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ORIGINAL RESEARCH

# Correlation Between the Thyroid Hormone Levels and Type 2 Diabetes Mellitus in Non-Alcoholic Fatty Liver Disease

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**Background:** Nonalcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus (T2DM) are significant metabolic disorders that frequently coexist and share interrelated pathophysiological mechanisms. Thyroid hormones (THs) play multifaceted roles in metabolic regulation. This study explored the association between THs—particularly the free triiodothyronine (FT3) to free thyroxine (FT4) ratio (FT3/FT4)—and T2DM among NAFLD individuals.

**Patients and Methods:** A total of 4942 patients with NAFLD hospitalized at the Affiliated Hospital of Hangzhou Normal University between 2020 and 2023 were retrospectively analyzed. Partial correlation analysis controlling for age and sex was conducted to investigate the relationships between THs and the FT3/FT4 ratio with hemoglobin A1c (HbA1c) and fasting blood glucose (FBG) in NAFLD patients with T2DM. Meanwhile, the association between the FT3/FT4 ratio and T2DM was assessed by binary logistic regression. Receiver operating characteristic (ROC) curve analysis was performed to assess the discriminatory ability of the FT3/FT4 ratio for T2DM.

**Results:** Patients with T2DM had significantly lower FT3, TT3, and the FT3/FT4 ratio, while higher FT4, compared with those without. Partial correlation analysis further showed the negative correlation of FT3, TT3, and the FT3/FT4 with HbA1c and FBG, with the FT3/FT4 ratio showing the strongest correlation with HbA1c ($r = -0.222$, $p < 0.001$). After adjusting for confounding factors, individuals in the highest FT3/FT4 quartile had a markedly reduced likelihood of T2DM relative to those in the lowest quartile (OR 0.27, 95% CI 0.23–0.33; $p < 0.001$). ROC analysis showed a moderate discriminatory performance of the FT3/FT4 ratio for T2DM (AUC up to 0.668).

**Conclusion:** In patients with NAFLD, a lower FT3/FT4 ratio was significantly associated with T2DM and poorer glycemic status. Compared with individual TH levels, the FT3/FT4 ratio may serve as a more integrative marker of metabolic risk in this population.

**Keywords:** nonalcoholic fatty liver disease, type 2 diabetes mellitus, FT3/FT4, hemoglobin A1c, fasting blood glucose

## Introduction

Type 2 diabetes mellitus (T2DM) characterized by insulin resistance and β-cell dysfunction is a common metabolic disorder primarily.[1] Nonalcoholic fatty liver disease (NAFLD) refers to the ectopic fat accumulation in the liver accompanied by low-grade chronic inflammation. Due to its strong association with insulin resistance, central obesity, dyslipidemia, and hypertension, it is widely recognized as the hepatic manifestation of metabolic syndrome.[2] As significant public health concerns, both T2DM and NAFLD have exhibited a marked global upward trend in prevalence. A growing body of evidence has established a strong association between the two conditions. Their frequent coexistence

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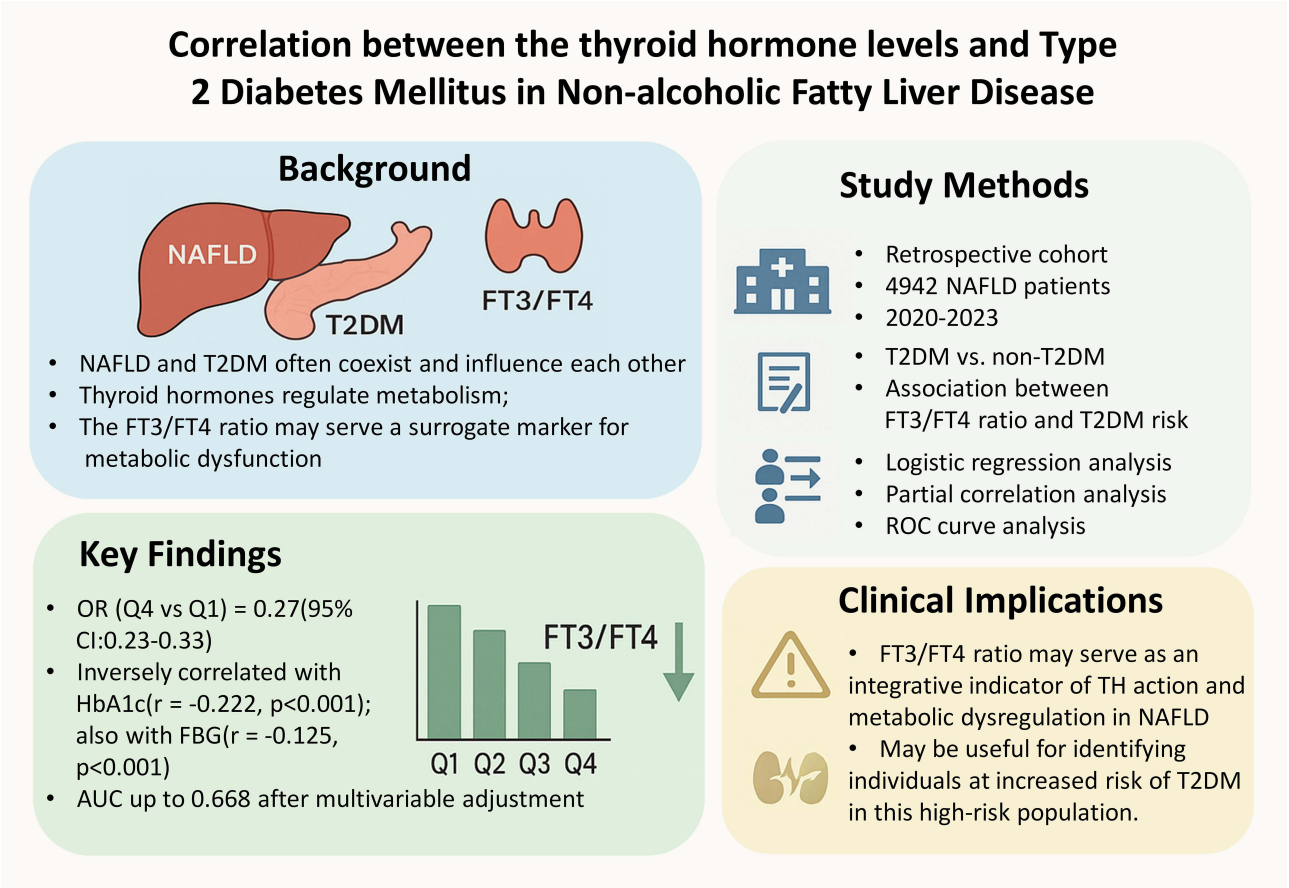
**Graphical Abstract**




