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The role of free triiodothyronine in high-density lipoprotein cholesterol metabolism

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Abstract

The aim of this study was to analyze the correlation between free triiodothyronine (FT3), free thyroxine (FT4), thyroid-stimulating hormone (TSH), and serum high-density lipoprotein cholesterol (HDL-C), and to explore the significance of FT3 in HDL-C metabolism in people with normal thyroid function.

A total of 461 Chinese, aged ≥28 years, from a college community in Nanning, Guangxi, were enrolled for a cross-sectional epidemiological investigation of metabolic syndrome from October 2016 to November 2016. Height, weight, blood pressure, total cholesterol, HDL-C, triglyceride (TG), fasting glucose (FPG), FT3, FT4, and TSH were measured for each individual. Multiple linear regression analysis was used to evaluate the correlation between FT3, FT4, TSH, and HDL-C.

After controlling for sex, age, body mass index (BMI), smoking, drinking, and other confounding factors, FT3 was negatively correlated with HDL-C levels, on average, when FT3 increased by 1 pmol/L, HDL-C decreased by 0.143 mmol /L with a statistically significant difference (P < .001). FT4 was positively correlated with HDL-C, and HDL-C increased by 0.016 mmol/L for every 1-pmol/L increase in FT4. TSH was negatively correlated with HDL-C, and HDL-C decreases by 0.010 mmol/L for every 1-μIU/mL increase in TSH, but the differences were not statistically significant (P > .05).

FT3 may be an important factor affecting HDL-C levels. The detection and regulation of thyroid hormone (especially FT3) in patients with low HDL-C, as well as the detection of HDL-C in patients with thyroid dysfunction, is important to prevent the occurrence of cardiovascular diseases.

Abbreviations: ABCA1 = ATP-binding cassette transporter 1, apoAI = apolipoprotein AI, BMI = body mass index, CE = cholesterol ester, CETP = cholesterol transporter protein, CM = chylomicrons, CYP7A1 = cholesterol 7α-hydroxylase, FC = free cholesterol, FPG = fasting glucose, FT3 = free triiodothyronine, FT4 = free thyroxine, HDL-C = high-density lipoprotein cholesterol, HMG-CoA = Hydroxymethyl glutaryl CoA, LDL = low-density lipoprotein, PBG = postprandial glucose, PL = phospholipid, SR-BI = scavenger receptor-BI, TG = triglyceride, TSH = thyroid stimulating hormone, VLDL = very-low-density lipoprotein, WC = waist circumference.

Keywords: free thyroid hormone, free triiodothyrogenine, high-density lipoprotein cholesterol, thyroid-stimulating hormone

1. Introduction

High-density lipoprotein cholesterol (HDL-C) is made up of roughly the same proportion of proteins and lipids, including cholesterol ester (CE), free cholesterol (FC), phospholipid (PL), and apolipoprotein AI (apoAI). HDL-C can reverse transport cholesterol, transport cholesterol from surrounding tissues to the liver for recycling or excretion in the form of bile acids, and thus reduce plasma cholesterol levels in the blood vessel walls and the occurrence of atherosclerosis. In addition, HDL-C plays in the role of antiatherosclerosis by oxidation because oxidized low-density lipoprotein (LDL) is closely related to the formation of atherosclerosis, whereas HDL-C can inhibit the oxidized modification or aggregation of LDL. HDL-C is also involved in antiatherosclerosis by anti-inflammation (inflammation plays a key role in the cause and instability of atherosclerotic plaques), antithrombotic and endothelial protection. Low HDL-C levels are considered to be an independent risk factor for coronary heart disease.[1,2] Low plasma HDL-C (<40 mg/dL for men and < 50 mg/dL for women) increases the risk of atherosclerotic disease, whereas high plasma HDL-C (>60 mg/dL) decreases the risk of atherosclerotic disease.[3] Further studies found that every 1-mg (0.03 mmol/L) increase in HDL-C reduces the risk of future coronary heart disease (CHD) by 2% to 3%.[4] HDL-C is a protective factor of cardiovascular diseases, and improving HDL-C levels is of great significance for the prevention of cardiovascular diseases.

