

The changes of thyroid hormone in euthyroid patients with diabetes

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Abstract

Background Thyroid dysfunction is suggested to be associated with diabetes, but it is not clear if the thyroid hormone levels are associated with diabetes in euthyroid adults. **Objective** To investigate the association between thyroid hormone levels and diabetes in euthyroid adults.

Methods Among the euthyroid adults who underwent health examination in West China Hospital, Sichuan University in 2016, patients with diabetes were identified according to the medical history, fasting blood glucose and HbA1c. Age and sex matched controls were identified from the population. The patients with diabetes group was further divided into two subgroups: patients with newly diagnosed diabetes (NDD) and with previously diagnosed diabetes (PDD). Independent t-test and multivariate logistic regression models were used to investigate the difference on the levels of thyroid stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3) and the ratio of FT4/FT3 between groups.

Results We included 32,557 participants, 2,271 with diabetes and 1,187 NDD. Compared to the patients without diabetes, the odds ratios (ORs) per one unit of TSH, FT4, FT4/FT3 ratio and FT3 in patients with diabetes were 0.88 [95% confidence interval (CI): 0.82-0.95], 1.11 (95% CI: 1.08-1.14), 2.05 (95%CI: 1.81-2.32) and 0.85 (95%CI: 0.78-0.93), respectively. Compared to NDD group, the ORs per one unit of TSH, FT4, FT4/FT3 ratio and FT3 of the PDD group were 0.81 (95%CI: 0.71-0.92), 1.08 (95%CI: 1.04-1.12), 1.76 (95%CI: 1.49-2.08) and 1.01 (95%CI: 0.92-1.12), respectively.

Conclusion In euthyroid adults, diabetes and its duration were significantly associated with thyroid hormone turnover. Patients with a previously diagnosed diabetes may be more likely to present elevated FT4/FT3 ratio, indicating an adaptive change of thyroid gland.

Introduction

Thyroid hormones play a key role in the energy metabolism, body shape, aging, and glucose and lipid metabolism in human (1–5). Accumulated evidence suggests that both hypothyroidism and hyperthyroidism are associated with the incidence of diabetes. Both too much or too little thyroid hormones have an impact on the progression of diabetes, and thyroid dysfunction is also involved in the occurrence and development of T2DM disease and affects the prognosis of diabetes. (6–10). Ashwini et al. believed that mild hypothyroidism protects adults from glucose tolerance and the body's redox balancing (11). Some in vitro and in vivo studies suggested that excessive thyroid hormone may impair the function of islet beta cells, while appropriate concentration of thyroid hormone can inhibit the apoptosis of islet beta cells and promote the proliferation of islet beta cells (12–14). Chaker et al. point out low and low-normal thyroid function are risk factors for incident diabetes, especially in individuals with prediabetes (15). However, the changes of thyroid hormone levels in euthyroid adults with diabetes are still unclear. It is also unknown whether the diabetic patient with normal thyroid function have thyroid hormone micro-disorder and how thyroid hormone levels change at different stages of diabetes in

euthyroid adults. This study aimed to investigate the association between the levels of thyroid hormones and diabetes among euthyroid population.

Methods

Study population

We retrospectively collected the health physical examination data from 1 January 2016 to 31 December 2016 in the Physical Examination Center of West China Hospital, Sichuan University.

We included the participants if they: 1) were aged between 20 to 79 years old; 2) had available data of TSH, FT4, FT3, thyroid autoantibodies [Thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TGAAb)], hemoglobin A1c (HbA1c), and fasting blood glucose (FBG); 3) agreed the scientific use of their health data and signed the informed consent.

We excluded the patients if their: 1) TPOAb or TGAAb were positive; 2) TSH levels were higher than 4.2 mU/L or lower than 0.27 mU/L according to the normal ranges of reference; 3) FT4 or FT3 were out of the normal ranges of reference (12.0 ~ 22.0 pmol/L and 3.60 ~ 7.50 pmol/L, respectively); 4) recorded history included thyroid surgery, diagnosed hypothyroidism, hyperthyroidism or thyroid malignancy; 5) comorbidities included malignancy, coronary artery disease, stroke, chronic obstructive pulmonary disease (COPD) or cirrhosis; 6) estimated glomerular filtration rate (eGFR) was less than 60 mL/(min·1.73 m²).

