



Serum level of free thyroxine is an independent risk factor for non-alcoholic fatty liver disease in euthyroid people

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Background: Non-alcoholic fatty liver disease (NAFLD) has become a major public health problem concern in recent decades. The specific mechanism of NAFLD is still not clear. Previous studies had shown the correlation between NAFLD and thyroid dysfunction. The correlation between thyroid hormones within the euthyroid range and NAFLD has not yet been clarified. This study sought to investigate the association between NAFLD and thyroid hormones in euthyroid patients.

Methods: A retrospective cross-sectional study was conducted at Beijing Tiantan Hospital from January 1, 2019, to October 1, 2021. Eighty-one NAFLD patients with normal thyroid function and 34 healthy individuals were enrolled. Participants' demographic information, biochemical parameters, and thyroid hormone levels were collected. The severity of NAFLD was assessed by abdominal computed tomography (CT). The association between NAFLD and thyroid hormones was analyzed.

Results: Patients in the NAFLD group were older and more likely to be female than those in the healthy control group ($P < 0.05$). Compared to the healthy control group, the serum levels of fasting plasma glucose (FPG), alanine transaminase (ALT), plasma aspartate transaminase (AST), triglyceride, gamma-glutamyl transferase (γ -GT), and uric acid (UA) were higher, but the levels of high-density lipoprotein cholesterol (HDL-C), and free thyroxine (FT_4) were lower in the NAFLD group ($P < 0.05$). NAFLD is more severe in females than males ($P < 0.05$). ALT, AST, low-density lipoprotein cholesterol (LDL-C), γ -GT, tetraiodothyronine, and free triiodothyronine (FT_3) levels increased significantly as the severity of NAFLD increased ($P < 0.05$). The results of the Spearman correlation analysis indicated that the severity of NAFLD was positively correlated with ALT ($r = 0.376$, $P = 0.001$), AST ($r = 0.275$, $P = 0.015$), and LDL ($r = 0.313$, $P = 0.007$). The multiple logistic regression analysis showed that age [odds ratio (OR) = 1.071; 95% confidence interval (CI): 1.010–1.136, $P = 0.021$], ALT (OR = 1.091; 95% CI: 1.034–1.150, $P = 0.001$), HDL-C (OR = 0.085; 95% CI: 0.010–0.690, $P = 0.021$), and FT_4 (OR = 0.738; 95% CI: 0.545–1.001, $P = 0.046$) were independently related to the risk of NAFLD in patients with normal thyroid function.

Conclusions: FT_4 within the normal range was lower in the NAFLD group compared to the healthy control group. The serum level of FT_4 is an independent risk factor of NAFLD in euthyroid people.

Keywords: Euthyroid; non-alcoholic fatty liver disease (NAFLD); thyroid hormones

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is a clinical and pathological syndrome caused by pathologic factors except alcohol or other known factors that injure liver (1). The main characteristic of NAFLD is fatty infiltration in >5% of hepatocytes (2). The disease spectrum of NAFLD includes benign non-alcoholic fatty liver, and the more severe non-alcoholic steatohepatitis (NASH), which is characterized by steatosis, hepatocellular ballooning, lobular inflammation, and almost always fibrosis, and can progress to liver cirrhosis and hepatocellular carcinoma (3). With changes in lifestyle and improvements in people's living standards, NAFLD has become an important cause of chronic liver disease worldwide, and has a prevalence rate of 25–30% in the general population (4,5). The economic burden of NAFLD has been projected to be approximately >100 billion dollars in the United States and about 35 billion dollars in Italy, Germany, the United Kingdom, and France (6). Presently, the prevalence rate of NAFLD in China is 29.2%. As a result of urbanization, it is estimated that by 2030 there will be 315 million NAFLD patients in China, and China will have the highest growth in the prevalence of NAFLD globally (7,8).

