The Relationship Between Thyroid Function and the Prevalence of Type 2 Diabetes Mellitus in Euthyroid Subjects

Yeqing Gu,[1] Huihui Li,[1] Xue Bao,[1] Qing Zhang,[3] Li Liu,[3] Ge Meng,[1] Hongmei Wu,[1] Huanmin Du,[1] Hongbin Shi,[3] Yang Xia,[1] Qian Su,[1] Liyun Fang,[1] Fei Yu,[1] Huijun Yang,[1] Bin Yu,[1] Shaomei Sun,[3] Xing Wang,[3] Ming Zhou,[3] Qiyu Jia,[3] Qi Guo,[2] Hong Chang,[1] Guolin Wang,[3] Guowei Huang,[1] Kun Song,[3] and Kaijun Niu[1,3]

[1]Nutritional Epidemiology Institute and School of Public Health, and [2]Department of Rehabilitation and Sports Medicine Tianjin Medical University, 300070 Tianjin, China; and [3]Health Management Centre, Tianjin Medical University General Hospital, 300070 Tianjin, China

Purpose: Thyroid hormones (THs) are primarily responsible for the regulation of energy balance and metabolism, suggesting that TH levels may contribute to the development of type 2 diabetes mellitus (T2DM). However, few studies have investigated the relationship between TH and T2DM in a general population. The aim of this study was to evaluate whether serum TH levels within the reference range are related to T2DM.

Methods: A cross-sectional study (n = 15,296) was performed in Tianjin, China. Serum free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH) levels were measured by chemiluminescence immunoassay, and T2DM was defined according to the American Diabetes Association criteria. Multiple logistic regression models were used to assess the sex-specific relationships between FT3, FT4, FT3/FT4 ratios, and TSH quintiles and T2DM.

Results: The prevalence of T2DM was 16.2% in males and 7.7% in females. In males, the multivariable-adjusted odds ratios (95% confidence interval) of T2DM for increasing quintiles of FT3, FT4, and FT3/FT4 ratios were 1.00, 0.75(0.63 to 0.89), 0.70(0.58 to 0.84), 0.63(0.52 to 0.76), 0.56 (0.46 to 0.68; *P* for trend < 0.0001); 1.00, 1.05(0.87 to 1.27), 1.16(0.96 to 1.40), 1.09(0.90 to 1.31), 1.29 (1.07 to 1.56; *P* for trend = 0.01); and 1.00, 0.69(0.58 to 0.83), 0.72(0.60 to 0.86), 0.59(0.48 to 0.71), and 0.55(0.46 to 0.66; *P* for trend < 0.0001), respectively. Similar results also were observed in females. In contrast, a strong negative correlation between TSH and T2DM was observed in males, but not in females.

Conclusions: This study demonstrated that decreased FT3, FT3/FT4 ratios, and increased FT4 levels are independently related to a higher prevalence of T2DM in both males and females, and TSH is inversely related to T2DM in males only. (***J Clin Endocrinol Metab*** **102: 434–442, 2017)**

Type 2 diabetes mellitus (T2DM) is the most common chronic endocrine disease, characterized by hyperglycemia resulting from impaired insulin secretion and/or insulin resistance (1). The long-term complications of T2DM can significantly increase the risks of cardiovascular disease (CVD) and cancer, among many other diseases, as well as significantly increase risk of mortality (2, 3). The global prevalence of diabetes mellitus is rapidly increasing due to an ageing population, urbanization and associated lifestyle changes. In 2013, an estimated 382 million people worldwide had diabetes mellitus, about 90 to 95% of whom had T2DM, and the

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Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval; CVD, cardiovascular disease; FT3, free triiodothyronine; FT4, free thyroxine; LDL, low-density lipoprotein; OR, odds ratio; SD, standard deviation; T2DM, type 2 diabetes mellitus; T3, triiodothyronine; T4, thyroxine;TC, total cholesterol; TG, triglyceride; TH, thyroid hormone; TSH, thyroid-stimulating hormone.

number will increase to 592 million (8.8% of adults aged 20 to 79 years) by 2035 (1). In particular, the latest national survey suggests that China has become the global epicenter of the T2DM epidemic with more than 11.6% of the adult population (aged 18 years and over) suffering from diabetes mellitus (4).

Clarifying the common pathophysiologic mechanisms of T2DM is a crucial step toward providing early prevention and treatment. Recently, increased interest has focused on the relationship between thyroid function and metabolic diseases, including T2DM (5). The thyroid function is primarily responsible for the regulation of energy balance and metabolism (6). Thyroid dysfunction increases muscle and adipose tissue insulin resistance (7) and decreases glucose transport in myocytes (8). Meanwhile, thyroid hormone (TH) stimulates the basal expressions of glucose transporters, which regulate the intracellular glucose uptake on the surface of myocytes (5). Moreover, recently studies have demonstrated that free triiodothyronine (FT3) regulates insulin secretion (9, 10). Because glucose metabolism and insulin secretion are most closely related to the pathogenesis of T2DM, it is hypothesized that TH is a useful predictive factor for developing T2DM. On the other hand, thyroid-stimulating hormone (TSH) binds to receptors on epithelial cells in the thyroid gland, stimulating synthesis and secretion of TH by negative feedback inhibition (11). However, to date, few studies have evaluated the relationship between TH, TSH, and T2DM in the general population with euthyroid status. The aim of this study was to investigate whether serum TH concentrations within the reference range as well as TSH levels are related to the prevalence of T2DM among a large-scale adult population.

Materials and Methods

Participants

A large prospective dynamic cohort study, called The Tianjin Chronic Low-Grade Systemic Inflammation and Health Cohort Study, was carried out in a general adult population living in Tianjin, China. The study was based on annual health examinations conducted in Tianjin Medical University General Hospital Health Management Center and focused on the relationship between chronic low-grade systemic inflammation and the health status. Participants who had received health examinations (including medical examinations such as blood tests, abdominal ultrasonography, *etc.*) and had completed questionnaires regarding their smoking and drinking habits and disease history over the course of January 2007 to December 2015 were recruited. Moreover, a detailed lifestyle questionnaire covering family income, marital status, employment status, educational level, physical activity, sleep habits, dietary habits, overall computer/mobile device usage time, television time, history of prior infections, and use of medicines, as well as physical performance tests were administered to randomly selected subjects from this population since May 2013.

This cross-sectional study used data from the Tianjin Chronic Low-Grade Systemic Inflammation and Health Cohort Study ranging from 2013 to 2015. The participant selection process was described in Fig. 1. During the research period, there were 18,682 participants who had received at least 1 health examination including blood glucose, TH, and TSH tests agreed to participate and provided written informed consent for their data to be analyzed. We excluded those with a history of CVD (n = 1461) or cancer (n = 286). Moreover, participants who having a level exceeding the standard reference range of TH and/or TSH [FT3 $<$3.5 pmol/L (n = 43) or $>$6.5 pmol/L (n = 237), free thyroxine (FT4) $<$11.5 pmol/L (n = 113) or $>$22.7 pmol/L (n = 84), TSH $<$0.55 mIU/L (n = 251) or $>$4.78 mIU/L (n = 938)] were excluded. Moreover, participants who had a history of thyroid disease, type 1 diabetes mellitus, or who had used antithyroid drugs were not included in the current study. Owing to these exclusions, the final cross-sectional study population comprised 15,269 participants including 8970 males [mean age $\pm$ standard deviation (SD): 48.1 $\pm$ 10.6 years] and 6299 females (mean age $\pm$ SD: 47.6 $\pm$ 11.2 years).

Assessment of T2DM

Levels of fasting blood sugar were measured by glucose oxidase method. Blood samples for analysis of HbA1c were mixed with ethylenediaminetetraacetic acid (as an anticoagulant) before testing. HbA1c separation and quantification were performed using a high-performance liquid chromatography analyzer (HLC-723 G8; Tosoh, Tokyo, Japan) with intra- and interassay coefficients of variation of $<$3%. To measure 2-hour serum glucose, subjects were given a standard 75-g glucose solution, and serum glucose was measured at 2 hours after administration during the oral glucose tolerance test. In undiagnosed participants, T2DM was defined as a fasting blood sugar level $\geq$126 mg/dl (7.0 mmol/L), oral glucose tolerance test $\geq$200 mg/dl (11.1 mmol/L), HbA1c $\geq$48 mmol/mol (6.5%), or a history of T2DM based on the American Diabetes Association 2013 criteria (12).

FT3, FT4, and TSH measurements

Serum FT3 and FT4 were measured by chemiluminescence immunoassay using ADVIA Centaur FT3 analyzer and ADVIA Centaur FT4 analyzer (Siemens Healthcare Diagnostics, New York, NY) and expressed as pmol/L. The measuring range of FT3 and FT4 were 0.3 to 30.8 pmol/L and 1.3 to 155 pmol/L, respectively. Serum TSH was measured by chemiluminescence immunoassay using ADVIA Centaur TSH3-Ultra analyzer (Siemens Healthcare Diagnostics) and expressed as mIU/L. The measuring range was 0.001 to 150 mIU/L. The reference ranges of FT3, FT4, and TSH were 3.70$\sim$6.93 pmol/L, 11.61$\sim$21.41 pmol/L, and 0.55$\sim$4.87 mIU/L, respectively. We divided participants into 5 categories (quintiles) according to the actual concentrations of FT3, FT4, and TSH.

Assessment of other variables

Blood pressure (BP) was measured twice in the right arm using an automatic device (Andon, Tianjin, China) after 5 minutes of rest in a seated position. The mean of these 2 measurements was taken as the BP value. Hypertension is defined as having a BP higher than 140/90 mm Hg (systolic BP/

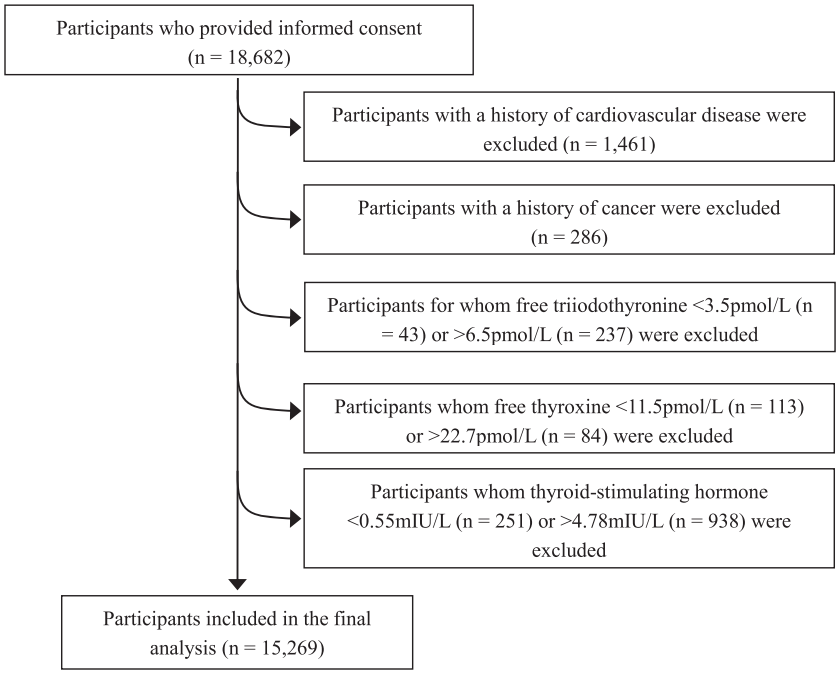

Figure 1. Flow diagram showing the selection of the study population.

diastolic BP) or having a history of hypertension. As for lipids, triglycerides (TGs) and total cholesterol (TC) were measured by enzymatic methods. Low-density lipoprotein (LDL) was measured by the polyvinyl sulfuric acid precipitation method, and high-density lipoprotein was measured by the chemical precipitation method using appropriate kits on a Cobas 8000 analyzer (Roche, Mannheim, Germany). Hyperlipidemia was defined as TC ≥5.17 mmol/L, TG ≥1.7 mmol/L, LDL ≥3.37 mmol/L, or history of hyperlipidemia. Height and body weight were measured using a standard protocol, and body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Waist circumference was measured at the umbilical level with subjects standing and breathing normally. Information on age, sex, and smoking and drinking status was obtained from a questionnaire survey. A detailed personal and family history of physical illness and current medications was noted from "yes" or "no" responses to relevant questions.

Statistical analysis

All statistical analyses were performed using the Statistical Analysis System 9.3 edition for Windows (SAS Institute Inc., Cary, NC). Because previous studies have reported that sex-specific difference was observed on the levels of TH, TSH, and the incident of T2DM (13, 14), we analyzed the relationships between TH, TSH, and T2DM by sex. Distributions of continuous variables were assessed for normality using the Kolmogorov-Smirnov (n > 2,000) or Shapiro-Wilk (n ≤ 2,000) test. Because the distributions of all the continuous variables were not normal in the current study, the natural logarithm was applied to normalize the data before statistical analysis. The continuous covariates after the log transformation approached normal distribution. Descriptive data are presented as the geometric mean [95% confidence interval (CI)] for adjusted continuous variables and as percentages for categorical variables. For baseline characteristics analysis, the differences among T2DM categories were examined using analysis of covariance for continuous variables and multiple logistic regression analysis for proportional variables after adjustment for age. The prevalence of T2DM was used as dependent variables, and quintiles of FT3, FT4, and TSH concentrations were used as independent variables. The multiple logistic regression models were used to examine the relationships between quintiles of FT3, FT4, and TSH and the prevalence of T2DM with adjustment for the covariates: age, BMI, waist circumference, smoking status, drinking status, hypertension, hyperlipidemia, and family history of CVD, hypertension, hyperlipidemia, and diabetes. Because the previous studies suggested an important role of thyroxine (T4) to triiodothyronine (T3) conversion (15–17), we additionally assessed the relationship between the quintiles of FT3/FT4 ratios and the prevalence of T2DM. Odds ratios (ORs) with their corresponding 95% CIs were calculated. Furthermore, because certain medicines (such as nonsteroidal anti-inflammatory drug, estrogen, antiepileptic drugs, *etc.*) may affect thyroid function (18, 19), a sensitivity analysis was performed after excluding the subjects who reported taking these drugs. All *P* values for linear trends were calculated using the median value of quintiles of FT3, FT4, FT3/FT4 ratios, and TSH. All tests were 2-tailed and $P < 0.05$ was defined as statistically significant.