not only substantially increases the risk of adverse cardiovascular events but also imposes an increasingly heavy burden on healthcare systems and socioeconomic resources.[3–5]

Thyroid hormones (THs), among the most critical endocrine regulators in the human body, play essential roles in growth, neurodevelopment, and the maintenance of metabolic homeostasis. THs also exert complex, multifactorial effects on glucose and lipid metabolism. In terms of glucose regulation, THs promote intestinal carbohydrate absorption, stimulate hepatic gluconeogenesis, enhance catecholamine-driven glycogenolysis, and influence insulin sensitivity through various mechanisms.[6] An expanding body of research has explored the relationship between thyroid function and diabetes, with particular emphasis on the pathophysiological mechanisms linking THs to insulin resistance.[7–11] Both overt hyperthyroidism and hypothyroidism have been shown to adversely affect glucose metabolism, leading to impaired glycemic control and varying levels of insulin resistance.[12] Interestingly, even within the euthyroid range, alterations in TH levels—particularly reduced serum free triiodothyronine (FT3)—have been independently associated with increased insulin resistance, highlighting the metabolic relevance of subtle thyroid dysfunction.[8,10]

In lipid metabolism, THs regulate hepatic lipid homeostasis through several mechanisms, including promoting the delivery of free fatty acids to the liver for re-esterification to triglycerides (TGs) and enhancing fatty acid β-oxidation, thereby influencing hepatic fat accumulation.[13] Both hypothyroidism and subclinical hypothyroidism contribute to NAFLD development by impairing mitochondrial fatty acid oxidation and disrupting lipoprotein metabolism.[14–17] Paradoxically, elevated FT3 and thyroid-stimulating hormone (TSH) levels have been observed in euthyroid patients with NAFLD, suggesting either a state of compensatory hyperthyroidism or tissue-specific resistance to THs.[18]

Given the complexity of TH signaling in metabolic tissues and the scarcity of data on the association between THs and T2DM specifically in patients with NAFLD, it is important to investigate the association between THs—particularly the free triiodothyronine to free thyroxine ratio (FT3/FT4)—and the presence of T2DM among patients with NAFLD. Exploring the potential mediating role of THs in the T2DM–NAFLD interplay may provide valuable insights for improving risk stratification, guiding therapeutic decisions, and informing prognosis in clinical settings.

# Materials and Methods

## Study Population

This retrospective study consecutively screened 5,978 patients with NAFLD who were hospitalized at the Affiliated Hospital of Hangzhou Normal University from 2020 to 2023. NAFLD diagnosis adhered to the Asia-Pacific Working Party consensus, defined as a clinical-pathological syndrome characterized primarily by hepatic steatosis after excluding excessive alcohol consumption (≥140 g/week for males, ≥70 g/week for females) and other known causes of hepatic steatosis.[19] Abdominal ultrasonography was performed by experienced sonographers using standardized procedures. Hepatic steatosis was identified based on characteristic imaging features, including increased liver echogenicity ("bright liver"), hepatorenal echo contrast, attenuation of the ultrasound beam, and blurring of intrahepatic vascular structures and diaphragm. The severity of NAFLD was semi-quantitatively graded into mild, moderate, and severe steatosis according to the degree of hepatic parenchymal echogenicity and posterior beam attenuation relative to the renal cortex.[19] The diagnosis of type 2 diabetes (T2DM) diagnosis followed the 2003 American Diabetes Association (ADA) guidelines.[20] Participants aged <18 (n = 11) or >80 years (n = 522), or those missing fast blood glucose (FBG) data (n = 149), total cholesterol (TC) data (n = 318), alanine aminotransferase (ALT) data (n = 36) were excluded. Ultimately, a total of 4942 subjects were enrolled in the final analysis (Figure 1).