Thyroid hormones are important hormones in maintaining metabolic homeostasis, and regulate *de novo* lipogenesis, fatty acid oxidation, cholesterol metabolism, and carbohydrate metabolism, and play important roles in hepatic lipid metabolism (9). Sinha *et al.* reported that hypothyroidism is associated with increased serum levels of triglycerides, cholesterol, and NAFLD (10). A large and updated meta-analysis found that hypothyroidism is significantly associated with the presence and severity of NAFLD (11). Ludwig *et al.* confirmed the association between hypothyroidism (both subclinical and clinical) and hepatic steatosis in NAFLD (12). There have been many studies on NAFLD and thyroid hormone. But the correlation between thyroid hormones within the euthyroid range and NAFLD has not yet been clarified. At present, fewer studies have explored the association between thyroid hormones and the severity of NAFLD in euthyroid subjects. In this study, we investigated the relationship between thyroid hormones and the occurrence and severity of NAFLD in euthyroid individuals to provide insights into new predictors and treatment targets for NAFLD.

We present the following article in accordance with the STROBE reporting checklist (available at [https://apm.](https://apm.amegroups.com/article/view/10.21037/apm-21-3890/rc)

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Methods

Study population

This retrospective cross-sectional study was conducted at Beijing Tiantan Hospital from January 1, 2019, to October 1, 2021. Eighty-one NAFLD patients with normal thyroid function and 34 healthy individuals were enrolled in the study. NAFLD was diagnosed according to the 2018 guidelines for the prevention and treatment of NAFLD (13).

All participants underwent abdominal computed tomography (CT). Subjects were excluded if they met any of the following exclusion criteria: (I) were aged <18 years; (II) engaged in significant alcohol consumption (>20 g/day for women and >30 g/day for men); (III) had liver disease caused by virus, alcohol, drug, autoimmunity, and/or total parenteral nutrition; (IV) had established hypertension, coronary heart disease, diabetes, hyperthyroidism, hypothyroidism, acute and chronic renal insufficiency, a tumor, or other serious acute and chronic diseases; and/or (V) had been treated with anti-thyroid drugs, thyroid hormone drugs, amiodarone, and/or other drugs affecting thyroid function.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Medical Ethics Committee of Beijing Tiantan Hospital (No. KY2016-042-01) and individual consent for this retrospective analysis was waived.

Clinical and laboratory data collection

Participants' demographic information (age and sex) was collected. Biochemical parameters, including fasting plasma glucose (FPG), alanine transaminase (ALT), plasma aspartate transaminase (AST), gamma-glutamyl transferase (γ -GT), alkaline phosphatase (ALP), total bilirubin (TBIL) and indirect bilirubin (IBIL), triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), blood urea nitrogen (BUN), uric acid (UA) and creatinine (Cr) were measured by a LABOSPECT 008 automatic analyzer. Thyroid function tests, including thyroid stimulating hormone (TSH), free thyroxine (FT₄), free triiodothyronine (FT₃), triiodothyronine (TT₃) and tetraiodothyronine (TT₄) were measured by the UniCel Dxl

800 Access automatic analyzer. All the blood samples were obtained intravenously after 8 hours of fasting.

Abdominal CT evaluation

Abdominal CT examinations were performed by Somatom Definition (Siemens Medical Solutions, Forchheim, Germany). The ratio of CT values of the liver and spleen in NAFLD is ≤ 1 . A mild degree of NAFLD is indicated by $0.7 < \text{liver/spleen CT value} \leq 1.0$, a moderate degree of NAFLD is indicated by $0.5 < \text{liver/spleen CT value} \leq 0.7$, and a severe degree of NAFLD is indicated by $\text{liver/spleen CT value} \leq 0.5$ (14).

Statistical analysis

The normally distributed continuous data are expressed as the mean \pm standard deviation (SD), and the non-normal distributed continuous variables are expressed as the median (P_{25} , P_{75}). Comparisons of continuous data between groups were performed by the Student's *t*-test or Mann-Whitney U test. Categorical variables were summarized in frequencies or percentages, and the χ^2 test was used to compare groups. A Spearman rank-correlation analysis was used for the correlation analysis. Logistic regression was used to investigate the risk factors related to NAFLD. All the statistical analyses were performed using SPSS 21.0 software. A *P* value < 0.05 (2-tailed) was considered statistically significant.

Results

Characteristics of the study participants in the NAFLD and healthy control groups

As *Table 1* shows, patients in the NAFLD were older and more likely to be female than individuals in the healthy control group ($P < 0.05$). Compared to the healthy control group, the serum levels of FPG, ALT, AST, TG, γ -GT, and UA were higher but the levels of HDL-C and FT_4 were lower in the NAFLD group ($P < 0.05$). There were no differences in the TC, LDL-C, Cr, TSH, TT_3 , TT_4 , and FT_3 levels between the NAFLD and healthy control groups ($P > 0.05$).