Related studies had shown an obvious correlation between thyroid disease and atherosclerotic cardiovascular disease, and the effect of thyroid hormones on blood lipids is one cause of coronary heart disease.[5] Hypothyroidism, as well as hyperthyroidism and subclinical hyperthyroidism, which leads to lower HDL in patients, is an important cause of dyslipidemia. The most common type of dyslipidemia is hypercholesterolemia.[6]

Previous studies have focused more on the correlation between thyroid hormones, TSH, and blood lipids (especially LDL, total cholesterol, and TG) in patients with hyperthyroidism or hypothyroidism, but few studies have been done on the correlation between normal thyroid function and HDL-C. Given the protective factor of HDL-C for cardiovascular disease, the purpose of our study is to analyze the relationship between FT3, FT4, TSH, and HDL-C through epidemiological investigation of metabolic syndromes in a college community in Nanning, Guangxi. We also wanted to explore the influence of FT3 on HDL-C metabolism in people with normal thyroid function and to understand whether the regulation of thyroid function can improve HDL-C levels and prevent the occurrence of cardiovascular diseases.

2. Methods

2.1. Objects of study

This study was approved by the Ethics Committee of the Guangxi Medical University Affiliated Tumor Hospital (Number: LW2018048), and written, informed consents were obtained from all participants.

By adopting the experimental epidemiological research method of random and cluster sampling, a street was randomly selected from one of the 7 districts in Nanning, Guangxi. A total of 603 Chinese, aged ≥28 years, in a college community in this street, were selected for a cross-sectional epidemiological study of metabolic syndromes, from October 2016 to November 2016. Those who were pregnant or taking lipid-lowering and steroid hormone drugs or those with certain diseases, including thyroid dysfunction, dyslipidemia, diabetes, diabetic nephropathy, gout and other metabolic diseases, as well as a history of severe liver and kidney diseases, were excluded. A total of 461 eligible subjects with normal thyroid function were enrolled.

According to the estimation method of the sample size, the minimum sample size is 384. In essence, when performing the research design, 461 valid samples were obtained for statistics and analysis. Therefore, the sample calculations are reasonable and sufficient to support our research conclusions.

2.2. Questionnaire survey

A questionnaire survey was conducted on the subjects to collect basic personal information (sex, age, and so on), personal hobbies (smoking, drinking, sports, and so on), previous medical and family history, and any medication they were using (blood lipid-lowering or steroid hormone drugs).

2.3. Physical examination

Physical examination of the subjects was conducted by highly trained professionals and included height, body weight, blood pressure (measured by an electronic upper arm sphygmomanometer certified by international standards), waist circumference (WC), hip circumference, and body mass index (BMI) which is equivalent to weight (kilogram)/height (square meter).

2.4. Laboratory assays

All subjects fasted for 8 to 14 hours before venous blood of the forearm was sampled. The blood samples were immediately centrifuged and cryopreserved (stored at −20°C) and tested within 2 hours. Biochemical indices of FT3, FT4, and TSH were all detected by electrochemical luminescence, and the detection instrument was the Roche Cobas e602 electrochemical luminometer from Germany. TG and HDL-C were detected by glycerol phosphate oxidase-peroxidase method, and FBG was detected by hexokinase method. The kits were purchased from Roche, Germany, and the detection instrument was the Roche Cobas c501 biochemical analyzer.

2.5. Diagnostic criteria

The reference range was based on the testing instruments and detection methods used in this study. The normal value range of TSH was 0.270 to 4.200 μIU/mL. The normal range of FT4 was 12.00 to 22.00 pmol/L. The normal range of FT3 was 3.10 to 6.80 pmol/L. When FT3, FT4, and TSH are all in the normal range, thyroid function is considered normal.

2.6. Statistical analysis

Stata12 software was used for statistical analysis. Bivariate correlation analysis was conducted according to the properties of variables, among which, t test was used for correlation analysis of classification variables and continuous variables, and Spearman correlation analysis was used for correlation analysis of bivariate variables. On the basis of correlation analysis, confounding factors such as sex, age, smoking, drinking, and exercise were controlled. HDL-C was the dependent variable and FT3, FT4, and TSH were the independent variables. Multiple linear regression analysis was conducted. The difference was considered statistically significant when $P < .05$.