This study was approved by the Ethics Committee of the Affiliated Hospital Hangzhou Normal University (No. 2025 (E2)-KS-143) and complies with the provisions of the Declaration of Helsinki.

## Data Collection

Patients' demographic information, including age, gender, and body mass index (BMI), were obtained from the hospital information system. Laboratory test results were extracted from the electronic laboratory database and included lipid profiles: TG, TC, HDL-C, low-density lipoprotein cholesterol (LDL-C), apolipoprotein A (apo A), apolipoprotein B (apo B); thyroid function parameters: FT3, FT4, total thyroxine (TT4), total triiodothyronine (TT3), TSH, the FT3/FT4 ratio;

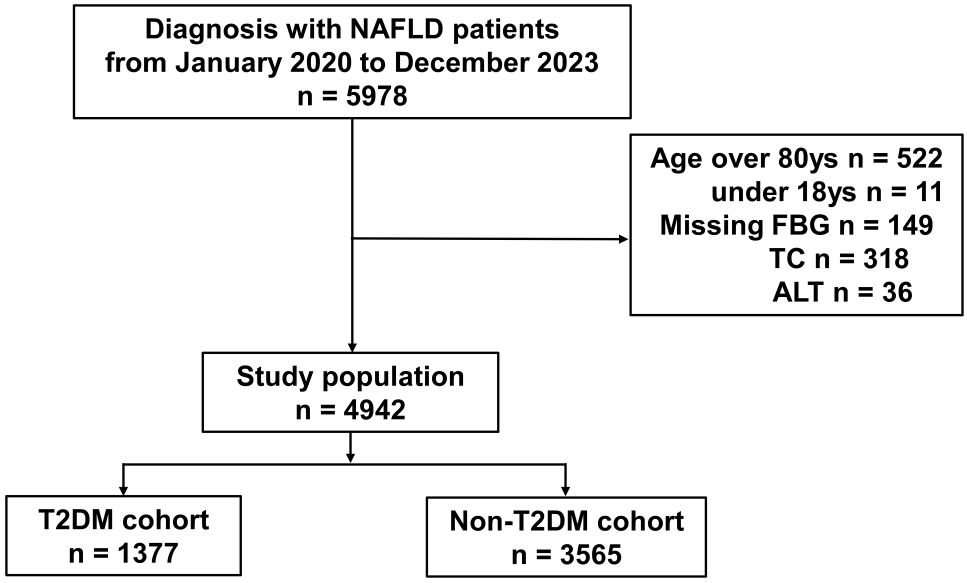



**Figure 1** Flow chart depicting the study population.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other metabolic-related indices: aspartate aminotransferase (AST), ALT, albumin, uric acid (UA), FBG, hemoglobin A1c (HbA1c), creatinine; and routine blood parameters: white blood cell count, neutrophils, lymphocyte, monocyte, platelets, and C-reactive protein at baseline. All patients fasted and refrained from drinking water for at least 8 hours prior to blood collection. Blood samples were analyzed using chemiluminescence assays on an automated analyzer. The FT3/FT4 ratios were grouped by quartiles: <25%, 25–50%, 50–75%, and ≥75%. Liver fibrosis severity was assessed using the following non-invasive indices: the fibrosis-4 (FIB-4) index, the AST-to-platelet ratio index (APRI), and NAFLD fibrosis score (NFS). Their calculation formulas are as follows:

$$\text{FIB}-4\ \text{index} = \frac{age(years) \times AST(U/L)}{platelet\ count(109/\text{L}) \times \sqrt{\text{ALT}\left(\frac{U}{L}\right)}}$$

APRI = AST/upper limit of normal]/platelet count [$10^9$/L] × 100

NFS = −1.675 + 0.037 × age (years) + 0.094 × BMI (kg/$m^2$) + 1.13 × impaired FPG/DM (yes = 1, no = 0) + 0.99 × AST/ALT ratio − 0.013 × platelet count (× $10^9$/L) − 0.66 * albumin (g/dL)

## Statistical Analysis

Normally distributed data are presented as mean ± standard deviation, while continuous variables with a skewed distribution are expressed as median and interquartile ranges. Intergroup comparisons were performed using the nonparametric Mann–Whitney *U*-test. Categorical variables were expressed as frequencies and percentages, and intergroup comparisons were performed using Fisher's exact test or the chi-square test. After controlling for age and sex, partial correlation analysis further evaluated the associations between THs (ie., TSH, FT3, FT4, TT4, and TT3) and the FT3/FT4 ratio with HbA1c and FBG among T2DM subjects with NAFLD. To assess the association between the FT3/FT4 ratio and T2DM, four stepwise adjusted logistic regression models were constructed: Model 0, unadjusted; Model 1, adjusted for age and sex; Model 2, further adjusted for BMI; Model 3, further adjusted for AST and ALT levels. The results were expressed as odds ratios (OR) with 95% confidence intervals (CI). Then, we determined the receiver operating characteristic (ROC) curves for each parameter, calculated the area under the curve (AUC), compared the AUC between different groups, and investigated the ability of these parameters to predict the development of T2DM in NAFLD.