Comparison of characteristics and the severity of NAFLD

According to the abdominal CT results, NAFLD patients were divided into mild ($n=26$), moderate ($n=24$), and severe

($n=31$) groups. NAFLD was more severe in female patients than male patients ($P < 0.05$). ALT, AST, LDL-C, γ -GT, TT_4 , and FT_3 levels increased significantly as the severity of NAFLD increased ($P < 0.05$). However, no statistically significant differences in FPG, TG, TC, HDL-C, Cr, UA, TSH, TT_3 , and FT_4 levels were observed among the groups ($P > 0.05$; see *Table 2*).

Spearman correlation of the characteristics and the severity of NAFLD

The results of the Spearman correlation analysis indicated that the severity of NAFLD was positively correlated with ALT ($r=0.376$, $P=0.001$), AST ($r=0.275$, $P=0.015$), and LDL ($r=0.313$, $P=0.007$).

Multivariate analysis

The results of the multiple logistic regression analysis showed that age [odds ratio (OR) = 1.071; 95% confidence interval (CI): 1.010–1.136, $P=0.021$], ALT (OR = 1.091; 95% CI: 1.034–1.150, $P=0.001$), HDL-C (OR = 0.085; 95% CI: 0.010–0.690, $P=0.021$), and FT_4 (OR = 0.738; 95% CI: 0.545–1.001, $P=0.046$) were independently related to the risk of NAFLD in participants with normal thyroid function.

Discussion

As a metabolic disease involving multiple systems, NAFLD has become a major public health concern in recent decades. With the global epidemic of obesity fueling metabolic conditions, the clinical and economic burden of NAFLD will become enormous (6). In the past 10 years, the liver transplantation rate caused by NASH has increased from 1.2% to 9.7% (15). It is estimated that NAFLD will become the leading cause of end-stage liver disease in the next decades. The specific mechanism of NAFLD is still not clear. The disease burden needs to be mitigated. As the hepatic manifestation of metabolic syndrome, NAFLD is associated with metabolic disorders, including central obesity, hyperlipidemia, diabetes, and hypertension (16).

In mammals, thyroid hormones play an important role in regulating lipid and carbohydrate metabolism, energy metabolism, and nervous system development. Thyroid hormones play an important role in maintaining liver homeostasis. Thyroid hormones have prominent effects on hepatic fatty acid and cholesterol synthesis and metabolism.

Table 1 Characteristics of the NAFLD and healthy control groups

| Characteristics | NAFLD group | Healthy control group | P value |
|--------------------------|--------------------|-----------------------|---------|
| n | 81 | 34 | |
| Age (years) | 44 [33, 54] | 34 [27, 44] | <0.05 |
| Sex (male/female) | 29/52 | 21/13 | <0.05 |
| FPG (mmol/L) | 5.19 (4.70, 6.36) | 5.08 (4.83, 5.42) | <0.05 |
| ALT (U/L) | 38.1 (23.5, 61.63) | 14.45 (11.70, 19.20) | <0.05 |
| AST (U/L) | 25 (17.88, 40.33) | 15.05 (13.48, 17.75) | <0.05 |
| TG (mmol/L) | 1.74 (1.07, 2.60) | 0.87 (0.52, 1.42) | <0.05 |
| TC (mmol/L) | 4.56 (3.77, 5.23) | 4.44 (3.88, 5.46) | 0.75 |
| HDL-C (mmol/L) | 1.22±0.33 | 1.59±0.32 | <0.01 |
| LDL-C (mmol/L) | 2.75±1.01 | 2.69±0.96 | 0.77 |
| γ-GT (U/L) | 40.3 (14.43, 55.7) | 20.75 (13.5, 30.48) | <0.05 |
| Cr (μmol/L) | 61.63±14.46 | 57.81±14.21 | 0.25 |
| UA (μmol/L) | 368.83±97.64 | 298.12±93.38 | <0.01 |
| TSH (μIU/mL) | 1.77 (1.17, 2.34) | 1.82 (1.16, 2.68) | 0.99 |
| TT ₃ (nmol/L) | 1.52±0.27 | 1.54±0.23 | 0.78 |
| TT ₄ (nmol/L) | 105.30±16.12 | 106.62±19.75 | 0.06 |
| FT ₃ (pmol/L) | 5.13±0.67 | 4.93±0.44 | 0.25 |
| FT ₄ (pmol/L) | 11.38±1.97 | 13.01±1.76 | <0.05 |