Grouping

Participants were identified as having diabetes if they had previous history of diagnosed diabetes or FBG > 7.0 mmol/L or HbA1c > 6.5% (16). The previous history of diagnosed diabetes was identified by patient self-report with validated records provided by well-trained physicians. Controls without diabetes were identified by 1:1 matching using sex, age (threshold < = 1 yrs) and BMI (threshold < = 0.5 kg/m²). The patients with diabetes were further divided into two subgroups, patients with newly diagnosed diabetes (NDD) group if they had elevated FBG (> 7.0 mmol/L) or HbA1c (> 6.5%) but free of self-reported previous diagnosed diabetes, and patients with previously diagnosed diabetes (PDD) group if they had history of diagnosed diabetes before the visit.

Data source

The data was from the Health Physical Examination Center dataset in West China Hospital of Sichuan University. The comorbidities were routinely collected by physician interviewing. Weight (kg), height (cm), waist circumference (WC, cm), and blood pressure were measured. Body mass index (BMI) was calculated using weight (kg) divided by the square of height (m²). Thyroid hormones and thyroid autoantibodies were tested using electrochemiluminescence immunoassay (Roche). Other parameters were tested using cobas8000 (Roche) in the clinical laboratory of the hospital, including HbA1c, triglyceride (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C),

alanine aminotransferase (ALT), aspartate aminotransferase (AST) and glutamyl transpeptidase (GGT). The eGFR was calculated using the CKD-EPI Creatinine Eq. (2009) (17).

Statistical analyses

The continuous variables, TG, HbA1c, FBG, FT3, HDL-C, ALT, AST, GGT and eGFR, had been tested to be non-normal distribution by Kolmogorov-Smirnov test, between groups, patients with diabetes vs. patients without non-diabetes, NDD vs. PDD groups. After these variables were transformed to more closely to normal distribution by log transformation, independent t-test was used to investigate the difference of these continuous variables between these groups. The comparison of categorized variables was conducted by using the Chi-squared test. To compare the levels of TSH, FT4, FT3 and the ratio of FT4/FT3 between patients with diabetes group and patients without diabetes group, we used three logistic regression models which were univariate model (Model 1); multivariate model adjusted for DBP and TG (Model 2); multivariate model adjusted for Model 2 + ALT and eGFR (Model 3). To compare the four thyroid hormone outcomes between NDD group and PDD group, four logistic regression models were performed, including univariate model (Model 1); multivariate model adjusted for age, sex and BMI (Model 2); multivariate model adjusted for Model 2 + DBP and TG (Model 3); multivariate model adjusted for Model 3 + ALT and eGFR (Model 4). The significance level of all analyses above was considered as 0.05, and all analyses were performed using SPSS 24.0.

Results

Baseline characteristics of the study subjects

According to the study population selection criteria, 32,557 participants were selected into our study from 170,896 people who underwent physical examinations in 2016 in West China Hospital, Sichuan University. There were 2,271 (7.0%) cases of diabetes, of which 1,187 cases were NDD and 1,084 cases were PDD. The process of study population selection was shown as flow chart (Fig. 1).

As shown in Table 1, average age and the percentage of previously diagnosed hypertension increased from patients without diabetes, NDD to PDD group. After patients with diabetes and without diabetes groups were matched by sex, age and BMI, patients with diabetes presented higher levels of FT4, TG, FPG, HbA1c, ALT, AST, GGT, eGFR, SBP, DBP, and WC, a higher FT4/FT3 ratio, a higher percentage of the previously diagnosed hypertension and a higher proportion of current alcohol drinking and smoking, but lower levels of TSH, FT3, LDL-C, and HDL-C than without diabetes group ($p < 0.01$). Compared to the NDD group, patients in PDD group showed higher levels of FT4, FPG, and HDL-C, a higher FT4/FT3 ratio ($P < 0.01$) and a higher portion of female ($P = 0.03$), but lower levels of FT3, TG, LDL-C, ALT, AST, GGT, SBP, DBP, BMI, and WC and a lower proportion of current alcohol drinking and smoking ($P < 0.05$). There were no statistically significant differences on the levels of TSH, eGFR, and HbA1c between NDD and PDD groups ($P > 0.05$).