Two-tailed tests were performed, with $p < 0.05$ indicating statistical significance. All statistical analyses were conducted using the R software version 4.2.2 (The R Foundation for Statistical Computing, Vienna, Austria).

# Results

## Characteristics of the Study Groups

A total of 4,942 patients with NAFLD were included (Figure 1). Among them, 1,377 (27.9%) had T2DM and 3,565 (72.1%) did not. Males accounted for 63% of the T2DM group and 66% of the non-T2DM group. Participants with T2DM tended to be older than those without. Laboratory findings differed significantly between the two groups (Table 1). The T2DM group had higher neutrophils, C-reactive protein, TG, HbA1c, FBG, creatinine and lower TC, LDL-C, HDL-C, non-HDL cholesterol, apoA, apoB, ALT, AST, UA levels than the non-T2DM group. In terms of thyroid function, the T2DM group had significantly lower T3 and FT3 levels and higher FT4 levels than the non-T2DM group (all $p < 0.05$). No significant differences were observed in TSH, T4, or BMI between the two groups (all $p > 0.05$). Regarding liver fibrosis, patients with T2DM had more advanced disease, as indicated by higher FIB-4 values [1.32 (0.92–1.87) vs. 1.19 (0.82–1.73), $p < 0.001$] and NFS values [−0.17 (−1.05 to 0.46) vs. −0.67 (−1.50 to 0.21), $p < 0.001$].

## Correlations Between THs and T2DM Risk

After adjusting for age and sex, partial correlation analysis demonstrated significant negative correlations between FT3, TT3, and the FT3/FT4 ratio with both FBG and HbA1c, whereas FT4 showed positive correlations with these glycemic markers (all $p < 0.001$). Among these, the FT3/FT4 ratio exhibited the strongest inverse correlation with HbA1c ($r = -0.222$, $p < 0.001$). No significant correlations were observed for TSH or TT4 with either HbA1c or FBG (Table 2).

**Table 1** Characteristics of the Participants According to Presence of T2DM

| Variables | Total Cohort (N=4942) | Non-T2DM Cohort (N=3565) | T2DM Cohort (N=1377) | *p* |
|---|---|---|---|---|
| Male, n (%) | 3147 (63.68) | 2245 (62.97) | 902 (65.50) | 0.104 |
| Age, years | 58 (48–67) | 57 (47–66) | 61 (53–69) | <0.001 |
| Height, m | 1.67 (1.6–1.72) | 1.66 (1.6–1.72) | 1.68 (1.6–1.72) | 0.836 |
| Weight, kg | 71 (63.5–80) | 71 (64–80) | 71 (63–80) | 0.702 |
| BMI, $kg/m^2$ | 25.88 (23.89–28.34) | 25.95 (23.92–28.40) | 25.72 (23.88–28.01) | 0.213 |
| Neutrophil, $\times10^9$/L | 3.86 (3.03–5.115) | 3.8 (3.01–5.08) | 4.03 (3.1–5.19) | 0.009 |
| Lymphocyte, $\times10^9$/L | 1.71 (1.32–2.16) | 1.72 (1.33–2.17) | 1.69 (1.32–2.13) | 0.306 |
| WBC, $\times10^9$/L | 1 (1–5.5) | 1 (1–5.55) | 1 (1–5.41) | 0.595 |
| Platelet, $\times10^9$/L | 213 (177–256) | 216 (180–259) | 206 (172–248) | <0.001 |
| Monocyte, $\times10^9$/L | 0.45 (0.36–0.58) | 0.45 (0.35–0.57) | 0.46 (0.37–0.58) | 0.005 |
| CRP, mg/L | 1.9 (1–4.765) | 1.8 (1–4.63) | 2.1 (1–5.1) | 0.003 |
| Albumin, g/L | 40.3 (37.6–43.3) | 40.6 (37.9–43.6) | 39.5 (36.9–42.6) | <0.001 |
| TC, mmol/L | 4.59 (3.85–5.36) | 4.64 (3.93–5.36) | 4.46 (3.61–5.32) | <0.001 |
| TG, mmol/L | 1.6 (1.15–2.26) | 1.57 (1.13–2.19) | 1.69 (1.2–2.42) | <0.001 |
| HDL-C, mmol/L | 1.03 (0.88–1.22) | 1.05 (0.9–1.24) | 0.99 (0.84–1.16) | <0.001 |
| LDL-C, mmol/L | 2.76 (2.17–3.29) | 2.79 (2.25–3.31) | 2.63 (1.97–3.24) | <0.001 |
| Non-HDLC, mmol/L | 3.55 (2.84–4.24) | 3.58 (2.92–4.23) | 3.47 (2.66–4.26) | <0.001 |
| Lp(a), mg/L | 114.8 (52.88–241.13) | 114.55 (53.53–237.18) | 115.7 (50.7–252.48) | 0.917 |
| apoB, g/L | 1.17 (1.03–1.33) | 1.18 (1.04–1.34) | 1.14 (1–1.3) | <0.001 |
| apoA, g/L | 0.95 (0.79–1.1) | 0.95 (0.8–1.09) | 0.93 (0.76–1.11) | 0.028 |
| UA, umol/L | 348 (285–420.5) | 354 (290.5–426) | 332 (272–403.25) | <0.001 |
| FBG, mmol/L | 5.98 (5.16–8.14) | 5.62 (5.03–6.68) | 8.45 (6.45–11.76) | <0.001 |
| HbA1c, % | 7.2 (6.4–8.4) | 6.8 (5.9–7.3) | 8.8 (7.6–10.5) | <0.001 |
| ALT, U/L | 26 (17–42) | 26 (18–43) | 25 (16–40) | <0.001 |
| AST, U/L | 23 (18–31) | 23 (19–32) | 22 (17–31) | <0.001 |
| Creatinine, umol/L | 63.6 (48.7–77) | 62.5 (43.7–76.3) | 66.5 (55.1–79.63) | <0.001 |
| Hcy, umol/L | 8.2 (6.5–12.2) | 8.2 (6.5–12.3) | 8.3 (6.525–12.2) | 0.88 |
| TT4, nmol/L | 97.26 (84.98–110.10) | 97.15 (85.15–109.92) | 97.59 (84.48–110.9) | 0.576 |
| TT3, nmol/L | 1.41 (1.21–1.6) | 1.44 (1.25–1.64) | 1.31 (1.12–1.49) | <0.001 |
| TSH, mIU/L | 1.4 (0.91–2.12) | 1.39 (0.91–2.13) | 1.4 (0.93–2.1) | 0.742 |
| FT3, pmol/L | 4.39 (3.87–4.88) | 4.48 (3.96–4.96) | 4.16 (3.66–4.66) | <0.001 |
| FT4, pmol/L | 13.1 (12.18–14.15) | 13.04 (12.1–14.03) | 13.37 (12.34–14.47) | <0.001 |