NAFLD, non-alcoholic fatty liver disease; FPG, fasting plasma glucose; ALT, alanine transaminase; AST, plasma aspartate transaminase; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; γ-GT, gamma-glutamyl transferase; Cr, creatinine; UA, uric acid; TSH, thyroid stimulating hormone; FT₃, free triiodothyronine; FT₄, free thyroxine; TT₃, triiodothyronine; TT₄, tetraiodothyronine.

It has been reported that the prevalence of NAFLD is significantly higher in subclinical hypothyroidism patients than in those with euthyroidism, and that TSH but not FT₄ is independently associated with NAFLD (17). In this study, we examined the correlation between thyroid hormones and NAFLD in euthyroid individuals, and found that the NAFLD participants were older and more likely to be female than the healthy control participants. Lin *et al.* reported that patients with metabolic associated fatty liver disease (MAFLD) were significantly older compared to NAFLD group (18). DiStefano *et al.* demonstrated that postmenopausal women have a higher risk of NAFLD and higher rates of severe hepatic fibrosis (19). Recent reports have shown that the prevalence of NAFLD in women has increased over the past 10 years, and the mortality rate of women has risen sharply compared to that of men (20,21). FPG, ALT, AST, TG, γ-GT, and UA serum levels

were higher but HDL-C and FT₄ levels were lower in the NAFLD group than the healthy control group in our study. No differences in the TC, LDL-C, Cr, TSH, TT₃, TT₄ and FT₃ levels were observed between the NAFLD and healthy control groups. As is well known, NAFLD is associated with insulin resistance (IR) and type 2 diabetes, which could explain the high FPG level in the NAFLD group (22). Many studies have investigated whether a high UA level is independently associated with NAFLD (23,24). The UA level was higher in the NAFLD participants than the healthy control participants in our study, but it was not independently related to NAFLD.

The association between thyroid hormones and the severity of NAFLD remains unclear. It is reported that altered thyroid profile was significantly associated with an increased incidence of NAFLD and low serum FT₄ was the only independent predictor of assessing significant

Table 2 Characteristics of patients with NAFLD in different severity groups

| Characteristics | Mild NAFLD | Moderate NAFLD | Severe NAFLD | P value |
|--------------------------|---------------------|----------------------|----------------------|---------|
| n | 26 | 24 | 31 | |
| Age (years) | 55 [45, 61] | 41 [31, 52] | 38 [32, 52] | 0.12 |
| Sex (male/female) | 20/6 | 18/6 | 14/17 | <0.05 |
| FPG (mmol/L) | 4.94 (4.39, 6.17) | 5.61 (4.95, 7.78) | 5.23 (4.78, 6.38) | 0.60 |
| ALT (U/L) | 22 (13.15, 32.48) | 49.85 (29.25, 84.57) | 46.55 (31.1, 102.58) | <0.05 |
| AST (U/L) | 8.90 (15.63, 27.13) | 26.95 (20.13, 42.22) | 29.55 (21.58, 48.68) | <0.05 |
| TG (mmol/L) | 1.45 (0.95, 2.45) | 1.36 (0.91, 2.46) | 1.99 (1.25, 2.87) | 0.69 |
| TC (mmol/L) | 3.97 (3.43, 4.55) | 4.67 (3.53, 5.12) | 4.86 (4.27, 5.50) | 0.23 |
| HDL-C (mmol/L) | 1.17±0.28 | 1.19±0.34 | 1.26±0.37 | 0.61 |
| LDL-C (mmol/L) | 2.50±1.12 | 2.52±0.88 | 3.14±0.91 | <0.05 |
| γ-GT (U/L) | 25.4 (18.05, 47.78) | 43.00 (33.28, 74.53) | 43.50 (26.58, 57.45) | <0.05 |
| Cr (μmol/L) | 65.99±15.97 | 64.65±15.42 | 58.75±14.74 | 0.19 |
| UA (μmol/L) | 368.45±112.30 | 365.51±107.57 | 371.74±77.89 | 0.98 |
| TSH (μIU/mL) | 1.88 (1.44, 2.43) | 1.64 (1.11, 2.05) | 1.87 (1.12, 2.57) | 0.39 |
| TT ₃ (nmol/L) | 1.46±0.27 | 1.59±0.24 | 1.51±0.29 | 0.32 |
| TT ₄ (nmol/L) | 97.97±13.63 | 110.28±17.98 | 107.60±15.13 | <0.05 |
| FT ₃ (pmol/L) | 4.86±0.55 | 5.38±0.65 | 5.20±0.72 | <0.05 |
| FT ₄ (pmol/L) | 11.07±1.67 | 11.68±2.55 | 11.44±1.78 | 0.60 |

