Circulating free triiodothyronine concentration is positively associated with β-cell function in euthyroid patients with obesity and type 2 diabetes

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Abstract
Objective: To investigate the relationship between thyroid hormone concentrations and β-cell function in euthyroid patients with obesity and type 2 diabetes.
Methods: We performed a single-center cross-sectional study of 254 patients with type 2 diabetes mellitus aged ≥40 years. The participants were allocated to an obesity group or non-obesity group on the basis of their body mass index (BMI). Their β-cell function was assessed by measuring C-peptide concentration during a 75-g oral glucose tolerance test (OGTT); and their serum free triiodothyronine (FT3), free thyroxine (FT4) and thyroid-stimulating hormone concentrations were measured.
Results: The serum FT3 concentration and the C-peptide concentrations at five time points of the OGTT were significantly higher in the obesity group than in the non-obesity group. FT3 was positively associated with the β-cell function of the obesity group, but not that of the non-obesity group, in multiple linear regression analysis, after adjustment for potential confounding factors. Serum FT3 concentration was also significantly associated with indices of obesity (BMI, waist circumference, body fat percentage, fat mass, fat mass/height^2 and visceral fat area).

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Conclusions: Obesity-associated high serum FT3 concentrations might affect β-cell function in euthyroid patients with obesity and type 2 diabetes.

Keywords
Free triiodothyronine, β-cell function, type 2 diabetes mellitus, obesity, euthyroidism, C-peptide

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Introduction
Type 2 diabetes mellitus (T2DM) and thyroid dysfunction are the two most commonly encountered endocrine disorders in clinical practice. The pathophysiological relationships between T2DM and thyroid dysfunction have been previously reviewed.1–3 Because islet β-cell dysfunction is a key component of the pathogenesis of T2DM, the relationships between thyroid hormones and β-cell function have been explored previously. Several studies have shown that hyperthyroidism is associated with greater glucose-induced insulin secretion, whereas hypothyroidism shows the opposite relationship.1–3 However, there have been few studies regarding the relationship between thyroid function and β-cell function in euthyroid individuals, and the results obtained have been contradictory.4–7 The circulating free triiodothyronine (FT3) concentration was found to be positively associated with β-cell function in euthyroid individuals with normal glucose tolerance (NGT) or prediabetes.4–6 Conversely, Li et al. found that free thyroxine (FT4), but not FT3, is independently and negatively associated with β-cell function in euthyroid patients with untreated T2DM.7 Therefore, the relationship between euthyroidism and β-cell function in patients with T2DM requires further exploration.

Thyroid hormones play key roles in the regulation of metabolism and energy expenditure.8 Previous studies have shown that the serum FT3 concentration is high in individuals with obesity.9 Indices of obesity, such as body mass index (BMI), waist circumference (WC) and fat percentage, are positively associated with FT3 concentration in euthyroid populations.10–12 The high FT3 concentrations in individuals with obesity are considered to be an adaptive response to maintain energy balance.13 Thus, obesity can affect the circulating concentrations of thyroid hormones. However, it is unclear whether the relationships between thyroid hormone concentrations and β-cell function are also affected by obesity. To investigate this further, we performed a cross-sectional study of euthyroid patients with T2DM in which we evaluated the relationships of thyroid hormone concentrations with β-cell function.

Materials and methods
Study participants
We performed a cross-sectional study of patients with T2DM, aged ≥40 years, who were recruited at Qilu Hospital of Shandong University between April 2017 and March 2020. Their islet function, thyroid function, and whole-body composition were evaluated. Participants with one or more of the following were excluded: 1) another type of diabetes; 2) severe liver dysfunction, defined using aspartate
aminotransferase (AST) or alanine aminotransferase (ALT) activities >120 U/L; 3) severe kidney dysfunction, defined using an estimated glomerular filtration rate (eGFR) <30 mL/minute/1.73 m²; 4) acute cerebral infarction or acute myocardial infarction; 5) malignant disease; and 6) history of thyroid disease, including hyperthyroidism, hypothyroidism, the use of thyroid medication, and thyroidectomy. Diabetes was diagnosed according to the 2006 World Health Organization (WHO) criteria.14 Obesity was defined using a BMI of ≥ 25 kg/m².15 The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Qilu Hospital, Cheeloo College of Medicine, Shandong University (approval number KYLL-202008-067). Written informed consent was obtained from all the participants. The reporting of this study conforms to the STROBE guidelines.16