(*Continued*)


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**Table 1** (Continued).

| Variables | Total Cohort (N=4942) | Non-T2DM Cohort (N=3565) | T2DM Cohort (N=1377) | *p* |
|---|---|---|---|---|
| FT3/FT4 ratio | 0.33 (0.29, 0.37) | 0.34 (0.30, 0.38) | 0.31 (0.27, 0.35) | <0.001 |
| FIB.4 | 1.23 (0.85–1.77) | 1.19 (0.82–1.73) | 1.32 (0.92–1.87) | <0.001 |
| APRI | 0.43 (0.31, 0.65) | 0.44 (0.31, 0.65) | 0.43 (0.29, 0.65) | 0.05 |
| NFS | −0.54 (−1.41, 0.30) | −0.67 (−1.50, 0.21) | −0.17 (−1.05, 0.46) | < 0.001 |

**Notes**: Data are presented as median (interquartile range) or percentage.
**Abbreviations**: BMI, body mass index; WBC, white blood cell; CRP, C-reactive protein; TC, total cholesterol; TG, total triglyceride; HDL-C, high-density lipoprotein cholesterol; UA, uric acid; LDL-C, low-density lipoprotein cholesterol; Lp(a), Lipoprotein(a); UA, uric acid; FBG, fasting blood glucose; HbAlc, hemoglobin A1c; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Hcy, Homocysteine; TT4, total thyroxine; TT3, total triiodothyronine; TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; FIB-4, Fibrosis-4; APRI, aspartate aminotransferase-to-platelet ratio index; NFS, NAFLD fibrosis score.

**Table 2** Correlations Between Thyroid Hormones and HbA1c, FBG After Controlling for Age and Gender

| Thyroid Index | HbA1c | *p* | FBG | *p* |
|---|---|---|---|---|
| FT3 | −0.147 | <0.001 | −0.082 | 0.003 |
| FT4 | 0.143 | <0.001 | 0.074 | 0.007 |
| FT3/FT4 | −0.222 | <0.001 | −0.125 | <0.001 |
| T3 | −0.217 | <0.001 | −0.109 | <0.001 |
| T4 | 0.043 | 0.12 | 0.025 | 0.35 |
| TSH | −0.025 | 0.355 | −0.027 | 0.32 |

**Abbreviations**: FT3, free triiodothyronine; FT4, free thyroxine; TT3, total triiodothyronine; TT4, total thyroxine; TSH, thyroid-stimulating hormone; FBG, fasting blood glucose; HbAlc, hemoglobin A1c;

The proportions of patients in the T2DM group across increasing FT3/FT4 ratio quartiles Q1, Q2, Q3, and Q4 were 37.5%, 27.1%, 21.7%, and 13.7%, respectively, whereas in the non-T2DM group 20.2%, 23.9%, 26.8%, and 29.1% (Figure 2). Consistently, logistic regression analysis showed that a higher FT3/FT4 ratio was associated with a lower risk of T2DM. Compared with the lowest quartile (Q1), the highest quartile (Q4) had a significantly reduced risk of T2DM across all models [Model 0: OR 0.25 (95% CI, 0.21–0.31; $p < 0.001$), Model 1: 0.27 (95% CI, 0.23–0.33; $p < 0.001$), and Model 2: 0.27 (95% CI, 0.23–0.33; $p < 0.001$)] (Table 3).

The results of the ROC curve analysis for the FT3/FT4 ratio are shown in Supplementary Figure 1. The AUC was 0.6426 without adjustment for variables, increased to 0.6675 after adjustment for age and sex, and further increased to 0.6681 after additional adjustment for ALT and AST.

## Discussion

Our study examined the relationship between TH levels and T2DM in patients with NAFLD, with a particular focus on the association between the FT3/FT4 ratio and glycemic parameters. After adjusting for age and sex, FT3, total TT3, and the FT3/FT4 ratio were negatively correlated with HbA1c and FBG, whereas FT4 was positively correlated with both glycemic markers. We identified a significant inverse association between the FT3/FT4 ratio and the presence of T2DM. These findings provide novel insights into the role of THs in patients with coexisting NAFLD and T2DM and may have clinical implications for risk assessment and early intervention strategies.

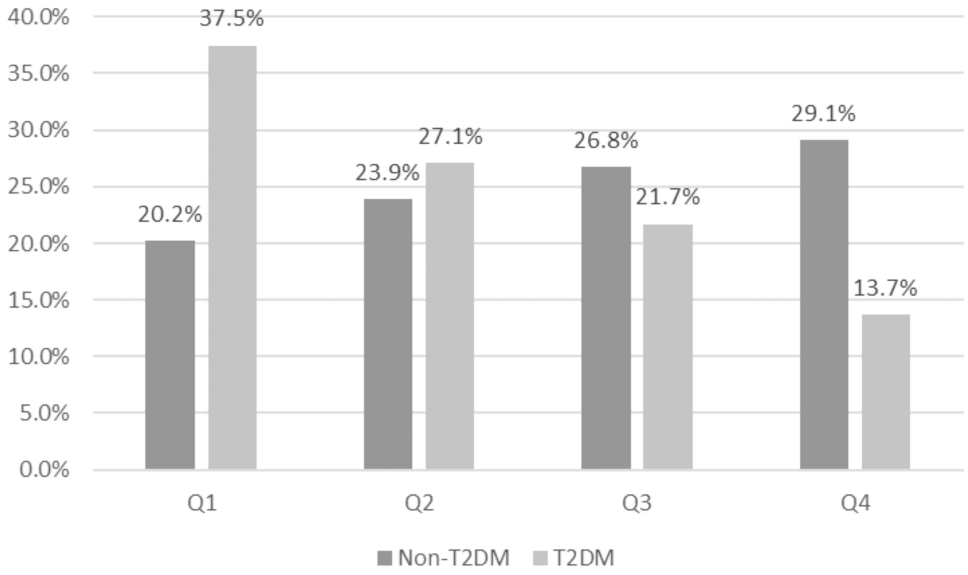


**Figure 2** Prevalence according to the quartiles of FT3/FT4 ratio in Non-T2DM and T2DM cohorts.

Compared with individual TH levels, the FT3/FT4 ratio may better reflect peripheral TH conversion and tissue-level TH sensitivity. In metabolically stressed conditions such as NAFLD, alterations in the FT3/FT4 ratio can occur despite normal circulating TH levels, making it a more sensitive indicator of subtle TH dysfunction related to metabolic disturbances. In this study, the most notable observation was the negative correlation between the FT3/FT4 ratio and T2DM risk, with the FT3/FT4 ratio showing the strongest negative correlation with HbA1c ($r = -0.222$, $p < 0.001$). These findings are in line with those of Farasat et al, who observed that a reduced T3/T4 ratio was significantly associated with both insulin resistance and hyperinsulinemia in a prediabetic cohort in Pakistan.[21] Similarly, a meta-analysis by Oscar et al suggested that patients with hypothyroidism and lower FT4 levels within the reference range had an elevated risk of developing T2DM.[10]

However, our findings diverge from those of several previous studies. A cross-sectional study indicated that TH sensitivity is closely linked to diabetes development, with the FT3/FT4 ratio serving as a potential marker of TH sensitivity. That study reported a positive association between TH levels (within the normal range) and insulin resistance.[22] Another study investigating the relationship between TH levels, body composition, and metabolic parameters found that a higher FT3/FT4 ratio was associated with increased insulin resistance in euthyroid young men.[23] Additionally, Sun et al reported that an elevated FT3/FT4 ratio was associated with a higher risk of diabetic peripheral neuropathy in euthyroid patients with T2DM.[24]

These discrepancies may be explained by differences in the populations studied. For instance, some studies involved healthy young individuals, while others, including ours, focused on patients with NAFLD. Such variations may reflect

**Table 3** Odds Ratios for T2DM in Different Quartiles of the FT3/FT4 Ratio

| T2DM | FT3/FT4 | Unadjusted | Model 1 | Model 2 |
|---|---|---|---|---|
| | | OR (95% CI, *P*-value) | OR (95% CI, *P*-value) | OR (95% CI, *P*-value) |
| Q1 | <0.29 | 1.00 | 1.00 | 1.00 |
| Q2 | 0.29–0.33 | 0.61 (0.52–0.72, p<0.001) | 0.64 (0.54–0.75, p<0.001) | 0.63 (0.53–0.74, p<0.001) |
| Q3 | 0.33–0.37 | 0.44 (0.37–0.52, p<0.001) | 0.46 (0.39–0.55, p<0.001 | 0.46 (0.38–0.54, p<0.001) |
| Q4 | >0.37 | 0.25 (0.21–0.31, p<0.001) | 0.27 (0.23–0.33, p<0.001) | 0.27 (0.22–0.33, p<0.001) |

**Notes**: Model 0 was unadjusted. Model 1 was adjusted for age, sex. Model 2 was adjusted for age, sex, ALT and AST levels.


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the dynamic nature of TH metabolism at different stages of metabolic disease. In healthy individuals, a higher FT3/FT4 ratio may represent a compensatory response to increased energy intake. In contrast, in metabolically impaired states such as NAFLD, a lower FT3/FT4 ratio may signify an adaptive response to underlying metabolic dysregulation.[12]

A reduced FT3/FT4 ratio may contribute to an increased risk of T2DM through several biological mechanisms. First, it may reflect impaired peripheral conversion of T4 to T3, a process primarily mediated by deiodinase enzymes D1 and D2. Inflammatory cytokines and oxidative stress—both commonly elevated in metabolic disorders—are known to inhibit deiodinase activity.[25] Mullur et al underscored the critical role of TH conversion in maintaining metabolic homeostasis, noting that altered deiodinase function can compromise metabolic regulation.[12] Given that the liver is a principal site of D1 expression and is responsible for the majority of circulating T3 production, hepatic dysfunction in NAFLD may directly impair this conversion process.[26] Supporting this, Ferrandino et al demonstrated that hypothyroidism results in reduced hepatic deiodinase expression and activity, thus limiting T4-to-T3 conversion.[27]

Second, a low FT3/FT4 ratio may indicate reduced tissue sensitivity to THs or tissue-specific TH resistance. Ferrannini et al proposed that insulin resistance and TH resistance share overlapping molecular mechanisms, including inflammation and lipotoxicity.[8] Mullur et al further explained that different tissues express distinct TH receptor subtypes, such as TRα and TRβ, leading to variable tissue-specific sensitivity to THs.[12] In the context of metabolic disorders, impaired hormone responsiveness in key metabolic tissues—such as the liver and skeletal muscle—could contribute to the observed association between a low FT3/FT4 ratio and elevated T2DM risk.

Third, mitochondrial dysfunction may serve as a critical link between a low FT3/FT4 ratio and impaired glucose metabolism. Crunkhorn and Patti emphasized that mitochondrial dysfunction plays a central role in the pathogenesis of both thyroid dysfunction and insulin resistance.[9] T3 enhances mitochondrial biogenesis and function by activating transcriptional co-regulators such as PGC-1α, NRF1, and TFAM. A lower FT3/FT4 ratio—indicating relative T3 deficiency—may impair mitochondrial activity, disrupt energy metabolism, and worsen insulin sensitivity. Since mitochondrial dysfunction is a shared pathological feature of both T2DM and NAFLD, it may represent a unifying mechanism connecting these two conditions.

After adjustment for age and sex, the predictive performance improved slightly (AUC = 0.6675), and further adjustment for ALT and AST yielded a marginal additional improvement (AUC = 0.6681). While these results suggest that the FT3/FT4 ratio may have some utility as a supplementary predictive marker, its moderate discriminative ability indicates it should be considered alongside other established risk factors rather than as a standalone diagnostic tool. Therefore, the FT3/FT4 ratio may serve as an integrative indicator of TH action and metabolic dysregulation in NAFLD. Patients with NAFLD and a lower FT3/FT4 ratio may benefit from enhanced glycemic monitoring and early therapeutic interventions. Kim et al noted that even subtle fluctuations in the TH levels within the reference range can influence NAFLD severity and metabolic risk.[17] Compared with single hormone measurements, the FT3/FT4 ratio may offer a more sensitive and integrative indicator of metabolic status, thereby improving risk prediction and guiding early clinical decision-making.

From a therapeutic perspective, targeting TH metabolism and sensitivity may offer novel strategies for managing both T2DM and NAFLD. Impaired conversion of T4 to the active hormone T3, reflected by a reduced FT3/FT4 ratio, may represent a modifiable factor in metabolic dysregulation. Ferrandino et al demonstrated that TH replacement therapy reversed hypothyroidism-induced NAFLD,[27] suggesting that patients with subclinical hypothyroidism and low FT3/FT4 ratios might benefit from targeted hormone replacement to improve metabolic and hepatic outcomes.