3. Results

3.1. The basic characteristics of the subjects

A total of 461 subjects, including 187 males and 274 females, were included in this study (Table 1). Among them, 22 were smokers and 439 were nonsmokers, the mean age was 45.64 years.

3.2. Statistical model test

Through the model test, F value of regression analysis was 23.94 ($P < .0001$), indicating that the model is valid. Through statistical

Table 1
Analysis of basic characteristics of samples.

	Sex (male/female)	Smoker (yes/no)		Age	BMI	FT3	FT4	TSH	HDL-C
n	187/274	22/439	$\overline{X}$	45.64	23.42	4.54	16.53	2.01	1.54
			SD	12.27	3.30	0.54	1.87	0.86	0.42

BMI = body mass index, FT3 = free triiodothyronine, FT4 = free thyroxine, HDL-C = high-density lipoprotein cholesterol, TSH = thyroid stimulating hormone.

Table 2

Bivariate correlation analysis between sex, smoking, age, BMI, FT3, FT4, TSH, and HDL-C.

		Sex (male/female)	Smoker (yes/no)		Age	BMI	FT3	FT4	TSH
HDL-C	Mean	1.34/1.67	1.36/1.54	Coef	−0.05	−0.48	−0.35	0.001	−0.07
	P	.000	.98	P	.29	.000	.000	.99	.16

BMI = body mass index, FT3 = free triiodothyronine, FT4 = free thyroxine, HDL-C = high-density lipoprotein cholesterol, TSH = thyroid-stimulating hormone.

analysis, it was found that adjust R^2 was 25.87%, indicating that the model has a high degree of interpretation.

After multiple regression analysis, this study performed a collinear test on the independent variables. In Stata12, the vif values of all independent variables are <2. The statistical results show that there is no autocorrelation problem in the independent variable.

Therefore, the research model used in this study can be considered to be reliable and the statistical results are statistically significant.

3.3. Bivariate correlation analysis between sex, smoking, age, BMI, FT3, FT4, TSH, and HDL-C

All independent variables and dependent variables were analyzed by bivariate correlation analysis (Table 2), among which, sex, smoking, and HDL-C were analyzed by t test and box plot, and Spearman correlation analysis and scatter plot were used for other the independent variables and HDL-C.

The results showed that women have higher HDL-C levels than men, and nonsmokers have higher HDL-C levels than smokers (Fig. 1). On average, HDL-C levels in men were 0.33 mmol/L lower than in women ($P < .001$), and the HDL-C levels of smokers were 0.18 mmol/L lower than that of nonsmokers ($P = .98$) (Table 2).

The scatter plot (Fig. 2) and Spearman correlation analysis (Table 2) showed that age was negatively correlated with HDL-C levels (the older the age, the lower the HDL-C levels were), which was consistent with our hypothesis, but the results were not statistically significant. BMI had a significant negative correlation with HDL-C levels ($P < .001$), indicating that the higher the BMI deviated from normal levels the lower the HDL-C level. FT3 was negatively correlated with HDL-C levels ($P < .001$), indicating that FT3 can reduce HDL-C levels. FT4 was positively correlated

with HDL-C levels ($P = .99$). TSH was negatively correlated with HDL-C levels ($P = .16$).

3.4. Multiple linear regression analysis between FT3, FT4, TSH, and HDL-C

To accurately determine the effect of FT3, FT4, and TSH on HDL-C levels, the influence of confounding factors such as sex, age, smoking, and BMI was eliminated. Bivariate correlation analysis established HDL-C as a dependent variable and FT3, FT4, TSH as independent variables. Multiple linear regression analysis results are shown in Table 3.

Statistical results showed that under the control of confounders, FT3 was still negatively correlated with HDL-C levels. On average, when FT3 increased by 1 pmol/L, HDL-C decreased by 0.143 mmol /L, and the statistical results were significant ($P < .001$). There was still a positive correlation between FT4 and HDL-C levels. On average, HDL-C increased by 0.016 mmol/L for every 1 pmol/L increase in FT4. TSH is still negatively correlated with HDL-C levels. On average, HDL-C decreases by 0.010 mmol/L for every 1 μIU/mL increase in TSH, but the statistical results were not significant ($P > .05$). The statistical results showed that FT3 was closely related to HDL-C levels.