NAFLD, non-alcoholic fatty liver disease; FPG, fasting plasma glucose; ALT, alanine transaminase; AST, plasma aspartate transaminase; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; γ-GT, gamma-glutamyl transferase; Cr, creatinine; UA, uric acid; TSH, thyroid stimulating hormone; FT₃, free triiodothyronine; FT₄, free thyroxine; TT₃, triiodothyronine; TT₄, tetraiodothyronine.

fibrosis in NAFLD participants (25). Tahara *et al.* found that TSH level was positively associated with the progression of liver fibrosis (17). Kim *et al.* reported that subclinical hypothyroidism is an independent predictor of histological NASH and advanced fibrosis (26). Manka suggested that lower FT₃ and FT₄ were associated with higher liver stiffness and a higher NAFLD fibrosis score, respectively (27). Guo *et al.* reported that FT₃ level is positively correlated with NAFLD severity in euthyroid participants (28). Tao *et al.* showed TSH and FT₄ levels were independent risk factors for NAFLD in euthyroid general subjects. However, their research did not study the association between thyroid hormones and the severity of NAFLD (29). In our study, the NAFLD patients were divided into mild, moderate and severe groups according to their abdominal CT results. NAFLD was found to be more severe in females than males, and the ALT, AST, LDL-C,

γ-GT, TT₄ and FT₃ levels significantly increased as the severity of NAFLD increased. However, only the ALT, AST and LDL levels were positively correlated with the severity of NAFLD according to the Spearman analysis. Our results suggest that thyroid hormones levels in the normal range were not related to the severity of NAFLD.

Jaruvongvanich *et al.* found no association between NAFLD and thyroid hormone (30). Another meta-analysis investigated the correlation between NAFLD and thyroid function (31). He *et al.* showed that individuals with subclinical and overt hypothyroidism are at higher risk for NAFLD than euthyroid subjects (32). Bano *et al.* observed that lower FT₄ and higher TSH levels are associated with an increased risk of NAFLD (33). Tan *et al.* found that a high TSH level was significantly associated with NAFLD in T2DM patients with euthyroid function (34). Huang *et al.* reported that high levels of FT₃ and TSH increased the risk

of NAFLD in euthyroid patients with T2DM (35). The present study showed that only FT₄ within the reference range was an independent risk factor of NAFLD. Xu *et al.* also reported that serum FT₄ level was significantly associated with the risk for NAFLD in elderly Chinese euthyroid participants (36). Liu *et al.* investigated that high levels of FT₃ were significantly associated with NAFLD among middle-aged euthyroid subjects independently of known metabolic risk factors, while only serum FT₄ levels were negatively associated with NAFLD in pre-menopausal women (37). The conflicting results may be caused by many reasons. Diagnostic accuracy of ultrasonography is inferior to pathological diagnosis by liver biopsy (38). It is reported that menopausal status could change the interactions between serum FT₄ level and metabolic syndrome components (39). Multi-center clinical trials are more conducive to reduce the deviation and obtain more definite results.

In conclusion, the major finding of our cross-sectional study was that FT₄ within the normal range was lower in the NAFLD group than the healthy control group. The TT₄ and FT₃ levels increased significantly as in the severity of increased. The serum level of FT₄ was an independent risk factor of NAFLD in euthyroid participants. These results could provide novel insights into the prediction and treatment of NAFLD.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://apm.amegroups.com/article/view/10.21037/apm-21-3890/coef>).

The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work, including ensuring that any questions related to the accuracy or integrity of any part of the work have been appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Medical Ethics Committee of Beijing Tiantan Hospital (No. KY2016-042-01) and individual consent for this retrospective analysis was waived.

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