Table 1
Baseline characteristics of participants.

Parameter	Control (n = 30354)	DM (n = 2271)			Matched control (n = 2243)	Matched DM (n = 2243)	P
		NDD (n = 1187)	PDD (n = 1084)	P			
Age/yr. (SD)	43.30 ± 11.01	51.66 ± 9.96	55.84 ± 9.51	< 0.001	53.42 ± 9.94	53.54 ± 9.85	0.68
Female/case (%)	12212 (40.32)	207 (17.44)	227 (20.94)	0.03	422 (18.81)	422 (18.81)	> 0.99
BMI (kg/m ² , SD)	23.58 ± 3.22	26.08 ± 3.18	24.97 ± 2.91	< 0.001	25.45 ± 2.98	25.47 ± 2.98	0.79
WC/ (cm, SD)	80.21 ± 10.03	89.17 ± 8.88	86.96 ± 8.69	< 0.001	86.76 ± 8.49	87.97 ± 8.64	< 0.001
Current smoking/case (%)	7356 (24.29)	474 (39.93)	352 (32.47)	< 0.001	25 (1.11)	819 (36.51)	< 0.001
Current drinking/case (%)	3630 (11.99)	263 (22.16)	175 (16.14)	< 0.001	12 (5.35)	437 (19.48)	< 0.001
Hypertension/case (%)	1891 (6.24)	239 (20.13)	318 (29.34)	< 0.001	333 (14.85)	541 (24.12)	< 0.001
SBP/ (mmHg, SD)	117.19 ± 15.54	129.57 ± 17.71	127.88 ± 17.24	0.02	125.10 ± 15.77	128.58 ± 17.46	< 0.001
DBP/ (mmHg, SD)	74.00 ± 10.61	80.70 ± 11.51	76.95 ± 10.46	< 0.001	77.96 ± 10.28	78.88 ± 11.16	0.004
FPG/ (mmol/L, SD) b	4.99 ± 0.52	8.30 ± 2.66	8.68 ± 3.03	0.01	5.15 ± 0.55	8.49 ± 2.86	< 0.001
HbA1c/ (%), SD) b	5.42 ± 0.35	7.34 ± 1.38	7.45 ± 1.59	0.22	5.56 ± 0.36	7.40 ± 1.49	< 0.001

TSH: thyroid stimulating hormone; FT4: free thyroxine; FT3: free triiodothyronine; TPOAb: thyroid peroxidase antibody; TGA: thyroglobulin antibody; HbA1c: hemoglobin A1c; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; BMI: body mass index; FPG: Fasting plasma glucose; TG: triglyceride; HDL: high density lipoprotein; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: glutamyl transpeptidase; DBP: diastolic blood pressure; SBP: Systolic blood pressure; WC: Waist circumference; DM: diabetes mellitus; NDD: newly diagnosed as diabetes; PDD: previously diagnosed as diabetes.

^b Transferred to normal distribution. 1 mmHg = 0.133 kPa.