Beyond traditional hormone therapy, selective TH receptor modulators have shown promise in experimental studies. As discussed by Mullur et al, these compounds selectively activate TH receptors in metabolically active tissues—such as the liver and muscle—while minimizing off-target effects and the risk of thyrotoxicosis.[12] Such tissue-specific agents could represent a next-generation therapeutic approach to address insulin resistance and hepatic steatosis in patients with low TH activity. Additionally, Crunkhorn and Patti highlighted mitochondrial dysfunction as a critical molecular link between altered thyroid signaling and insulin resistance.[9] Since T3 enhances mitochondrial biogenesis and oxidative phosphorylation, reduced T3 availability may impair cellular energy metabolism. This suggests that interventions that restore mitochondrial function—such as structured exercise, caloric restriction, or pharmacologic agents like metformin—may be particularly effective in patients with NAFLD and low FT3/FT4 ratios.

Consistent with this framework, our study found that FT3 levels were significantly lower and FT4 levels were higher in the T2DM group than in the non-T2DM group. FT3 demonstrated negative correlations with both FBG and HbA1c, whereas FT4 was positively associated with these glycemic indicators. These patterns support the presence of a "low T3 syndrome" in T2DM, an endocrine state commonly observed in chronic diseases. Characterized by low circulating T3 and normal or slightly elevated T4 levels, this syndrome is thought to reflect an adaptive response to illness. Emerging evidence suggests several mechanisms underlying this phenomenon in metabolic disorders: systemic inflammation may suppress hypothalamic thyrotropin-releasing hormone and pituitary TSH secretion, downregulate TH-binding proteins, inhibit deiodinase-mediated T4-to-T3 conversion, and promote the generation of reverse T3, an inactive metabolite.[28] Collectively, the individual associations of FT3 and FT4 with glycemic parameters further reinforce the relevance of the FT3/FT4 ratio as an integrated marker of TH–related metabolic alterations.

Despite the strength of our findings, several limitations should be noted. First, NAFLD was diagnosed using ultrasonography, which, although widely accepted for epidemiological and clinical studies, has limited sensitivity for mild steatosis and cannot distinguish steatohepatitis or fibrosis stages. Differences in NAFLD diagnostic criteria and modalities across studies may lead to heterogeneity in disease severity, potentially contributing to inconsistent findings regarding the association between TH and glucose metabolism. Second, although we adjusted for age and sex, residual confounding from unmeasured factors such as medication use, nutritional status, smoking, and physical activity may have influenced both TH levels and metabolic outcomes. Third, we did not include direct measures of insulin resistance, such as the homeostatic model assessment of insulin resistance or the hyperinsulinemic-euglycemic clamp, which limits our ability to draw causal inferences about thyroid function and insulin sensitivity. Finally, the study cohort consisted exclusively of hospitalized patients with NAFLD, who typically represent more severe cases. As a result, the findings may not be generalizable to the broader outpatient or community-based NAFLD population.

## Conclusion

In patients with NAFLD, the FT3/FT4 ratio was inversely associated with the presence of T2DM and showed a stronger association than individual TH levels. Lower FT3/FT4 ratios were consistently related to poorer glycemic status, including higher FBG and HbA1c levels. These findings suggest that the FT3/FT4 ratio may serve as an integrative indicator of TH action and metabolic dysregulation in NAFLD, and may be useful for identifying individuals at increased risk of T2DM in this high-risk population.

## Data Sharing Statement

The dataset generated and/or analyzed during the current study are not publicly available but are available from the corresponding author and the first author on reasonable request.

## Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Hangzhou Normal University Affiliated Hospital and informed consent has been waived (protocol code No. 2025(E2)-KS-143). The study complied with the provisions of the Declaration of Helsinki.

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## Author Contributions

Liya Bian: Conceptualization, Investigation, Methodology, Formal Analysis, Writing - original draft; Writing - review & editing; Hua Fan: Conceptualization, Investigation, Methodology, Formal Analysis, Writing - original draft, Validation; Qingwen Yu: Conceptualization, Investigation, Methodology, Formal Analysis, Writing - original draft, Validation; Xiyun Rao: Formal analysis, Resources, Data Curation, Investigation, Writing - original draft; Ting Tang: Formal

analysis, Resources, Data Curation, Investigation, Writing - original draft; Lanlan Feng: Formal analysis, Resources, Data Curation, Investigation, Writing - original draft; Yongmin Shi: Formal analysis, Resources, Data Curation, Investigation, Writing - original draft; Xuhan Tong: Formal analysis, Resources, Data Curation, Investigation, Writing - original draft; Xingwei Zhang: Formal analysis, Resources, Data Curation, Investigation, Writing – review & editing; Jiake Tang: Formal analysis, Resources, Data Curation, Investigation, Writing – review & editing; Xianguo Qu: Resources, Data Curation, Investigation, Writing – review & editing, Supervision; Pengwei Zhang: Conceptualization, Resources, Supervision, Writing - Review & Editing, Methodology; Mingwei Wang: Conceptualization, Resources, Supervision, Writing - Review & Editing.

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## Disclosure

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