Results

The prevalence of T2DM is 16.2% (1449/8970) and 7.7% (488/6,99) in males and females, respectively. Among participants with T2DM, 482 participants [368 (25.4%) males and 114 (23.4%) females] reported that they take medications for diabetes. FT3 and FT4 levels were both significantly higher in males than in females [means (SD), in males: 5.5 (0.5) pmol/L, 16.8 (2.0) pmol/L; in females: 5.0 (0.5) pmol/L, 15.7 (1.8) pmol/L, both $P < 0.0001$], whereas the TSH level was significantly lower in males than in females [means (SD), in males: 1.9 (0.8) mIU/L; in females: 2.3 (1.0) mIU/L, $P < 0.0001$].

Age-adjusted participant characteristics in relation to T2DM were presented in Table 1. Compared with participants without T2DM, those with T2DM tended to be older and to have higher BMI, waist circumference, TC, TG, systolic BP, diastolic BP, the proportion of family history of hyperlipidemia and diabetes, and lower high-density lipoprotein (all *P* values < 0.01) in both males and females. However, there are also some differences between males and females. Compared with participants without T2DM, males with T2DM tended to have lower FT3 and FT3/FT4 ratios and higher FT4 levels (all *P* values < 0.05); and females with T2DM tended to have

Table 1. Age-Adjusted Participant Characteristics by T2DM Status (n = 15,269)

	T2DM Status (Males)			T2DM Status (Females)		
	No	Yes	*P* Value[a]	No	Yes	*P* Value[a]
No. of subjects	7521	1449	—	5811	488	—
Age (y)	46.0 (45.8 to 46.2)[b]	52.2 (51.6 to 52.8)	<0.0001	45.7 (45.4 to 45.9)	54.5 (53.4 to 55.7)	<0.0001
BMI (kg/m2)	25.8 (25.7 to 25.9)	27.2 (27.0 to 27.4)	<0.0001	23.6 (23.5 to 23.6)	25.0 (24.7 to 25.2)	<0.0001
WC (cm)	90.2 (90.0 to 90.4)	94.1 (93.6 to 94.6)	<0.0001	78.7 (78.5 to 78.9)	82.4 (81.6 to 83.1)	<0.0001
TC (mmol/L)	4.9 (4.9 to 4.9)	5.0 (4.9 to 5.0)	<0.01	4.9 (4.8 to 4.9)	5.0 (4.9 to 5.1)	<0.01
LDL (mmol/L)	2.9 (2.8 to 2.9)	2.9 (2.8 to 2.9)	0.88	2.7 (2.7 to 2.8)	2.9 (2.8 to 2.9)	<0.01
HDL (mmol/L)	1.2 (1.2 to 1.2)	1.1 (1.1 to 1.1)	<0.0001	1.5 (1.5 to 1.5)	1.4 (1.3 to 1.4)	<0.0001
TG (mmol/L)	1.5 (1.5 to 1.5)	1.9 (1.8 to 1.9)	<0.0001	1.1 (1.0 to 1.1)	1.3 (1.2 to 1.3)	<0.0001
SBP (mmHg)	125.5 (125.2 to 125.9)	130.0 (129.1 to 130.8)	<0.0001	119.1 (118.7 to 119.5)	126.9 (125.5 to 128.4)	<0.0001
DBP (mmHg)	81.2 (80.9 to 81.4)	84.0 (83.4 to 84.6)	<0.0001	73.6 (73.4 to 73.9)	76.6 (75.6 to 77.5)	<0.0001
FT3 (pmol/L)	5.5 (5.4 to 5.5)	5.4 (5.3 to 5.4)	<0.0001	4.9 (4.9 to 5.0)	4.9 (4.9 to 4.9)	0.07
FT4 (pmol/L)	16.7 (16.6 to 16.7)	16.8 (16.7 to 16.9)	0.02	15.5 (15.5 to 15.6)	15.9 (15.7 to 16.0)	<0.0001
TSH (mIU/L)	1.8 (1.7 to 1.8)	1.7 (1.7 to 1.8)	0.32	2.1 (2.1 to 2.1)	2.1 (2.0 to 2.1)	0.48
FT3/FT4 ratios	0.327 (0.326 to 0.328)	0.319 (0.317 to 0.321)	<0.0001	0.318 (0.317 to 0.319)	0.309 (0.305 to 0.312)	<0.0001
Smoking status (%)						
Smoker	44.9	47.5	0.29	3.1	4.2	0.81
Ex-smoker	8.3	9.7	0.88	0.6	0.9	0.32
Nonsmoker	46.7	42.8	0.33	96.4	94.9	0.54
Drinker (%)						
Everyday	7.6	7.5	0.26	0.6	1.1	0.33
Sometime	71.8	69.9	0.44	34.2	24.7	0.03
Ex-drinker	4.5	4.2	0.57	5.3	3.5	0.51
Nondrinker	16.1	18.5	0.84	59.9	70.7	0.03
Family history of diseases (%)						
CVD	41.4	44.2	0.42	40.3	44.9	0.26
Hypertension	55.0	58.1	0.09	55.4	58.2	0.42
Hyperlipidemia	8.5	15.7	<0.0001	8.4	14.1	<0.0001
Diabetes	34.9	53.2	<0.0001	36.2	52.3	<0.0001

Abbreviations: HDL, high-density lipoprotein; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure.

[a]Analysis of covariance or multiple logistic regression analysis.

[b]Geometric mean (95% CI; all such values).

higher LDL and FT4 levels and lower FT3/FT4 ratios (all *P* values < 0.01). No significant differences were observed among the TSH levels, proportion of current smokers, alcohol consumers and the proportion of those with a family history of CVD and hypertension (all *P* values > 0.05) in both males and females.

The crude and adjusted relationship between FT3, FT4, TSH, and the prevalence of T2DM was indicated in Table 2. In males, the adjusted ORs (95% CI) of T2DM were related to the gradual increase of the FT3, FT4, FT3/FT4 ratios, and TSH concentrations as compared with participants who had the lowest concentrations and were as follows: FT3: 0.75 (0.63 to 0.89), 0.70 (0.58 to 0.84), 0.63 (0.52 to 0.76), and 0.56 (0.46 to 0.68; *P* for trend < 0.0001); FT4: 1.05 (0.87 to 1.27), 1.16 (0.96 to 1.40), 1.09 (0.90 to 1.31), and 1.29 (1.07 to 1.56; *P* for trend = 0.01); FT3/FT4 ratios: 0.69 (0.58 to 0.83), 0.72 (0.60 to 0.86), 0.59 (0.48 to 0.71), and 0.55 (0.46 to 0.66; *P* for trend < 0.0001); and TSH: 0.89 (0.74 to 1.08), 0.94 (0.78 to 1.13), 0.76 (0.63 to 0.92), and 0.80 (0.67 to 0.97; *P* for trend = 0.01). In females, the adjusted ORs between FT3, FT4, FT3/FT4 ratios, TSH, and the prevalence of T2DM were as follows: FT3: 1.00, 0.97 (0.72 to 1.30), 0.91 (0.67 to 1.22), 0.71 (0.52 to 0.96), 0.63 (0.46 to 0.86; *P* for trend < 0.01); FT4: 1.00, 0.81 (0.58 to 1.13), 1.15 (0.84 to 1.58), 1.12 (0.81 to 1.54), and 1.54 (1.14 to 2.08; *P* for trend < 0.0001); FT3/FT4 ratios: 1.00, 0.79 (0.59 to 1.05), 0.56 (0.41 to 0.76), 0.64 (0.47 to 0.85), and 0.57 (0.42 to 0.78; *P* for trend < 0.0001); and TSH: 1.00, 1.22 (0.91 to 1.66), 0.83 (0.60 to 1.15), 0.89 (0.65 to 1.22), and 0.82 (0.60 to 1.12; *P* for trend = 0.04).

We further performed a sensitivity analysis after excluding the subjects who reported taking certain medicines (such as nonsteroidal anti-inflammatory drug, estrogen, antiepileptic drugs, *etc.*; n = 220). However, the relationship between TH, TSH and T2DM did not change. The adjusted OR (95% CI) of T2DM for increasing quintiles of TH and TSH for males were as follows: FT3: 1.00 (reference), 0.75 (0.63 to 0.89), 0.70 (0.58 to 0.84), 0.63 (0.53 to 0.76), and 0.56 (0.46 to 0.69; *P* for trend < 0.0001); FT4: 1.00 (reference), 1.05 (0.87 to 1.27), 1.14 (0.94 to 1.38), 1.09 (0.90 to 1.32), and 1.29 (1.07 to 1.57; *P* for trend = 0.01); FT3/FT4 ratios: 1.00 (reference), 0.70 (0.58 to 0.84), 0.73 (0.61 to 0.87), 0.59 (0.49 to 0.71), and 0.55 (0.46 to 0.67; *P* for trend

Table 2. Adjusted Relationships of Quintiles of Serum FT3, FT4, FT3/FT4 Ratios, and TSH Concentrations to T2DM (n = 15,269)

	Quintiles of TSH (mIU/L), FT3/FT4 (pmol/L), or FT3/FT4 Ratios (Range)					
	Level 1	Level 2	Level 3	Level 4	Level 5	*P* for Trend[a]
Males						
FT3 concentration (pmol/L, range)	3.50 to 5.07	5.08 to 5.35	5.36 to 5.56	5.57 to 5.85	5.86 to 6.50	—
Number of subjects	1822	1843	1659	1851	1795	—
Number of diabetes	430	316	253	248	202	—
Crude	Reference	0.67 (0.57 to 0.79)[b]	0.58 (0.49 to 0.69)	0.50 (0.42 to 0.59)	0.41 (0.34 to 0.49)	<0.0001
Age- and BMI-adjusted	Reference	0.75 (0.63 to 0.89)	0.67 (0.56 to 0.81)	0.62 (0.52 to 0.74)	0.56 (0.46 to 0.68)	<0.0001
Multiple adjusted[c]	Reference	0.75 (0.63 to 0.89)	0.70 (0.58 to 0.84)	0.63 (0.52 to 0.76)	0.56 (0.46 to 0.68)	<0.0001
FT4 concentration (pmol/L, range)	11.50 to 15.08	15.09 to 16.20	16.21 to 17.23	17.24 to 18.48	18.49 to 22.69	—
Number of subjects	1802	1789	1791	1793	1795	—
Number of diabetes	309	287	292	272	289	—
Crude	Reference	0.92 (0.77 to 1.10)	0.94 (0.79 to 1.12)	0.86 (0.72 to 1.03)	0.93 (0.78 to 1.11)	0.31
Age- and BMI-adjusted	Reference	1.10 (0.91 to 1.32)	1.18 (0.98 to 1.42)	1.16 (0.96 to 1.39)	1.32 (1.10 to 1.59)	<0.01
Multiple adjusted[c]	Reference	1.05 (0.87 to 1.27)	1.16 (0.96 to 1.40)	1.09 (0.9 to 1.31)	1.29 (1.07 to 1.56)	0.01
FT3/FT4 ratios	0.18 to 0.29	0.30 to 0.32	0.33 to 0.34	0.35 to 0.36	0.37 to 0.56	—
Number of subjects	1795	1793	1794	1794	1794	—
Number of diabetes	385	280	283	248	253	—
Crude	Reference	0.68 (0.57 to 0.80)	0.69 (0.58 to 0.81)	0.59 (0.49 to 0.70)	0.60 (0.51 to 0.72)	<0.0001
Age- and BMI-adjusted	Reference	0.70 (0.58 to 0.83)	0.71 (0.59 to 0.84)	0.58 (0.48 to 0.69)	0.54 (0.45 to 0.65)	<0.0001
Multiple adjusted[c]	Reference	0.69 (0.58 to 0.83)	0.72 (0.60 to 0.86)	0.59 (0.48 to 0.71)	0.55 (0.46 to 0.66)	<0.0001
TSH concentration (mIU/L, range)	0.55 to 1.22	1.23 to 1.57	1.58 to 1.97	1.98 to 2.58	2.59 to 4.78	—
Number of subjects	1795	1794	1791	1795	1795	
Number of diabetes	313	275	300	261	300	—
Crude	Reference	0.86 (0.72 to 1.02)	0.95 (0.80 to 1.13)	0.81 (0.67 to 0.96)	0.95 (0.80 to 1.13)	0.63
Age- and BMI-adjusted	Reference	0.91 (0.76 to 1.09)	0.95 (0.80 to 1.14)	0.78 (0.65 to 0.94)	0.88 (0.73 to 1.05)	0.09
Multiple adjusted[c]	Reference	0.89 (0.74 to 1.08)	0.94 (0.78 to 1.13)	0.76 (0.63 to 0.92)	0.80 (0.67 to 0.97)	0.01
Females						
FT3 concentration (pmol/L, range)	3.50 to 4.59	4.60 to 4.84	4.85 to 5.05	5.06 to 5.32	5.33 to 6.50	—
Number of subjects	1298	1280	1179	1272	1270	—
Number of diabetes	112	106	100	90	80	—
Crude	Reference	0.96 (0.73 to 1.26)	0.98 (0.74 to 1.30)	0.81 (0.60 to 1.07)	0.72 (0.53 to 0.97)	0.02
Age- and BMI-adjusted	Reference	0.99 (0.74 to 1.32)	0.95 (0.71 to 1.28)	0.74 (0.55 to 1.00)	0.65 (0.48 to 0.89)	0.01
Multiple adjusted[c]	Reference	0.97 (0.72 to 1.30)	0.91 (0.67 to 1.22)	0.71 (0.52 to 0.96)	0.63 (0.46 to 0.86)	<0.01
FT4 concentration (pmol/L, range)	11.50 to 14.08	14.09 to 15.08	15.09 to 15.97	15.98 to 17.15	17.16 to 22.46	—
Number of subjects	1264	1263	1250	1255	1267	—
Number of diabetes	85	72	102	95	134	—
Crude	Reference	0.84 (0.61 to 1.16)	1.23 (0.91 to 1.67)	1.14 (0.84 to 1.54)	1.64 (1.24 to 2.19)	<0.0001
Age- and BMI-adjusted	Reference	0.85 (0.61 to 1.19)	1.21 (0.89 to 1.65)	1.19 (0.87 to 1.63)	1.66 (1.24 to 2.24)	<0.0001
Multiple adjusted[c]	Reference	0.81 (0.58 to 1.13)	1.15 (0.84 to 1.58)	1.12 (0.81 to 1.54)	1.54 (1.14 to 2.08)	<0.001
FT3/FT4 ratios	0.16 to 0.29	0.30 to 0.31	0.32 to 0.33	0.34 to 0.35	0.36 to 0.53	—
Number of subjects	1261	1259	1259	1260	1260	—
Number of diabetes	136	102	79	90	81	—
Crude	Reference	0.73 (0.56 to 0.95)	0.55 (0.41 to 0.74)	0.64 (0.48 to 0.84)	0.57 (0.43 to 0.76)	<0.0001
Age- and BMI-adjusted	Reference	0.78 (0.59 to 1.03)	0.54 (0.40 to 0.73)	0.61 (0.46 to 0.82)	0.54 (0.40 to 0.72)	<0.0001
Multiple adjusted[c]	Reference	0.79 (0.59, 1.05)	0.56 (0.41, 0.76)	0.64 (0.47, 0.85)	0.57 (0.42, 0.78)	<0.0001
TSH concentration (mIU/L, range)	0.55 to 1.42	1.43 to 1.89	1.90 to 2.42	2.43 to 3.13	3.14 to 4.78	—
Number of subjects	1260	1263	1256	1260	1260	—
Number of diabetes	89	119	84	96	100	—
Crude	Reference	1.37 (1.03 to 1.83)	0.94 (0.69 to 1.29)	1.09 (0.80 to 1.47)	1.13 (0.84 to 1.53)	0.94
Age- and BMI-adjusted	Reference	1.27 (0.94 to 1.71)	0.89 (0.65 to 1.23)	0.96 (0.70 to 1.31)	0.90 (0.67 to 1.23)	0.15
Multiple adjusted[c]	Reference	1.22 (0.91 to 1.66)	0.83 (0.60 to 1.15)	0.89 (0.65 to 1.22)	0.82 (0.60 to 1.12)	0.04

T2DM was defined as a fasting blood sugar level ≥126 mg/dl (7.0 mmol/L), oral glucose tolerance test ≥200 mg/dl (11.1mmol/L), $HbA1_c \geq 48$ mmol/mol (6.5%), or a history of diabetes based on the American Diabetes Association 2013 criteria.

[a]Multiple logistic regression analysis.

[b]Adjusted ORs (95% CI; all such values).

[c]Adjusted for age, BMI, waist circumference, smoking status, drinking status, hypertension, hyperlipidemia, and family history of cardiovascular diseases, hypertension, hyperlipidemia, and diabetes.

< 0.0001); and TSH: 1.00 (reference), 0.89 (0.74 to 1.08), 0.93 (0.77 to 1.12), 0.75 (0.62 to 0.91), and 0.80 (0.66 to 0.97; *P* for trend < 0.01). In females, the adjusted OR (95% CI) of T2DM for increasing quintiles of TH and TSH were as follows: FT3: 1.00 (reference), 0.95 (0.71 to 1.29), 0.87 (0.64 to 1.18), 0.70 (0.51 to 0.95), and 0.62 (0.45 to 0.86; *P* for trend < 0.001); FT4: 1.00 (reference), 0.88 (0.62 to 1.24), 1.21 (0.88 to 1.68), 1.20 (0.86 to 1.66), and 1.67 (1.23 to 2.28; *P* for trend < 0.0001); FT3/FT4 ratios: 1.00 (reference), 0.77 (0.57 to 1.02), 0.52 (0.38 to 0.71), 0.61 (0.45 to 0.82), and 0.53 (0.39 to 0.72; *P* for trend < 0.0001); and TSH: 1.00 (reference), 1.17 (0.86 to 1.59), 0.83 (0.60 to 1.15), 0.83 (0.60 to 1.14), and 0.77 (0.56 to 1.06; *P* for trend = 0.02).

Discussion

The current study has assessed the relationships between TH, TSH, and T2DM in an adult population. The results suggest that, after adjustment for confounding factors in both males and females, a higher prevalence of T2DM has a negative correlation to FT3 and a positive correlation to FT4. Furthermore, a negative correlation was observed between TSH and T2DM in males, but not in females. To our knowledge, this study firstly demonstrated that TH levels within reference range are significantly related to the prevalence of T2DM.

We adjusted for multiple potentially confounding factors in our analysis. This study suggests that numerous factors (age, sex, BMI, drinking, smoking status, family history of some diseases) are correlated with the prevalence of T2DM. Because studies have shown that serum TH and TSH levels are related to age (20) and BMI (21), we first adjusted for these 2 variables. Adjustment for age and BMI significantly affected the relationship between serum FT4 levels and T2DM in males, leading us to conclude that age and BMI are major confounding factors. We subsequently adjusted for waist circumference, smoking status, drinking status, hypertension, hyperlipidemia, TC, TG [influential factors on TH and TSH levels (22–24)], and genetic factors, such as family history of CVD, hypertension, hyperlipidemia, and diabetes [influential factors on T2DM (25)]. However, after these adjustments, serum FT3 levels had a more obvious correlation with T2DM in both males and females.

Several studies have explored the relationship between TH, TSH, and insulin resistance or glucose levels. Four cross-sectional studies reported that serum FT4 was negatively related to insulin resistance, fasting insulin or the homoeostasis model assessment index for insulin resistance, whereas a positive relationship was found between TSH and insulin resistance (26–29). Two other cross-sectional and a small-scale case-control studies found a positive correlation among higher T3 (30), T3 to T4 ratio (31), FT3 and FT4 (32) levels, and high fasting glucose levels and insulin resistance. In contrast, a cross-sectional study showed that FT3, FT3 to FT4 ratio, and TSH are significantly and negatively associated with HbA1c levels in patients with T2DM (33). Although the reasons for these discrepancies remain unclear, the differences in confounding factors, study setting, small sample sizes for some studies, use of T3 instead of FT3, and the difference of outcome indicators might partly explain the cause for conflicting results. On the other hand, to date, few studies have illustrated the relationship between TH, TSH, and T2DM in the general population. This study demonstrates that T2DM is negatively related to FT3 and positively related to FT4 in both males and females. Further studies are necessary to explore whether these results can also be observed in other adult populations.