Parameter	Control (n = 30354)	DM (n = 2271)			Matched control (n = 2243)	Matched DM (n = 2243)	P
		NDD (n = 1187)	PDD (n = 1084)	P			
TG/ (mmol/L, SD) ^b	1.51 ± 1.20	2.74 ± 2.42	2.01 ± 1.74	< 0.001	1.67 ± 1.073	2.40 ± 2.16	< 0.001
LDL-C/ (mmol/L, SD)	2.74 ± 0.73	2.94 ± 0.81	2.76 ± 0.79	< 0.001	2.90 ± 0.72	2.85 ± 0.81	< 0.001
HDL-C/ (mmol/L, SD) ^b	1.41 ± 0.40	1.19 ± 0.34	1.26 ± 0.37	< 0.001	1.31 ± 0.34	1.21 ± 0.35	< 0.001
TSH/ (mU/L, SD)	2.29 ± 0.87	2.26 ± 0.89	2.28 ± 0.88	0.69	2.35 ± 0.89	2.27 ± 0.88	0.001
FT4/ (pmol/L, SD)	16.90 ± 2.31	16.96 ± 2.30	17.23 ± 2.41	0.01	16.62 ± 2.22	17.09 ± 2.35	0.001
FT3/ (pmol/L, SD) ^b	5.06 ± 0.86	5.11 ± 1.02	4.88 ± 0.88	< 0.001	5.07 ± 0.65	5.00 ± 0.97	< 0.001
FT4/FT3 (SD)	3.38 ± 0.48	3.38 ± 0.56	3.58 ± 0.55	< 0.001	3.31 ± 0.48	3.47 ± 0.56	0.004
ALT/ (IU/L, SD) ^b	27.98 ± 24.99	38.24 ± 32.53	29.77 ± 18.33	< 0.001	31.35 ± 23.80	34.11 ± 27.06	< 0.001
AST/ (IU/L, SD) ^b	25.96 ± 15.00	30.23 ± 17.58	26.39 ± 13.37	< 0.001	27.85 ± 12.91	28.32 ± 15.83	< 0.14
GGT/ (IU/L, SD) ^b	33.85 ± 42.95	69.38 ± 119.11	43.92 ± 94.03	< 0.001	36.33 ± 40.82	57.32 ± 109.16	< 0.001
eGFR (mL/(min·1.73 m ²), SD) ^b	97.03 ± 17.55	89.99 ± 14.33	89.13 ± 13.58	0.22	86.33 ± 14.25	89.64 ± 13.98	< 0.001

TSH: thyroid stimulating hormone; FT4: free thyroxine; FT3: free triiodothyronine; TPOAb: thyroid peroxidase antibody; TGAb: thyroglobulin antibody; HbA1c: hemoglobin A1c; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; BMI: body mass index; FPG: Fasting plasma glucose; TG: triglyceride; HDL: high density lipoprotein; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: glutamyl transpeptidase; DBP: diastolic blood pressure; SBP: Systolic blood pressure; WC: Waist circumference; DM: diabetes mellitus; NDD: newly diagnosed as diabetes; PDD: previously diagnosed as diabetes.

^b Transferred to normal distribution. 1 mmHg = 0.133 kPa.

The changes of thyroid parameters in patients with diabetes and without diabetes groups

As shown in Table 2, diabetes was associated with lower TSH and FT3 levels but higher FT4 level and FT4/FT3 ratio in all three models. Compared to patients without diabetes, the ORs per one unit and their 95% CIs of TSH, FT4, FT3 and FT4/FT3 in patients with diabetes were 0.88 (0.82–0.95), 1.11 (1.08–1.14), 0.85 (0.78–0.93) and 2.05 (1.81–2.32) in Model 3, respectively ($P < 0.001$).

Table 2
The association between diabetes and thyroid parameters..