Data collection

The medical records system of Qilu Hospital was used to collect all the data, including the age, sex, BMI, waist circumference (WC), blood pressure (BP), duration of diabetes, history of insulin treatment and smoking habits of the participants. Fasting venous blood samples were collected for the measurement of the glucose, HbA1c, triglyceride, total cholesterol, creatinine, and thyroid hormone concentrations, including those of FT₃, FT₄ and thyroid-stimulating hormone (TSH). Body fat percentage, fat mass, fat mass/height² and visceral fat area (VFA) were measured using a dual-energy X-ray absorptiometry scanner (Hologic, Inc., Bedford, MA, USA). eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula.17

To avoid an effect of insulin treatment, we measured serum C-peptide concentration as an index of β-cell function. All the participants underwent a 75-g oral glucose tolerance test (OGTT), and C-peptide concentrations were measured 0, 30, 60, 120 and 180 minutes after glucose administration. Because exogenous insulin was being administered by some of the participants, β-cell function was assessed using the area under the curve (AUC) of the C-peptide concentration, calculated using the trapezoidal rule18 (AUC₀–₃₀ minutes, AUC₀–₆₀ minutes, AUC₀–₁₂₀ minutes and AUC₀–₁₈₀ minutes).

Statistical analysis

SPSS software version 22.0 (IBM, Inc., Armonk, NY, USA) was used to analyze the data. The distributions of the datasets were assessed using the Kolmogorov–Smirnov test. Continuous, normally distributed data are presented as the mean ± standard deviation (SD); continuous, non-normally distributed data are presented as the median (interquartile range) and categorical data are presented as number (%). Normally distributed datasets were compared using Student’s t-test, non-normally distributed datasets were compared using the Mann–Whitney U-test and categorical datasets were compared using the chi-square test. Multiple linear regression analysis was used to explore the relationships of thyroid hormones with β-cell function and indices of obesity. P < 0.05 was regarded as indicating statistical significance.

Results

General characteristics of the participants

A total of 283 patients with T2DM who were ≥40 years old were recruited, of whom 29 were excluded for the reasons given above. Therefore, data from 254 participants (113 women) were analyzed. The participants were allocated to two groups on the basis of their BMI. As shown in
Table 1. General characteristics of the participants