Our results showed a similar relationship between TH and T2DM in both males and females, but sex difference was observed in the relationship between TSH and T2DM. Still, detailed molecular mechanisms remain unclear, because sex hormones (such as estrogen, and testosterone, etc.) can regulate the thyroid function (34), and estrogen levels affect the development of T2DM (35). The difference in sex hormones may partly explain the sex-difference in the relationship between TSH and T2DM. However, because levels of sex hormones such as testosterone and estrogen were not measured in this study, further research is needed to explore this issue. In addition, because the sample size was smaller for females and the prevalence of T2DM was markedly lower in females (7.7%) than in males (16.2%), the precision and statistical power of the analysis may be lower for females. Further large-scale population studies are required to confirm the above findings. On the other hand, in males, the significance of the relationship between FT3 and T2DM started from the second quintile, but from the fourth quintile in females. Because FT3 concentrations on the fourth quintile in females are equivalent to the second quintile in males, it is speculated that the increased prevalence of T2DM depends on the concentrations of FT3 regardless of sex. Further studies are needed to clarify this hypothesis.

Multiple putative mechanisms could explain the relationship between thyroid function and T2DM. On the 1 hand, T3 regulates hepatic gluconeogenesis and antagonize insulin action (36), even in the euthyroid state (28). T3 modulates mRNA and protein expression of the glucose transporter 4, adenosine monophosphate–activated protein kinase, and acetyl coenzyme A carboxylase in skeletal muscle (37). Furthermore, increases in plasma T3 levels impair the ability of insulin to suppress hepatic glucose production and to increase glucose uptake in

muscle (38). Interestingly, even subtle increases in the levels of T3 or T4 within the physiological range have been shown to induce insulin resistance (39). On the other hand, inadequate insulin secretion is an early event in the natural history of T2DM (40). There is convincing evidence from independent research that T3 directly increases islet β-cell mass via thyroid hormone receptor α-dependent pathways (41). Moreover, insulin secretion from β-cells is potentially controlled by the truncated mitochondrial T3 receptor p43 (42). These changes have been associated with a decrease in specific glucose transporters, namely GLUT2 and Kir6.2, and may thus be more broadly mediated by the control of intracellular glucose availability, which may have implications for other actions of T3 (5). FT3 is also a powerful inducer of pancreatic acinar cell proliferation in rodents (43). FT3 promotes expression of important proteins involved in both glucose and lipid metabolism that may influence insulin secretion (44). Finally, an interaction between TSH and insulin sensitivity has been proposed by several studies (45). Nonetheless, no direct effect of insulin or insulin resistance on thyroid function in humans has yet been demonstrated.

Interestingly, the current study has also found a strong and inverse link between the FT3/FT4 ratios and T2DM. It is known that TSH upregulates deiodinase expression and activity (46, 47). Higher peripheral deiodinase activity increases conversion of FT4 to FT3 (15, 16, 48). Thus, FT3/FT4 ratios can be considered an indicator of peripheral deiodinase activity. Because the inhibition of peripheral deiodinase activity lowers basal metabolic rate (48, 49), and basal metabolic rate is closely related to the pathogenesis of T2DM, it is possible that the FT3/FT4 ratios were inversely related to T2DM because of the regulation of basal metabolic rate by deiodinase-mediated TH signaling (49). In contrast, 3 small-scale cross-sectional studies reported that the FT3/FT4 ratio positively correlates with the homeostasis model assessment for insulin resistance in obese adolescents with nonalcoholic fatty liver disease (n = 200) (15), with both waist circumference and BMI in obese women aged 18 to 68 years (n = 201) (17), and with nonalcoholic fatty liver disease in patients with euthyroidism or hypothyroidism (n = 115) (16). The differences in population and sample size may be the cause for the observational discrepancies between the aforementioned studies and the current study. Furthermore, a recent study suggested that as TSH levels increase, FT3/FT4 ratios increase until age 40, but this differential increase does not occur in older age groups (50). Based on this finding, we performed a stratified analysis to ascertain whether age ($<$40 years or $\geq$40 years) confounds the relationship between FT3/FT4 ratios and T2DM. However, in the final multiple logistic regression model, similar results were observed in subjects from different age groups (P for interaction = 0.54 in males and 0.58 in females). Therefore, we speculated that although age mediates the TSH regulation of FT3/FT4 ratios, FT3/FT4 ratios are significantly related to T2DM independent of age. Further studies are needed to explore the potential mechanisms underlying this association.

The current study has several limitations. Firstly, this is a cross-sectional study, which is impossible to infer causality. Further cohort studies and intervention trials should be undertaken to establish a causal relationship between TH and T2DM. However, the present large-scale cross-sectional study supports the important hypothesis that TH levels even within the euthyroid range, may contribute to the development of T2DM in the general population. Secondly, because this population-based study was carried out among apparently healthy adult population, and only euthyroid subjects were included in the final analysis, only 1 serum TH test and 1 TSH test were measured in this study. Therefore, further high-quality research is necessary to confirm these results. Thirdly, although we adjusted for a considerable number of potentially confounding factors, we cannot exclude the possibility that T2DM is affected by other lifestyle variables including supplementation of iodine, which is intrinsically related to TH levels. Thus, a well-designed randomized controlled trial is required to verify these results. Finally, although the participants with thyroid disease were excluded, serum thyroperoxidase antibodies levels were not routinely checked in the general population. Therefore, we cannot fully exclude the possibility that the relationship between the categories of TH, TSH, and T2DM is affected by these patients with positive thyroperoxidase antibodies.

Conclusion

Decreased FT3 and FT3/FT4 ratios and increased FT4 levels were independently related to the prevalence of T2DM among the adult population. A significantly negative relationship between TSH and T2DM was observed in males but not in females. Future studies should be aimed at clarifying the cause-and-effect relationship between TH and T2DM.

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Address all correspondence and requests for reprints to: Kaijun Niu, Nutritional Epidemiology Institute and School of Public Health, Tianjin Medical University, 22 Qixiangtai Road, Heping District, Tianjin 300070, China. E-mail: nkj0809@gmail.com or niukaijun@tmu.edu.cn.

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References

1. Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE. Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes Res Clin Pract*. 2014;**103**(2):137–149.
2. Leon BM, Maddox TM. Diabetes and cardiovascular disease: Epidemiology, biological mechanisms, treatment recommendations and future research. *World J Diabetes*. 2015;**6**(13):1246–1258.
3. Hua F, Yu JJ, Hu ZW. Diabetes and cancer, common threads and missing links. *Cancer Lett*. 2016;**374**(1):54–61.
4. Yang W, Lu J, Weng J, Jia W, Ji L, Xiao J, Shan Z, Liu J, Tian H, Ji Q, Zhu D, Ge J, Lin L, Chen L, Guo X, Zhao Z, Li Q, Zhou Z, Shan G, He J; China National Diabetes and Metabolic Disorders Study Group. Prevalence of diabetes among men and women in China. *N Engl J Med*. 2010;**362**(12):1090–1101.
5. Iwen KA, Schröder E, Brabant G. Thyroid hormones and the metabolic syndrome. *Eur Thyroid J*. 2013;**2**(2):83–92.
6. Bahi L, Garnier A, Fortin D, Serrurier B, Veksler V, Bigard AX, Ventura-Clapier R. Differential effects of thyroid hormones on energy metabolism of rat slow- and fast-twitch muscles. *J Cell Physiol*. 2005;**203**(3):589–598.
7. Dimitriadis G, Mitrou P, Lambadiari V, Boutati E, Maratou E, Panagiotakos DB, Koukkou E, Tzanela M, Thalassinos N, Raptis SA. Insulin action in adipose tissue and muscle in hypothyroidism. *J Clin Endocrinol Metab*. 2006;**91**(12):4930–4937.
8. Maratou E, Hadjidakis DJ, Kollias A, Tsegka K, Peppa M, Alevizaki M, Mitrou P, Lambadiari V, Boutati E, Nikzas D, Tountas N, Economopoulos T, Raptis SA, Dimitriadis G. Studies of insulin resistance in patients with clinical and subclinical hypothyroidism. *Eur J Endocrinol*. 2009;**160**(5):785–790.
9. Oda T, Taneichi H, Takahashi K, Togashi H, Hangai M, Nakagawa R, Ono M, Matsui M, Sasai T, Nagasawa K, Honma H, Kajiwara T, Takahashi Y, Takebe N, Ishigaki Y, Satoh J. Positive association of free triiodothyronine with pancreatic β-cell function in people with prediabetes. *Diabet Med*. 2015;**32**(2): 213–219.
10. Kim TK, Lee JS, Jung HS, Ha TK, Kim SM, Han N, Lee EJ, Kim TN, Kwon MJ, Lee SH, Kim MK, Rhee BD, Park JH. Triiodothyronine induces proliferation of pancreatic β-cells through the MAPK/ERK pathway. *Exp Clin Endocrinol Diabetes*. 2014;**122**(4):240–245.
11. Sternberg RM, Thoemke KR, Korte JJ, Moen SM, Olson JM, Korte L, Tietge JE, Degitz SJ, Jr. Control of pituitary thyroid-stimulating hormone synthesis and secretion by thyroid hormones during Xenopus metamorphosis. *Gen Comp Endocrinol*. 2011;**173**(3): 428–437.
12. American Diabetes Association. Standards of medical care in diabetes: 2013. *Diabetes Care*. 2013;**36**(Suppl 1):S11–S66.
13. Porcu E, Medici M, Pistis G, Volpato CB, Wilson SG, Cappola AR, Bos SD, Deelen J, den Heijer M, Freathy RM, Lahti J, Liu C, Lopez LM, Nolte IM, O'Connell JR, Tanaka T, Trompet S, Arnold A, Bandinelli S, Beekman M, Böhringer S, Brown SJ, Buckley BM, Camaschella C, de Craen AJ, Davies G, de Visser MC, Ford I, Forsen T, Frayling TM, Fugazzola L, Gögele M, Hattersley AT, Hermus AR, Hofman A, Houwing-Duistermaat JJ, Jensen RA, Kajantie E, Kloppenburg M, Lim EM, Masciullo C, Mariotti S, Minelli C, Mitchell BD, Nagaraja R, Netea-Maier RT, Palotie A, Persani L, Piras MG, Psaty BM, Räikkönen K, Richards JB, Rivadeneira F, Sala C, Sabra MM, Sattar N, Shields BM, Soranzo N, Starr JM, Stott DJ, Sweep FC, Usala G, van der Klauw MM, van Heemst D, van Mullem A, Vermeulen SH, Visser WE, Walsh JP, Westendorp RG, Widen E, Zhai G, Cucca F, Deary IJ, Eriksson JG, Ferrucci L, Fox CS, Jukema JW, Kiemeney LA, Pramstaller PP, Schlessinger D, Shuldiner AR, Slagboom EP, Uitterlinden AG, Vaidya B, Visser TJ, Wolffenbuttel BH, Meulenbelt I, Rotter JI, Spector TD, Hicks AA, Toniolo D, Sanna S, Peeters RP, Naitza S. A meta-analysis of thyroid-related traits reveals novel loci and gender-specific differences in the regulation of thyroid function. *PLoS Genet*. 2013;**9**(2):e1003266.
14. Krag MO, Hasselbalch L, Siersma V, Nielsen AB, Reventlow S, Malterud K, de Fine Olivarius N. The impact of gender on the long-term morbidity and mortality of patients with type 2 diabetes receiving structured personal care: a 13 year follow-up study. *Diabetologia*. 2016;**59**(2):275–285.
15. Bilgin H, Pirgon Ö. Thyroid function in obese children with non-alcoholic fatty liver disease. *J Clin Res Pediatr Endocrinol*. 2014; **6**(3):152–157.
16. Gökmen FY, Ahbab S, Ataoğlu HE, Türker BC, Çetin F, Türker F, Mamaç RY, Yenigün M. FT3/FT4 ratio predicts non-alcoholic fatty liver disease independent of metabolic parameters in patients with euthyroidism and hypothyroidism. *Clinics (Sao Paulo)*. 2016; **71**(4):221–225.
17. De Pergola G, Ciampolillo A, Paolotti S, Trerotoli P, Giorgino R. Free triiodothyronine and thyroid stimulating hormone are directly associated with waist circumference, independently of insulin resistance, metabolic parameters and blood pressure in overweight and obese women. *Clin Endocrinol (Oxf)*. 2007;**67**(2):265–269.
18. Davies PH, Franklyn JA. The effects of drugs on tests of thyroid function. *Eur J Clin Pharmacol*. 1991;**40**(5):439–451.
19. Hamed SA. The effect of antiepileptic drugs on thyroid hormonal function: causes and implications. *Expert Rev Clin Pharmacol*. 2015;**8**(6):741–750.
20. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, Franklyn JA, Hershman JM, Burman KD, Denke MA, Gorman C, Cooper RS, Weissman NJ. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *JAMA*. 2004; **291**(2):228–238.
21. Knudsen N, Laurberg P, Rasmussen LB, Bülow I, Perrild H, Ovesen L, Jørgensen T. Small differences in thyroid function may be important for body mass index and the occurrence of obesity in the population. *J Clin Endocrinol Metab*. 2005;**90**(7):4019–4024.
22. Altinova AE, Törüner FB, Aktürk M, Bukan N, Cakir N, Ayvaz G, Arslan M. Adiponectin levels and cardiovascular risk factors in hypothyroidism and hyperthyroidism. *Clin Endocrinol (Oxf)*. 2006;**65**(4):530–535.
23. Asvold BO, Bjøro T, Nilsen TI, Vatten LJ. Tobacco smoking and thyroid function: a population-based study. *Arch Intern Med*. 2007;**167**(13):1428–1432.
24. Balhara YP, Deb KS. Impact of alcohol use on thyroid function. *Indian J Endocrinol Metab*. 2013;**17**(4):580–587.
25. Bergvall N, Cnattingius S. Familial (shared environmental and genetic) factors and the foetal origins of cardiovascular diseases and type 2 diabetes: a review of the literature. *J Intern Med*. 2008; **264**(3):205–223.

26. Park SB, Choi HC, Joo NS. The relation of thyroid function to components of the metabolic syndrome in Korean men and women. *J Korean Med Sci*. 2011;**26**(4):540–545.
27. Mehran L, Amouzegar A, Tohidi M, Moayedi M, Azizi F. Serum free thyroxine concentration is associated with metabolic syndrome in euthyroid subjects. *Thyroid*. 2014;**24**(11):1566–1574.
28. Garduño-Garcia JdeJ, Alvirde-Garcia U, López-Carrasco G, Padilla Mendoza ME, Mehta R, Arellano-Campos O, Choza R, Sauque L, Garay-Sevilla ME, Malacara JM, Gomez-Perez FJ, Aguilar-Salinas CA. TSH and free thyroxine concentrations are associated with differing metabolic markers in euthyroid subjects. *Eur J Endocrinol*. 2010;**163**(2):273–278.
29. Roos A, Bakker SJ, Links TP, Gans RO, Wolffenbuttel BH. Thyroid function is associated with components of the metabolic syndrome in euthyroid subjects. *J Clin Endocrinol Metab*. 2007;**92**(2): 491–496.
30. Luna-Vazquez F, Cruz-Lumbreras R, Rodríguez-Castelán J, Cervantes-Rodríguez M, Rodríguez-Antolín J, Arroyo-Helguera O, Castelán F, Martínez-Gómez M, Cuevas E. Association between the serum concentration of triiodothyronine with components of metabolic syndrome, cardiovascular risk, and diet in euthyroid post-menopausal women without and with metabolic syndrome. *Springerplus*. 2014;**3**:266.
31. Kim HJ, Bae JC, Park HK, Byun DW, Suh K, Yoo MH, Kim JH, Min YK, Kim SW, Chung JH. Triiodothyronine levels are independently associated with metabolic syndrome in euthyroid middle-aged subjects. *Endocrinol Metab (Seoul)*. 2016;**31**(2): 311–319.
32. Lambadiari V, Mitrou P, Maratou E, Raptis AE, Tountas N, Raptis SA, Dimitriadis G. Thyroid hormones are positively associated with insulin resistance early in the development of type 2 diabetes. *Endocrine*. 2011;**39**(1):28–32.
33. Taneichi H, Sasai T, Ohara M, Honma H, Nagasawa K, Takahashi T, Ishii M, Fujiwara F, Yamashina M, Kajiwara T, Takabe N, Takahashi K, Satoh J. Higher serum free triiodothyronine levels within the normal range are associated with metabolic syndrome components in type 2 diabetic subjects with euthyroidism. *Tohoku J Exp Med*. 2011;**224**(3):173–178.
34. Boucai L, Hollowell JG, Surks MI. An approach for development of age-, gender-, and ethnicity-specific thyrotropin reference limits. *Thyroid*. 2011;**21**(1):5–11.
35. Mauvais-Jarvis F, Clegg DJ, Hevener AL. The role of estrogens in control of energy balance and glucose homeostasis. *Endocr Rev*. 2013;**34**(3):309–338.
36. Kim SR, Tull ES, Talbott EO, Vogt MT, Kuller LH. A hypothesis of synergism: the interrelationship of T3 and insulin to disturbances in metabolic homeostasis. *Med Hypotheses*. 2002;**59**(6):660–666.
37. Crunkhorn S, Patti ME. Links between thyroid hormone action, oxidative metabolism, and diabetes risk? *Thyroid*. 2008;**18**(2): 227–237.
38. Dimitriadis G, Baker B, Marsh H, Mandarino L, Rizza R, Bergman R, Haymond M, Gerich J. Effect of thyroid hormone excess on action, secretion, and metabolism of insulin in humans. *Am J Physiol*. 1985;**248**(5 Pt 1):E593–E601.
39. Yavuz DG, Yüksel M, Deyneli O, Ozen Y, Aydin H, Akalin S. Association of serum paraoxonase activity with insulin sensitivity and oxidative stress in hyperthyroid and TSH-suppressed nodular goitre patients. *Clin Endocrinol (Oxf)*. 2004;**61**(4): 515–521.
40. Lillioja S, Mott DM, Spraul M, Ferraro R, Foley JE, Ravussin E, Knowler WC, Bennett PH, Bogardus C. Insulin resistance and insulin secretory dysfunction as precursors of non-insulin-dependent diabetes mellitus. Prospective studies of Pima Indians. *N Engl J Med*. 1993;**329**(27):1988–1992.
41. Lin Y, Sun Z. Thyroid hormone potentiates insulin signaling and attenuates hyperglycemia and insulin resistance in a mouse model of type 2 diabetes. *Br J Pharmacol*. 2011;**162**(3):597–610.
42. Blanchet E, Bertrand C, Annicotte JS, Schlernitzauer A, Pessemesse L, Levin J, Fouret G, Feillet-Coudray C, Bonafos B, Fajas L, Cabello G, Wrutniak-Cabello C, Casas F. Mitochondrial T3 receptor p43 regulates insulin secretion and glucose homeostasis. *FASEB J*. 2012;**26**(1):40–50.
43. Ledda-Columbano GM, Perra A, Pibiri M, Molotzu F, Columbano A. Induction of pancreatic acinar cell proliferation by thyroid hormone. *J Endocrinol*. 2005;**185**(3):393–399.
44. Jansen MS, Cook GA, Song S, Park EA. Thyroid hormone regulates carnitine palmitoyltransferase Ialpha gene expression through elements in the promoter and first intron. *J Biol Chem*. 2000;**275**(45): 34989–34997.
45. Bastemir M, Akin F, Emral R, Alkis E. Impact of insulin sensitivity in relationship with prolactin and thyroid stimulating hormone. *Exp Clin Endocrinol Diabetes*. 2007;**115**(4):257–260.
46. Imai Y, Toyoda N, Maeda A, Kadobayashi T, Fangzheng G, Nishikawa M, Iwasaka T. Type 2 iodothyronine deiodinase expression is upregulated by the protein kinase A-dependent pathway and is downregulated by the protein kinase C-dependent pathway in cultured human thyroid cells. *Thyroid*. 2001;**11**(10):899–907.
47. Borges M, Ingbar SH, Silva JE. Iodothyronine deiodinase activities in FRTL5 cells: predominance of type I 5′-deiodinase. *Endocrinology*. 1990;**126**(6):3059–3068.
48. Köhrle J. Thyroid hormone transporters in health and disease: advances in thyroid hormone deiodination. *Best Pract Res Clin Endocrinol Metab*. 2007;**21**(2):173–191.
49. Gereben B, Zavacki AM, Ribich S, Kim BW, Huang SA, Simonides WS, Zeöld A, Bianco AC. Cellular and molecular basis of deiodinase-regulated thyroid hormone signaling. *Endocr Rev*. 2008;**29**(7):898–938.
50. Strich D, Karavani G, Edri S, Gillis D. TSH enhancement of FT4 to FT3 conversion is age dependent. *Eur J Endocrinol*. 2016;**175**(1): 49–54.