	Model1		Model2		Model3	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
TSH	0.90 (0.84–0.96)	0.001	0.88 (0.82–0.94)	< 0.001	0.88 (0.82–0.95)	< 0.001
FT4	1.10 (1.07–1.13)	< 0.001	1.11 (1.08–1.14)	< 0.001	1.11 (1.08–1.14)	< 0.001
FT3	0.89 (0.82–0.97)	< 0.001	0.86 (0.78–0.93)	< 0.001	0.85 (0.78–0.93)	< 0.001
FT4/FT3	1.84 (1.64–2.07)	< 0.001	2.02 (1.79–2.28)	< 0.001	2.05 (1.81–2.32)	< 0.001
a. Model 1: univariate; Model 2: DBP and TG; Model 3: DBP, TG, ALT and eGFR.						
b. TSH: Thyroid Stimulating Hormone; FT4: Free thyroxine; FT3: Free triiodothyronine; DBP: Diastolic blood pressure; eGFR: estimated glomerular filtration rate; TG: triglyceride; ALT: alanine aminotransferase.						
The changes of thyroid parameters in NDD and PDD groups						
As shown in Table 3, patients in PDD group presented lower FT3 level but higher FT4 level and FT4/FT3 ratio in all four models. Compared to NDD group, the ORs per one unit and their 95% CIs of FT4, FT3 and FT4/FT3 in PDD group were 1.08 (1.04–1.12; $P < 0.001$), 0.81 (0.71–0.92; $P = 0.002$) and 1.76 (1.49–2.08; $P < 0.001$) in Model 4, respectively.						

Table 3

The difference of thyroid parameters between newly diagnosed diabetes and previously diagnosed diabetes.

	Model1		Model2		Model 3		Model4	
	OR (95% CI)	P						
TSH	1.02 (0.93– 1.12)	0.69	1.00 (0.91– 1.10)	0.98	1.01 (0.91– 1.11)	0.91	1.01 (0.92– 1.12)	0.78
FT4	1.05 (1.01– 1.09)	0.01	1.08 (1.04– 1.12)	< 0.001	1.08 (1.04– 1.12)	< 0.001	1.08 (1.04– 1.12)	< 0.001
FT3	0.67 (0.59– 0.76)	< 0.001	0.80 (0.70– 0.91)	0.001	0.79 (0.69– 0.90)	< 0.001	0.81 (0.71– 0.92)	0.002
FT4/FT3	1.97 (1.68– 2.31)	< 0.001	1.80 (1.52– 2.12)	< 0.001	1.82 (1.54– 2.15)	< 0.001	1.76 (1.49– 2.08)	< 0.001
a. Model1: none (univariate); Model2: age, sex, BMI; Model 3: age, sex, BMI, DBP and TG; Model4: age, sex, BMI, DBP, TG, ALT and eGFR.								
b. TSH: Thyroid Stimulating Hormone; FT4: Free thyroxine; FT3: Free triiodothyronine; DBP: Diastolic blood pressure; BMI: body mass index; eGFR: estimated glomerular filtration rate; TG: triglyceride; ALT: alanine aminotransferase.								

Discussion

This cross-sectional population-based study suggested that thyroid hormone profiles were associated with diabetes and its duration in euthyroid adults. FT4/FT3 ratio elevated significantly in patients with diabetes, especially in those with PDD, indicating the progression of diabetes may go along with a decreased turnover of thyroxine (18,19) and increased chances of developing euthyroid sickness syndrome (ESS) (20–23).

The association between diabetes and thyroid dysfunction including hyperthyroidism and hypothyroidism was well established in previous literature (6,7). Our study observed euthyroid adults, suggesting euthyroid participants with diabetes had lower TSH, FT3 levels, and higher FT4 level and FT4/FT3 ratio than those without diabetes, which is in line with another cross-sectional study from China (24). Interestingly, two longitudinal studies from Korea did not prove a statistically significant association between the incidence of diabetes and the suppressed TSH level, but the individual-level changes of TSH (25,26). However, a cohort study from Rotterdam suggested that higher TSH levels and lower FT4 levels within the reference range of thyroid function were associated with a higher risk of diabetes (15), while