| Characteristic                          | All participants (n = 254) | Non-obesity group (n = 99) | Obesity group (n = 155) | P-value |
|----------------------------------------|----------------------------|---------------------------|------------------------|---------|
| Women (n, %)                           | 113 (44.5%)                | 55 (55.6%)                | 58 (37.4%)             | 0.006   |
| Age (years)                            | 59.46 ± 8.37               | 60.24 ± 7.76              | 58.95 ± 8.72           | 0.232   |
| BMI (kg/m²)                            | 26.04 ± 4.15               | 22.23 ± 1.99              | 28.48 ± 3.24           | <0.001  |
| WC (cm)                                | 95.62 ± 11.36              | 87.53 ± 9.01              | 100.78 ± 9.56          | <0.001  |
| Systolic BP (mmHg)                     | 138.24 ± 18.79             | 135.20 ± 19.62            | 140.17 ± 18.04         | 0.039   |
| Diastolic BP (mmHg)                    | 79.46 ± 11.91              | 76.73 ± 11.47             | 81.20 ± 11.89          | 0.003   |
| FBG (mmol/L)                           | 8.13 ± 2.73                | 7.87 ± 2.67               | 8.30 ± 2.76            | 0.230   |
| HbA1c (%)                              | 8.53 ± 1.88                | 8.56 ± 2.08               | 8.51 ± 1.75            | 0.828   |
| Duration of diabetes (months)          | 138.00 (72.00–216.00)      | 132.00 (84.00–216.00)     | 144.00 (72.00–216.00)  | 0.832   |
| Insulin treatment (n, %)               | 126 (49.6%)                | 55 (55.6%)                | 71 (45.8%)             | 0.157   |
| Triglyceride (mmol/L)                  | 1.47 (1.04–2.15)           | 1.27 (0.87–1.89)          | 1.60 (1.18–2.19)       | 0.003   |
| Cholesterol (mmol/L)                   | 4.58 ± 1.05                | 4.62 ± 1.11               | 4.56 ± 1.01            | 0.635   |
| Smoking (n, %)                         | 71 (28.0%)                 | 26 (26.3%)                | 45 (29.0%)             | 0.668   |
| eGFR (mL/minute/1.73 m²)               | 95.60 ± 15.38              | 96.03 ± 15.02             | 95.33 ± 15.65          | 0.727   |
| Body fat percentage (%)                | 31.79 ± 6.29               | 29.07 ± 5.96              | 33.53 ± 5.88           | <0.001  |
| Fat mass (kg)                          | 22.51 ± 6.64               | 17.27 ± 3.84              | 25.86 ± 5.83           | <0.001  |
| Fat mass/height² (kg/m²)               | 8.19 ± 2.47                | 6.39 ± 1.54               | 9.34 ± 2.26            | <0.001  |
| VFA (cm²)                              | 144.48 ± 51.48             | 107.24 ± 40.50            | 168.43 ± 42.89         | <0.001  |

Data are expressed as mean ± SD, median (interquartile range) or number (%); and were analyzed using Student’s t-test, the Mann–Whitney U-test, or the chi-square test, respectively. BMI, body mass index; WC, waist circumference; BP, blood pressure; FBG, fasting blood glucose; eGFR, estimated glomerular filtration rate; VFA, visceral fat area. Significant P values (< 0.05) are indicated in bold.

The obesity group had significantly higher BMI, WC, body fat percentage, fat mass, fat mass/height² and VFA (all P < 0.01) than the non-obesity group. In addition, the proportion of men, BP (both P < 0.05) and serum triglyceride concentration (P < 0.01) were higher in the obesity group.

**Serum thyroid hormone concentrations and β-cell function in the obesity and non-obesity groups**

To evaluate the effect of obesity on the relationships between thyroid hormones and β-cell function, we first compared the serum thyroid hormone concentrations and β-cell function of the obesity and non-obesity groups. As shown in Figure 1, the FT₃ concentration of the obesity group was significantly higher than that of the non-obesity group (P < 0.01), whereas the FT₄ and TSH concentrations did not significantly differ between the groups. In addition, the C-peptide concentrations at five time points of the OGTT (Figure 2a) and the AUCs for C-peptide (Figure 2b–2e) were higher in the obesity group than in the non-obesity group (all P < 0.01).

**Results of the multiple linear regression analysis of the relationships between thyroid hormone concentrations and β-cell function**

Next, we explored the relationships between thyroid hormone concentrations and β-cell function in the participants. As shown in Table 2, before adjustment (model 1), the FT₃ concentration was positively associated with all the indices of β-cell function (all at least P < 0.05), and TSH was positively associated with AUC₀–60 minutes, AUC₀–120 minutes and AUC₀–180 minutes.
After adjustment for age, sex, SBP, duration of diabetes, HbA1c, triglyceride, cholesterol, smoking habits and eGFR (model 2), FT3 was also positively associated with AUC0–60 minutes, AUC0–120 minutes and AUC0–180 minutes (P < 0.05). However, after further adjustment for BMI in model 3, the association of FT3 with β-cell function disappeared, which implies that obesity might mediate the relationship between FT3 and β-cell function.

The associations of thyroid hormone concentrations with β-cell function in the non-obesity and obesity groups are presented in Table 3. Interestingly, after adjustment for age, sex, SBP, duration of diabetes, HbA1c, triglyceride, cholesterol, smoking habits and eGFR, a close association of FT3 with β-cell function was present in the obesity group (P < 0.01 for each measure), but not in the non-obesity group.

**Results of the multiple linear regression analysis of the relationships of thyroid hormone concentrations with obesity**

Finally, we evaluated the relationships between thyroid hormone concentrations and obesity in euthyroid patients with T2DM. As shown in Table 4, after adjustment for age, sex, SBP, duration of
Table 2. Results of the multiple linear regression analysis of the relationships between thyroid hormones and indices of β-cell function, as the dependent variable

| Dependent variable | Model 1 | Model 2 | Model 3 |
|--------------------|---------|---------|---------|
|                    | β Coefficient | P-value | β Coefficient | P-value | β Coefficient | P-value |
| FT3                |          |         |          |         |          |         |
| Fasting C-peptide  | 0.269    | 0.019   | 0.156    | 0.207   | 0.069    | 0.567   |
| AUC0–30 minutes    | 0.190    | 0.008   | 0.139    | 0.064   | 0.085    | 0.246   |
| AUC0–60 minutes    | 0.499    | 0.003   | 0.395    | 0.024   | 0.258    | 0.126   |
| AUC0–120 minutes   | 1.310    | 0.003   | 1.093    | 0.013   | 0.787    | 0.066   |
| AUC0–180 minutes   | 2.066    | 0.005   | 1.806    | 0.013   | 1.345    | 0.060   |
| FT4                |          |         |          |         |          |         |
| Fasting C-peptide  | 0.017    | 0.516   | 0.004    | 0.861   | 0.017    | 0.486   |
| AUC0–30 minutes    | −0.006   | 0.749   | −0.011   | 0.480   | −0.001   | 0.924   |
| AUC0–60 minutes    | −0.040   | 0.337   | −0.051   | 0.181   | −0.025   | 0.483   |
| AUC0–120 minutes   | −0.133   | 0.216   | −0.145   | 0.126   | −0.089   | 0.336   |
| AUC0–180 minutes   | −0.207   | 0.256   | −0.215   | 0.173   | −0.128   | 0.405   |
| TSH                |          |         |          |         |          |         |
| Fasting C-peptide  | 0.042    | 0.517   | 0.005    | 0.942   | −0.020   | 0.742   |
| AUC0–30 minutes    | 0.075    | 0.058   | 0.046    | 0.216   | 0.026    | 0.479   |
| AUC0–60 minutes    | 0.212    | 0.022   | 0.132    | 0.127   | 0.080    | 0.338   |
| AUC0–120 minutes   | 0.577    | 0.016   | 0.315    | 0.149   | 0.195    | 0.357   |
| AUC0–180 minutes   | 0.901    | 0.027   | 0.382    | 0.292   | 0.197    | 0.577   |

Model 1: Unadjusted. Model 2: Adjusted for age, sex, SBP, duration of diabetes, HbA1c, triglyceride, cholesterol, smoking habits and eGFR. Model 3: Adjusted for age, sex, SBP, duration of diabetes, HbA1c, triglyceride, cholesterol, smoking habits, eGFR and BMI. AUC, area under the C-peptide concentration curve; SBP, systolic blood pressure; HbA1c, glycosylated hemoglobin; eGFR, estimated glomerular filtration rate; BMI, body mass index. Significant P values (< 0.05) are indicated in bold.

Table 3. Results of the multiple linear regression analysis of the relationships between thyroid hormones and indices of β-cell function, as the dependent variable, in the non-obesity and obesity groups

| Dependent variable | FT3 | FT4 | TSH |
|--------------------|-----|-----|-----|
|                    | β Coefficient | P-value | β Coefficient | P-value | β Coefficient | P-value |
| Non-obesity group  |     |     |     |          |         |          |         |
| Fasting C-peptide  | −0.318 | 0.142 | −0.020 | 0.656 | −0.099 | 0.391 |
| AUC0–30 minutes    | −0.125 | 0.216 | −0.027 | 0.209 | 0.017 | 0.746 |
| AUC0–60 minutes    | −0.227 | 0.268 | −0.077 | 0.077 | 0.079 | 0.453 |
| AUC0–120 minutes   | −0.444 | 0.447 | −0.214 | 0.084 | 0.288 | 0.332 |
| AUC0–180 minutes   | −0.612 | 0.560 | −0.376 | 0.092 | 0.457 | 0.392 |
| Obesity group      |     |     |     |          |         |          |         |
| Fasting C-peptide  | 0.417 | 0.005 | 0.011 | 0.727 | 0.078 | 0.301 |
| AUC0–30 minutes    | 0.316 | 0.002 | 0.001 | 0.952 | 0.050 | 0.338 |
| AUC0–60 minutes    | 0.781 | 0.002 | −0.022 | 0.700 | 0.109 | 0.388 |
| AUC0–120 minutes   | 1.957 | 0.002 | −0.078 | 0.573 | 0.170 | 0.585 |
| AUC0–180 minutes   | 3.086 | 0.002 | −0.081 | 0.717 | 0.083 | 0.870 |

Data were adjusted for age, sex, SBP, duration of diabetes, glycosylated hemoglobin, triglyceride, cholesterol, smoking habits and estimated glomerular filtration rate. AUC, area under the curve; FT3, free triiodothyronine; FT4, free thyroxine, TSH, thyroid-stimulating hormone. Significant P values (< 0.05) are indicated in bold.
diabetes, HbA1c, triglyceride, cholesterol, smoking habits and eGFR, FT3 was significantly associated with all the indices of obesity assessed (BMI, WC, body fat percentage, fat mass, fat mass/height$^2$ and VFA; all at least $P < 0.05$).

**Discussion**

In the present study, we have shown that the serum FT3 and C-peptide concentrations of euthyroid patients with obesity and T2DM are higher than in those without obesity. Further analysis showed that FT3 concentration is positively associated with $\beta$-cell function in patients with obesity and T2DM, but not in those with T2DM but no obesity.

It has been shown that T3 induces the proliferation of pancreatic $\beta$-cells through activation of the phosphoinositol 3-kinase/AKT and mitogen-activated protein kinase/extracellular signal-regulated kinase pathways.\textsuperscript{19–21} However, these findings were principally made *in vitro* or using concentrations of T3 that were outside the normal range. The effects of physiological concentrations of thyroid hormones on $\beta$-cell function remain unclear, especially in patients with T2DM. To date, there have been only a few studies of the relationship between thyroid hormone concentrations within the normal range and $\beta$-cell function.\textsuperscript{4–7,22} Ortega *et al.*\textsuperscript{4} and Stephan *et al.*\textsuperscript{5} found that the plasma FT3 concentration is positively associated with insulin secretion in euthyroid individuals with normal glucose tolerance (NGT), and Oda *et al.*\textsuperscript{6} found that FT3 is positively associated with both basal and glucose-stimulated insulin secretion in euthyroid individuals with prediabetes. However, the results obtained for patients with T2DM have been contradictory. Li *et al.*\textsuperscript{7} found that FT4, but not FT3, is negatively associated with homeostasis model of assessment (HOMA)-$\beta$ in patients with untreated T2DM, while Taneichi *et al.*\textsuperscript{22} found that FT3 is not associated with urine C-peptide concentration in patients with T2DM. These inconsistent results may be attributable to the differing study populations or the indices reflecting $\beta$-cell function used in these studies.

Recent studies have shown that serum FT3 concentrations within normal range are relatively high in individuals with obesity and positively associated with multiple indices of obesity.\textsuperscript{9–12} This is considered to be an adaptive response to maintain energy