4. Discussion

HDL-C is mainly secreted by the liver and small intestine. The body cannot completely decompose cholesterol, but can excrete it in the liver as bile acid or directly through the bile in the form of free cholesterol. Cholesterol clearance pathways include the HDL receptor pathway and the cholesterol transporter protein (CETP) pathway. Hydroxymethyl glutaryl CoA (HMG-CoA) reductase is a rate-limiting enzyme for cholesterol synthesis, and cholesterol 7α-hydroxylase (CYP7A1) is a key enzyme for cholesterol
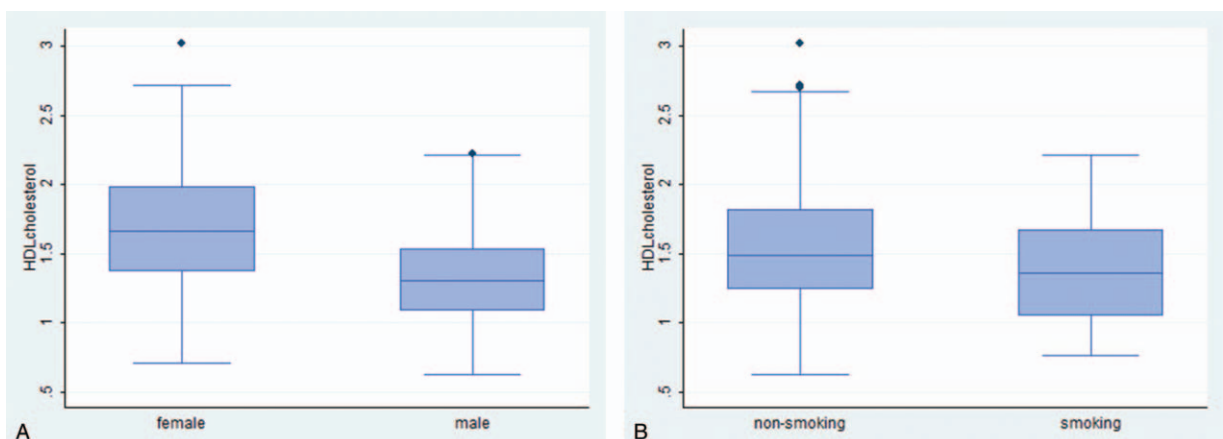

Figure 1. Comparison of HDL-C levels in (A) different sexes and (B) smokers and nonsmokers. HDL = high-density lipoprotein.
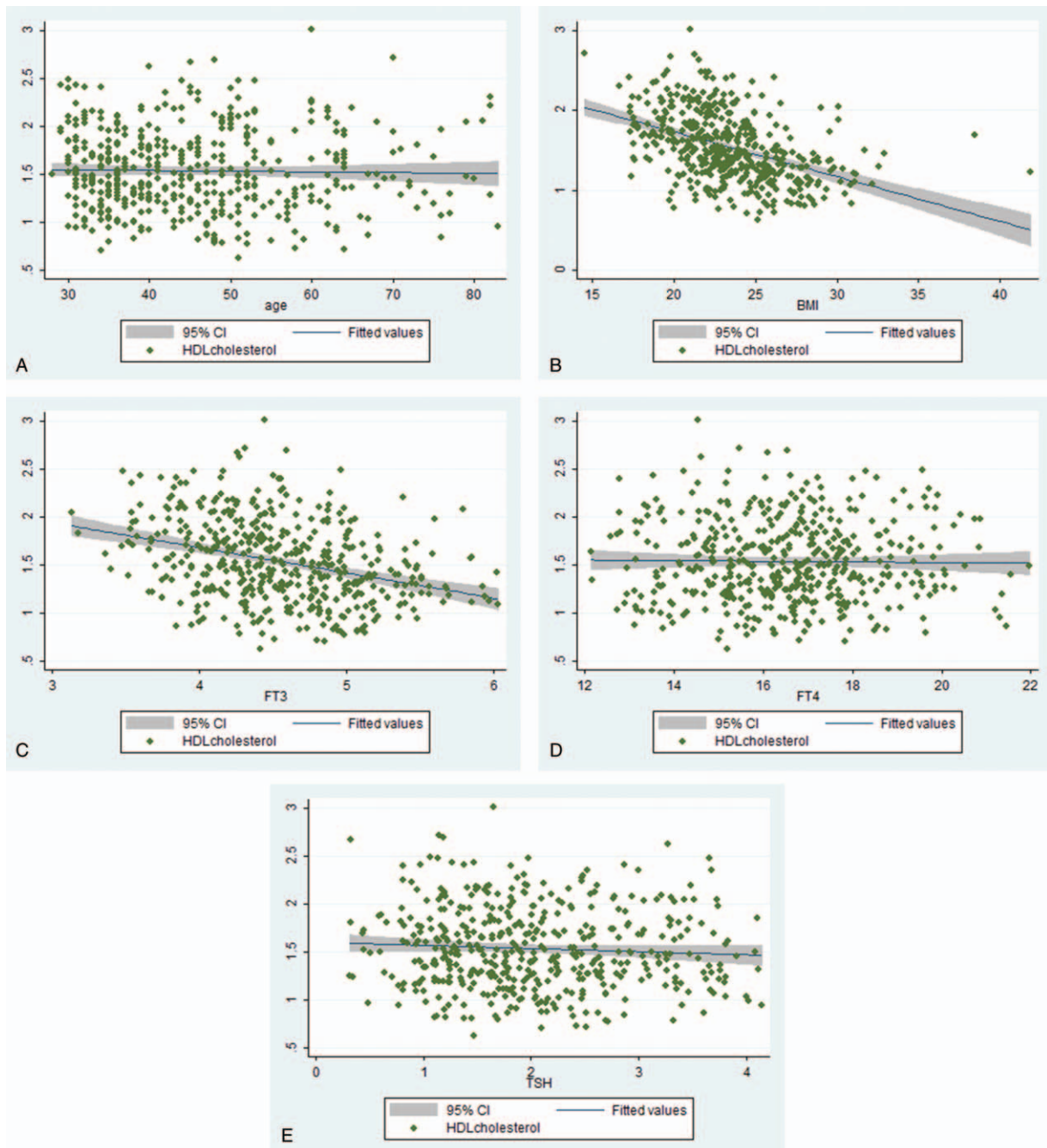
Figure 2. The relationship between HDL-C levels, (A) age, (B) BMI, (C) FT3, (D) FT4, and (E) TSH. BMI=body mass index, FT3=free triiodothyronine, FT4=free thyroxine, HDL=high-density lipoprotein, TSH=thyroid-stimulating hormone.

catabolism. Thyroid hormones have a dual regulation effect on cholesterol. It can induce the synthesis of HMG-CoA reductase in hepatic cells and improve the activity of HMG-CoA to increase cholesterol synthesis. By regulating CYP7A1 transcription, increasing the activity of CYP7A1, and upregulating the hepatic LDL receptor, it can promote the decomposition of cholesterol, which has a greater role than synthesis, and the overall regulatory effect reduces serum cholesterol levels.[7,8]

In our study, we found that FT3 was negatively correlated with HDL-C levels, and the results of multiple linear regression analysis controlling for sex, age, BMI, smoking, drinking, and other confounding factors showed that for every 1-pmol/L

increase in FT3, HDL-C decreased by 0.143 mmol/L, and the difference was statistically significant ($P < .001$). FT3 can possibly reduce HDL-C levels in 3 ways. First, FT3 increases the mRNA levels of CYP7A1, promotes the synthesis of bile acids, and thus leads to the decrease of serum cholesterol. Second, FT3 can increase the scavenger receptor-BI (SR-BI) protein levels of liver and promote the transport of cholesterol. SR-BI is a high-density lipoprotein receptor, which can improve the affinity of HDL and selectively absorb HDL-derived lipids into the liver. Third, the protein that affects HDL-C metabolism in the liver is ATP-binding cassette transporter 1 (ABCA1). Thyroid hormones reduce the formation of HDL by downregulating hepatic

Table 3

Multiple linear regression analysis between FT3, FT4, TSH, and HDL-C.

Independent Variables	Coef	Standard Error	95% confidence intervals	P
Sex	−0.165	0.443	−0.249∼−0.081	.000
Smoking	0.024	0.082	−0.138∼0.186	.769
Age	0.000	0.001	−0.002∼0.003	.794
BMI	−0.040	0.006	−0.051∼−0.029	.000
FT3*	−0.143	0.040	−0.221∼−0.065	.000
FT4*	0.016	0.010	0.005∼0.036	.129
TSH*	−0.010	0.020	−0.049∼0.030	.635

BMI = body mass index, FT3 = free triiodothyronine, FT4 = free thyroxine, HDL-C = high-density lipoprotein cholesterol, TSH = thyroid stimulating hormone.
* Confounders were controlled for sex, age, smoking, and BMI.

ABCA1, thus lowering HDL-C.[9–11] The research of Lin et al also supports similar results.

FT4 was positively correlated with HDL-C. On average, HDL-C increased by 0.016 mmol/L for every 1-pmol/L increase in FT4. The inconsistent changes of HDL-C levels caused by thyroid hormones may be because FT4 also increases the roles of CETP and hepatic lipase (HL). CETP can transfer cholesterol esters from HDL_2 to LDL, very-low-density lipoprotein (VLDL), and chylomicrons (CM). CETP then transfers TG from VLDL and LDL to HDL_2, which then hydrolyzes and releases apoAI and PLs under the action of HL, and then concentrates to form HDL_3, resulting in a decreased HDL_2 and increased HDL_3. HDL_2 and HDL_3 dominate the plasma, whereas HDL_3 accounts for a higher proportion than HDL_2 (1/3 and 2/3, respectively). Therefore, HDL-C levels are elevated when FT4 is elevated. We should not only control the FT3 levels to increase HDL-C, but also avoid the decrease of HDL-C caused by the decrease of FT4 levels.

The results of our study suggest that FT3 plays an important role in the metabolism of HDL-C in people with normal thyroid function. FT3 is also negatively correlated with HDL-C in the normal range. Therefore, patients with hyperthyroidism should pay more attention to the detection of HDL-C. On the one hand, avoiding low levels of HDL-C promotes atherosclerosis, but on the other hand, by adjusting thyroid hormone levels to increase HDL-C levels, HDL-C can play a role in cardiovascular protection. However, FT4 is positively correlated with HDL-C. We should not only control the FT3 levels to increase HDL-C, but also avoid the decrease of HDL-C caused by the decrease of FT4 levels. Currently, the most commonly used levothyroxine is T4 supplement, but there is no drug for FT3. In future studies, further elucidation of the role of thyroid function in HDL-C may provide new direction for the prevention of cardiovascular diseases and the study of new drugs.

Although the correlation between FT3 and HDL-C in people with normal thyroid function has been fully analyzed in our study, there are still some deficiencies. The main problem being that the causal relationship between FT3 and HDL-C cannot be accurately obtained through the statistical analysis of cross-sectional data, which should be proved more rigorously through the analysis of time series. In addition, the data of our study come from a certain community, and the sample size is relatively limited, which cannot be generalized to all populations. In future studies, further elucidation of the role of thyroid function in

HDL-C may provide new direction for the prevention of cardiovascular diseases and the study of new drugs.

5. Conclusions

Through cross-sectional epidemiological investigation, we found that there was a significant negative correlation between normal FT3 levels and HDL-C, suggesting that FT3 plays an important role in the metabolism of HDL-C. Based on the results of this study, we should pay more attention to the detection of HDL-C levels in patients with thyroid dysfunction, avoid the occurrence of cardiovascular diseases caused by low HDL-C, and also pay attention to the detection of thyroid function in patients with low HDL-C, find out the cause of low HDL-C levels, through adjusting the thyroid hormone levels to increase the levels of HDL-C, so as to play a role in cardiovascular protection.

Author contributions

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