another cohort study in Netherland showed no association between plasma TSH levels and incident T2DM (27). The difference of these results can be explained by the study population. All participants with thyroid autoimmunity were excluded from our analysis. They are found in over 10% in the population and likely to develop early stage of thyroid dysfunction, which may elevate or reduce the TSH levels. None of the previous studies excluded the impact of thyroid autoimmunity, which may slightly affect the results (15, 25–27). To be noted, two cohort studies from Netherland included Caucasian adults with higher cardiovascular risks than our study population (15,27), while the Korean study are more in line with us (25,26). It suggests this association can be ethnicity-based, and needs more validation in different populations. The suppressed TSH level in the PDD group may be partially explained by the increased risk of ESS and metformin therapy in these population (9,28,29). The changes of thyroid hormone profiles might be due to that oxidative stress, related to long-term diabetes and its complications, could induce inhibition of type 1 (D1) 5'deiodinases in liver and kidneys which results in a decrement of peripheral deiodinase activity (20). This change downregulates the transformation from tetraiodothyronine (T4) to triiodothyronine (T3), but upregulates the transformation from tetraiodothyronine (T4) to reverse triiodothyronine (rT3) (30,31), meaning the FT3 level declined and the FT4/FT3 ratio evaluated as the duration grew, indicating the typical change of ESS (32) along with the deterioration of diabetes.

Our study has some strengths. Firstly, the study population enrolled large population with confirmed euthyroid adults, which may better reflect the pathophysiological changes of thyroid hormones in patients with diabetes. Secondly, matched controls were used and three multivariate models in the study showed consistent results, which suggested the robustness of our results.

However, our study has several limitations. Firstly, this study is a cross-sectional study, failing to conclude the causation between thyroid hormone profiles and diabetic development. Secondly, the study population was recruited from the health examination population, possibly different from the community-based population. Thirdly, we could not access the detailed duration of diabetes or the undergoing treatment of the patients, which might be unadjusted biases in the study, but we could conclude the duration of PDD was longer than that of NDD, since all patients in NDD were diagnosed in 2016, while all patients in PDD were diagnosed before 2016.

Conclusion

Our study found a reduced thyroid hormone turnover in euthyroid patients with diabetes, especially in those with longer diabetes duration, which manifested the diabetes incidence and deterioration was accompanied with decreased thyroid hormone turnover. To determine our results, we need to conduct a longitudinal study of normal thyroid adults without thyroid autoimmunity in our other study.

Abbreviations

NDD
newly diagnosed as diabetes;

PDD
previously diagnosed as diabetes;
TSH
thyroid stimulating hormone;
FT4
free thyroxine;
FT3
free triiodothyronine;
Odds ratios
ORs;
Confidence interval
CI;
TPOAb
thyroid peroxidase antibody;
TGA
thyroglobulin antibody;
HbA1c
hemoglobin A1c;
COPD
chronic obstructive pulmonary disease;
eGFR
estimated glomerular filtration rate;
BMI
body mass index;
FPG
Fasting plasma glucose;
TG
triglyceride;
HDL
high density lipoprotein;
LDL-C
low density lipoprotein cholesterol;
HDL-C
high density lipoprotein cholesterol;
ALT
alanine aminotransferase;
AST
aspartate aminotransferase;
GGT
glutamyl transpeptidase;

DBP
diastolic blood pressure;
SBP
Systolic blood pressure;
WC
Waist circumference;
DM
diabetes mellitus;
Reverse triiodothyronine
rT3;
Type 1 deiodinases
D1;
Euthyroid sickness syndrome
ESS;
Tetraiodothyronine
T4;
Triiodothyronine
T3.

Declarations

Ethics approval and consent to participate

This study is approved by the ethical committee of West China Hospital, Sichuan University (No. 2015-202). Only subjects were included if they signed informed consent agreeing the scientific use of their health data.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors have no conflicts of interest to declare. No financial disclose.

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Authors' contributions

(I) Conception and design: SYL, SJL and ZMA; (II) Administrative support: FZ, YH and ZMA; (III) Provision of study materials or patients: Physical Examination Center, West China Hospital, Sichuan University; (IV) Collection and assembly of data: KQ, FZ, QW, ZL and YH; (V) Data analysis and interpretation: KQ, FZ, QW, SQL and SYL; (VI) Manuscript drafting: KQ, YZ and SYL; Critical revise: all authors; (VII) Final approval of manuscript: All authors.