| Table 4. Results of the multiple linear regression analysis of the relationships between thyroid hormones and indices of obesity, as the dependent variable |
|-----------------|------------|---------------|-----------------|---------------|
| Dependent variable | $\beta$ Coefficient | $P$-value | $\beta$ Coefficient | $P$-value | $\beta$ Coefficient | $P$-value |
|-----------------|-----------------|-----------|-----------------|-----------|-----------------|-----------|
| BMI | 1.363 | 0.006 | -0.179 | 0.084 | 0.395 | 0.127 |
| WC | 3.114 | 0.022 | -0.090 | 0.749 | 0.577 | 0.413 |
| Body fat percentage | 2.039 | 0.001 | -0.111 | 0.386 | 0.598 | 0.061 |
| Fat mass | 2.138 | 0.010 | -0.217 | 0.206 | 0.585 | 0.173 |
| Fat mass/height$^2$ | 0.871 | 0.003 | -0.088 | 0.150 | 0.214 | 0.160 |
| VFA | 15.466 | 0.012 | -1.432 | 0.263 | 3.372 | 0.292 |

Data were adjusted for age, sex, SBP, duration of diabetes, HbA1c, triglyceride, cholesterol, smoking and eGFR. AUC, area under the C-peptide concentration curve; FT3, free triiodothyronine; FT4, free thyroxine, TSH, thyroid-stimulating hormone; BMI, body mass index; WC, waist circumference; VFA, visceral fat area. Significant $P$ values ($< 0.05$) are indicated in bold.
balance because thyroid hormones play major roles in the regulation of metabolism and energy expenditure. Given that FT₃ has been shown to induce the proliferation of pancreatic β-cells, we wished to determine whether the high FT₃ concentrations of patients with obesity affect β-cell function. To this end, we first compared the thyroid hormone concentrations and β-cell function of patients with or without obesity. As expected, both the serum FT₃ and C-peptide concentrations were higher in patients with both T2DM and obesity. Next, we investigated the relationships between thyroid hormone concentrations and β-cell function in all the participants, and as expected, FT₃ was found to be positively associated with β-cell function (models 1 and 2, Table 2). However, when BMI was added, the relationship between FT₃ and β-cell function disappeared (model 3), which implies that obesity might affect the relationship between FT₃ and β-cell function. To test this hypothesis, the relationships of thyroid hormone concentrations with β-cell function were explored separately in the non-obesity and obesity groups, and the association of FT₃ with β-cell function was only identified in the latter group. These data suggest that serum FT₃ concentrations may increase in patients with T2DM and obesity as an adaptive response to maintain energy balance and that high physiological concentrations of FT₃ might affect the secretion of C-peptide. Finally, we evaluated the relationships between thyroid hormones and obesity, and found that FT₃ is significantly associated with a number of indices of obesity, as shown in previous studies.

The principal strength of the present study was that all the participants underwent a 75-g OGTT, and we used the AUC of C-peptide to assess β-cell function, which is currently regarded as the gold standard measure of β-cell function. However, the study also had some limitations. First, it was cross-sectional study; therefore, we cannot draw conclusions regarding the cause-and-effect relationship between obesity, thyroid hormone concentrations within the normal range and β-cell function. However, our findings suggest why FT₃ concentrations within the normal range are positively associated with β-cell function in patients with obesity. Second, the study included patients with previously diagnosed T2DM, and therefore their previous use of insulin might have affected the serum concentrations of insulin measured. However, in the present study, we used C-peptide, rather than insulin, concentration to assess β-cell function, which should have improved the accuracy of the results. Third, other factors that affect the secretion of thyroid hormones, such as iodine intake, and other factors that affect C-peptide production, such as free fatty acid and incretin concentrations, were not adjusted for in the analyses, which might have affected the results.

Conclusions

In the present study, we have shown that the serum FT₃ and C-peptide concentrations of patients with both obesity and T2DM are higher than those of patients who do not have obesity. In addition, the FT₃ concentration is positively associated with β-cell function in patients with both obesity and T2DM, but not in those without obesity. Thus, obesity might affect the relationship between FT₃ and β-cell function in euthyroid patients with T2DM. However, further prospective studies and mechanistic research are needed to corroborate the findings of the study.

Author contributions

JBL and KL designed the study and drafted the manuscript. LG and AXM collected the data. JBL, KL, LG, XFY and XHG performed the
analyses. All the authors approved the final version of the manuscript.

**Declaration of conflicting interest**

The authors declare that there is no conflict of interest.

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