, availability and diagnostic accuracy, which made the measurement of muscle mass convincing. Additionally, owing to the potential effects of drug therapy on thyroid function and skeletal muscle mass, we identified specific drug use categories (biguanides, sulfonylureas, dipeptidyl aminopeptidase-4, insulin, antihyperlipidemia drugs) as related confounding variables. The comprehensive confounder analyses strengthen the validity of the present study.

However, the present study had several limitations that warrant mention. First, we examined the hospitalized adult patients with type 2 diabetes mellitus, which might not be generalizable to the overall population with type 2 diabetes mellitus. Second, the causal and prospective relationship could not be established due to the nature of the cross-sectional study. Third, we did not have detailed data regarding diet and physical activity, which made it impossible for us to control the potential confounders and, thus, would bias the present results to some extent. Additionally, the results of subgroup analysis were exploratory, and should be interpreted with caution because of multiple comparisons involved. Further studies are warranted to investigate the associations of thyroid function and sarcopenia in various patient populations with type 2 diabetes.

SCHyper was an independent risk factor for presarcopenia in patients with type 2 diabetes mellitus, but SCHypo was not. In the Euthy group with type 2 diabetes mellitus, a high FT4 : FT3 ratio was significantly associated with an increased risk of presarcopenia in different strata (age, sex or BMI), but no correlation was observed between thyroid function and the older-aged participants. The present findings provided a novel insight into the role of the FT4 : FT3 ratio in presarcopenia in euthyroid patients with type 2 diabetes mellitus. Further prospective studies are required to identify the effects of subtle THs variations on presarcopenia among patients with type 2 diabetes mellitus, particularly in different subgroups.

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DISCLOSURE

The authors declare no conflict of interest.

Approval of the research protocol: The study was approved by the institutional review board of Tianjin Medical University General Hospital.

Informed consent: The study was carried out in accordance with the Declaration of Helsinki in 1995 (as revised in Fortaleza, Brazil, October 2013). The requirement to obtain informed consent was waived, because we used an electronic dataset compiled from medical records from the Department of Endocrinology and Metabolism, Tianjin Medical University General Hospital.

Registry and the registration no. of the study/trial: 2 July 2020 and No. IRB2020-YX-027-01.

Animal studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Multivariate logistic regression of risk factors for presarcopenia in type 2 diabetes patients with subclinical hyperthyroidism.

Table S2 | Statistical difference of skeletal muscle mass index in thyroid hormone concentration quartiles among type 2 diabetes mellitus patients with euthyroidism.