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Figures

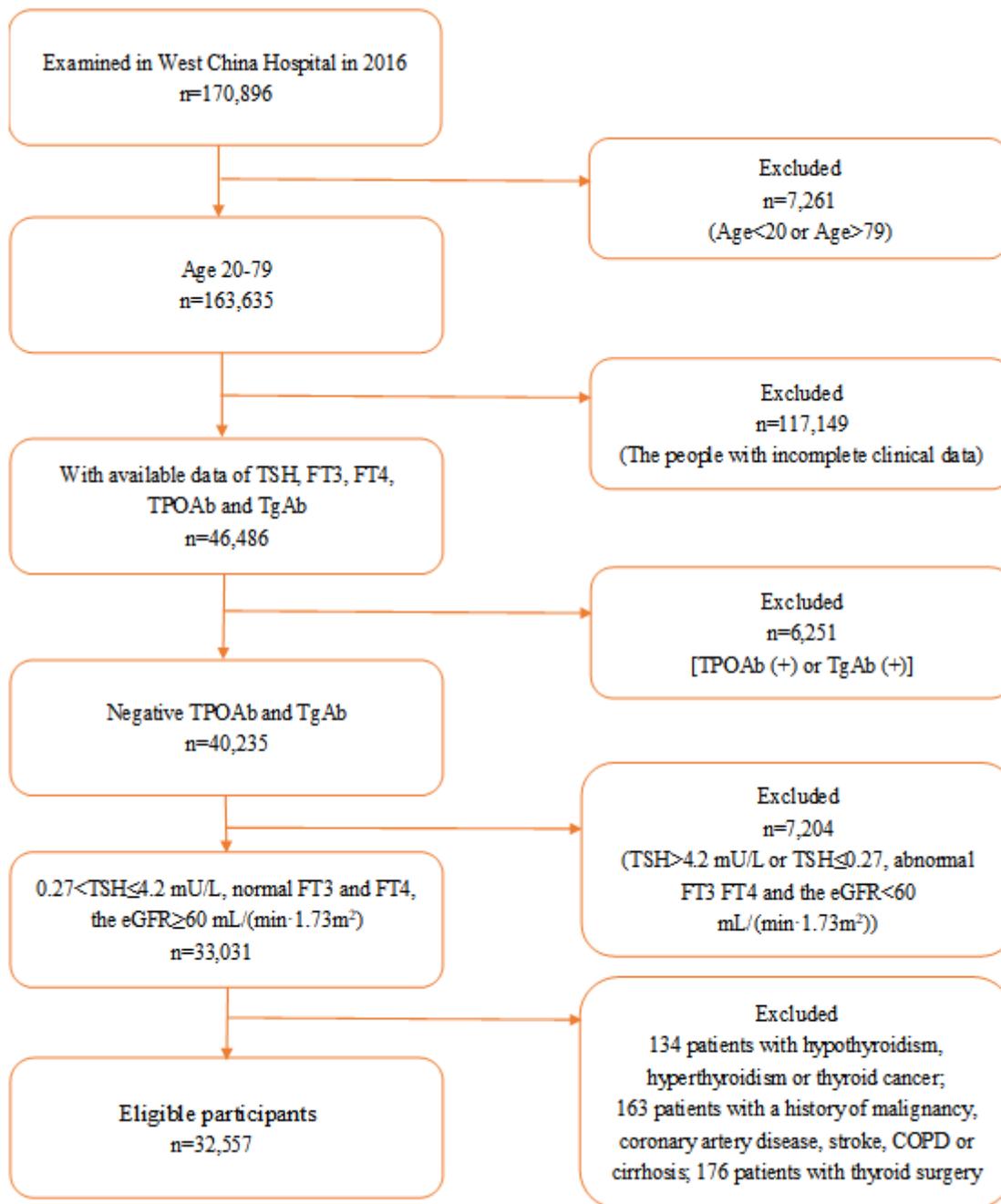


Figure 1

Screening process of the participants. a. TSH: thyroid stimulating hormone; FT4: free thyroxine; FT3: free triiodothyronine; TPOAb: thyroid peroxidase antibody; TGAb: thyroglobulin antibody; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate.