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CLINICAL STUDY

Associations between thyroid hormone levels and regional fat accumulation in euthyroid men

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Abstract

Objective: Body adiposity, especially ectopic fat accumulation, has a range of metabolic and cardiovascular effects. This study aimed to investigate whether thyroid function is associated with various regional fat quantities in euthyroid subjects.

Methods: A total of 100 euthyroid men (free triiodothyronine (fT_3), 4.77 ± 1.21 pg/ml; free thyroxine (fT_4), 1.38 ± 0.21 ng/dl; and TSH, 2.09 ± 0.91 μIU/ml) were enrolled in this cross-sectional study. We measured accumulated regional fat using 64-slice multi-detector computed tomography. Multiple linear regression analysis was used to determine whether accumulated fat in each region was associated with clinical parameters after adjusting for age.

Results: FT_3 was inversely correlated with BMI ($r=-0.232$, $P=0.029$) and LDL cholesterol level ($r=-0.277$, $P=0.019$). FT_4 was inversely correlated with waist circumference ($r=-0.350$, $P=0.008$) and BMI ($r=-0.355$, $P<0.001$). In multiple linear regression analysis, fT_3 and fT_4 levels were significantly associated with pericardial fat volume (fT_3: $B=-0.079$, 95% CI -0.142 to -0.017, $P=0.013$; fT_4: $B=-0.411$, 95% CI -0.780 to -0.042, $P=0.030$) in euthyroid men, independent of age. FT_3 level was inversely associated with intramuscular fat area ($B=-0.059$, 95% CI -0.106 to -0.011, $P=0.016$) and hepatic fat quantity ($B=-0.237$, 95% CI -0.441 to -0.033, $P=0.024$) in euthyroid men, independent of age.

Conclusions: In euthyroid men, low levels of fT_3 and fT_4 were significantly associated with increased pericardial fat volume and BMI.

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Introduction

Thyroid hormone regulates basal metabolic rate, energy expenditure, and body weight. Overt hypothyroidism is associated with weight gain and increased adiposity, which could be one of the reasons for the increased cardiovascular risk observed in hypothyroid patients along with hyperlipidemia, hypercoagulability, and systolic and diastolic hypertension, which are features of hypothyroidism (1, 2). Not only overt thyroid dysfunction but also subtle variation of thyroid function within the normal range has been reported to be associated with the presence and severity of coronary artery disease (CAD) (3, 4, 5).

Obesity is an important cause of insulin resistance (IR) and is also associated with cardiovascular morbidity and mortality. However, the level of cardiovascular risk may vary between different cases of obesity, with body fat distribution constituting an important risk factor. Ectopic fat accumulated as non-subcutaneous adipose tissue has a significant association with IR, which, depending on the location of ectopic fat depots, leads to a range of metabolic and cardiovascular effects (6). Among various regional fat depots, accumulated pericardial fat was previously reported to be associated with coronary artery calcium and coronary heart disease, possibly because it aggravates vessel wall inflammation (7, 8, 9). These findings indicate that a milder variation in thyroid hormone levels, within the normal range, may play a role in pericardial fat deposition and aggravate coronary atherosclerosis. However, there are no reports investigating the effects of thyroid function on body fat distribution, and little is known as to whether thyroid function is associated with body adiposity in euthyroid subjects.

Multidetector computed tomography (MDCT) is used to quantify adipose tissue or lipid content within an organ. It offers volumetric assessment of adipose tissue and assessment of multiple fat depots with fine resolution and excellent reproducibility (6). MDCT is a screening tool for CAD. As the risk of CAD is higher in

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men than in women, and body fat distribution differs between the sexes, we enrolled only male subjects. Thus, in this study, we investigated whether thyroid function is associated with body adiposity and body fat distribution using 64-slice MDCT to measure regional fat in euthyroid men.

Materials and methods

Subjects

From March 2005 to May 2010, we enrolled men aged >30 years voluntarily undergoing 64-slice MDCT to assess CAD during a health check at the Seoul National University Bundang Hospital Health Promotion Centre. A total of 113 subjects agreed to enroll in this study and to provide serum for measurement of thyroid hormone and clinical data, including results of MDCT imaging. Thirteen had an abnormal level of TSH and/or thyroid hormone and 100 had normal levels of TSH and free thyroxine (fT_4). To avoid potential confounding influences on thyroid functions, we excluded subjects (1) who had malignant disease, tuberculosis, or malabsorption syndrome (2); whose aspartate aminotransferase (AST)/alanine aminotransferase (ALT) levels were twofold more than the upper normal limits (3); whose serum creatinine was more than 1.5 mg/dl (4); who had a history of thyroid disease (5); or who were taking thyroxine medication or an antithyroid drug. The final sample comprised 100 euthyroid men.

We identified risk factors by assessing medical histories, demographic data, baseline clinical profiles, and concomitant medications. The study was approved by the Local Ethics Committee, and all subjects gave written, informed consent.

Measurement of anthropometric and biochemical parameters

Body weight, height, waist circumference, and blood pressure were measured at enrollment. BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Total cholesterol, triglyceride, HDL cholesterol (HDL-C), LDL cholesterol (LDL-C), AST, ALT, fasting plasma glucose, HbA1c, and plasma insulin levels were measured after ≥12 h of fasting. We used the following validated formula for homeostasis model assessment of IR (HOMA-IR) (10): HOMA-IR = (fasting glucose (mg/dl) × fasting insulin (μIU/ml))/(22.5 × 18).

Thyroid hormone measurement

The serum for measurement of TSH, free triiodothyronine (fT_3), and fT_4 were drawn after ≥12 h of fasting and prior to MDCT. Serum-fT_3 (Thermo Fisher Scientific, Hennigsdorf, Germany), fT_4, and TSH (DiaSorin, Saluggia, Italy) were determined by an immunoradiometric assay using a commercial kit. The reference ranges for fT_3, fT_4, and TSH were 2.3–5.3 pg/ml, 0.78–1.94 ng/dl, and 0.4–4.0 mIU/ml respectively. Because all the participants were visiting our hospital for routine health screening and had no acute or serious health problems, potential confounding by nonthyroidal illness, such as sepsis and cachexia, would be negligible. We collected information about use of antihypertensive, antidiabetic, and lipid-lowering medications. Nine subjects had taken usual doses of diuretics as antihypertensives and eight had taken β-blockers. We confirmed that all of them took their last dose of medication about 24 h before blood sampling to minimize its interference with thyroid function.

Computed tomography protocol

A 64-slice MDCT protocol was used to detect CAD during a routine health examination of each subject. Subjects with a heart rate of >70 beats/min received 10–30 mg i.v. esmolol (Jeil Pharm, Seoul, Korea) before MDCT imaging. CT angiography was performed with a 64-slice MDCT scanner (Brilliance 64, Philips Medical Systems, Best, The Netherlands). A standard scanning protocol was used, as described previously (11). Further, 10-mm-slice CT images of the liver and spleen, abdomen (L4–L5), and mid-thigh levels were added to this protocol to assess any additional ectopic fat.

Quantification of regional fat

The volume of pericardial adipose tissue was measured in milliliters by a single observer with a dedicated three-dimensional computer workstation (Rapidia 2.8, Infinitt, Seoul, Korea). Pericardial adipose tissue volume was segmented by isolating the pericardial adipose tissue and heart from the thorax using specific anatomical landmarks. The superior limit was determined as the point at which the main pulmonary artery begins to divide. The analyzed volume was inferiorly segmented from the liver and abdominal cavity by manually tracing the pericardium in the axial view every 5 mm, from top to bottom, with the software automatically interpolating between user-defined traces (12). After segmentation of the heart and pericardial adipose tissue from the remainder of the thorax, a threshold of −190 to −30 HU was applied to isolate the adipose tissue-containing voxels. The adipose tissue voxels were then added to arrive at a value for pericardial adipose tissue volume in milliliters. The examinations were performed in random order, with the observer blinded to other information about the subject.

Abdominal visceral fat area and abdominal subcutaneous fat area were assessed at the level of the L4–L5 intervertebral disc space, with a threshold of −250 to −50 HU and with the same software. Skeletal muscle attenuation was determined by measuring the mean

value of all pixels within the range of 0 to +100 HU. Adipose tissue area ranged from −250 to −50 HU. The mid-thigh skeletal muscle area was compartmentalized into areas of normal-density muscle (+31 to +100 HU) and low-density muscle (0 to +30 HU) (13).

Hepatic fat was measured with noncontrast CT. The images were reviewed by a single observer blinded to other data. CT attenuation of three distinct circular areas and the spleen area was measured to generate mean values. Care was taken to avoid inclusion of visually distinct vasculature and biliary structures in the regions of interest. We calculated the difference in liver and spleen attenuation as mean hepatic HU−mean splenic HU, with a smaller difference indicating a greater quantity of hepatic fat (14).

Statistical analysis

Values of all normally distributed variables are expressed as mean±S.D. and values of variables with non-normal distribution are expressed as medians and interquartile ranges. Total cholesterol, triglyceride, HDL-C, LDL-C, fasting plasma glucose, HbA1c, plasma insulin, HOMA-IR, pericardial fat volume, abdominal visceral and subcutaneous fat areas, hepatic fat quantity, and intramuscular fat area were not normally distributed, so data for these variables were log-transformed to reduce skewness. We estimated the results by calculating antilogarithms, for ease of interpretation. Associations among regional fat quantity, clinical parameters, and thyroid hormone levels were identified using Pearson's correlation. We used multiple linear regression analysis to determine whether accumulated fat in each region was associated with clinical parameters after adjusting for age. A P value of 0.05 or less was considered statistically significant. All analyses were performed using SPSS 17.0 for Windows.

Results

Clinical and biochemical characteristics of subjects

A total of 100 euthyroid men participated in our study. Mean TSH, fT_4, and fT_3 levels were 2.09 μIU/ml, 1.38 ng/dl, and 4.77 pg/ml respectively. The clinical and biochemical characteristics of the study population are summarized in Table 1.

Table 1 Clinical and biochemical characteristics of study subjects.

Characteristics (*n*, unit)	**Mean±S.D. or median** (IQR)[a]
Age (100, years)	55±9
BMI (100, kg/m^2)	25.5±2.4
Waist circumference (60, cm)	90.7±6.5
SBP (100, mmHg)	128±14
DBP (100, mmHg)	80±11
TSH (100, μIU/ml)	2.09±0.91
Free T_4 (100, ng/dl)	1.38±0.21
Free T_3 (90, pg/ml)	4.77±1.21
FPG (100, mmol/l)[b]	6.49 (5.77, 7.88)
HbA1c (100, %)[b]	6.3 (5.9, 7.3)
TC (100, mmol/l)	5.32±1.17
TG (83, mmol/l)[b]	1.60 (1.11, 2.32)
HDL-C (83, mmol/l)	1.28±0.27
LDL-C (83, mmol/l)	2.89±0.79
HOMA-IR (88)[b]	2.94 (2.15, 4.60)
Insulin (89, pmol/l)[b]	66.8 (51.7, 89.8)
AST (100, U/l)[b]	23 (20, 28)
ALT (100, U/l)[b]	25 (19, 38)
Cr (100, μmol/l)[b]	97.2 (88.4, 106.1)
Pericardial fat volume (100, cm^3)[b]	94.5 (65.6, 123.7)
Abdominal visceral fat area(100, cm^2)[b]	147.3 (106.9, 185.1)
Abdominal subcutaneous fat area (100, cm^2)[b]	131.7 (106.0, 174.1)
Intramuscular fat area (100, cm^2)[b]	41.9 (33.1, 48.7)
Hepatic fat (77, liver–spleen HU difference)[b]	2.6 (−5.5, 9.8)
Current smoker (%)	42

n, number of subjects; IQR, interquartile range; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; HU, Hounsfield unit.
[a]Log-transformed variables were expressed by medians with IQR.
[b]Log-transformed variables.

Correlation between thyroid function and clinical and biochemical parameters

FT_3 level was inversely correlated with BMI ($r=-0.232$, $P=0.029$) and LDL-C ($r=-0.277$, $P=0.019$) (Table 2). FT_4 level was inversely correlated with waist circumference ($r=-0.350$, $P=0.008$) and BMI ($r=-0.355$, $P<0.001$). Serum TSH level was inversely correlated with serum fasting triglyceride level ($r=-0.229$, $P=0.037$). All these correlations remained significant in multiple linear regression analysis after adjusting for age.

Association between regional fat quantity and thyroid function in euthyroid men

In multiple linear regression analysis, fT_3 level and fT_4 level were each significantly associated with pericardial fat volume in euthyroid men, independent of age (fT_3: $B=-0.079$, 95% CI −0.142 to −0.017, $P=0.013$; fT_4: $B=-0.411$, 95% CI −0.780 to −0.042, $P=0.030$; Table 3). However, there was no significant association between pericardial fat volume and TSH. There was no significant association between thyroid function and abdominal visceral fat area or abdominal subcutaneous fat area.

Ectopic fat deposition in insulin-sensitive tissue, such as liver and muscle, is very important because it induces IR. In multiple linear regression analysis, fT_3 level was inversely associated with intramuscular fat area ($B=-0.059$, 95% CI −0.106 to −0.011, $P=0.016$) and hepatic fat quantity ($B=-0.237$, 95% CI −0.411 to −0.033, $P=0.024$) in euthyroid men, independent of age (Table 3).

Table 2 Pearson correlation coefficients between thyroid function and clinical and biochemical parameters.

	Free T_3	Free T_4	TSH	Pericardial fat volume[a]	Abdominal visceral fat area[a]	Abdominal subcutaneous fat area[a]	Intramuscular fat area[a]	Hepatic fat[a]
Age	−0.050	0.143	−0.103	0.333†	0.080	–0.154	−0.125	0.220
Waist circumference	−0.184	−0.350*	0.183	0.608†	0.577†	0.622†	0.426*	0.095
BMI	−0.232*	−0.355†	0.096	0.420†	0.476†	0.713†	0.572†	−0.294*
SBP	−0.061	0.022	0.004	−0.082	−0.039	0.060	−0.016	−0.123
DBP	0.006	−0.130	0.046	−0.062	0.116	0.002	0.126	−0.244
FPG[a]	0.045	0.052	−0.173	−0.008	0.046	−0.158	0.082	−0.093
HbA1c[a]	0.018	0.095	−0.090	−0.026	0.032	−0.170	0.094	0.077
TC	−0.101	−0.069	−0.008	−0.038	−0.032	−0.092	−0.001	0.205
TG[a]	0.032	−0.117	−0.229*	0.106	0.211	0.026	0.121	−0.171
HDL	0.029	0.005	0.053	0.060	−0.010	−0.038	−0.030	0.419*
LDL	−0.277*	−0.093	0.060	0.065	0.003	0.048	0.083	0.391*
Insulin[a]	−0.268*	−0.172	−0.014	0.242*	0.345*	0.388†	0.347*	−0.372*
HOMA-IR[a]	−0.155	−0.198	−0.118	0.198	0.292*	0.227*	0.327*	−0.317*
TSH	−0.240*	−0.301*	–	−0.041	−0.085	−0.004	−0.056	0.024
Free T_3	–	0.530†	−0.240*	−0.268*	−0.154	−0.162	−0.286*	−0.038
Free T_4	0.530†		−0.301*	−0.139	−0.218*	−0.221*	−0.220*	0.155

*$P<0.05$ from Pearson's correlation analysis. †$P<0.001$ from Pearson correlation analysis.
[a]Log-transformed variables.

Discussion

In this study in euthyroid men, lower levels of fT_3 or fT_4 were significantly associated with increased pericardial fat deposition, independent of age. Moreover, fT_3 level was inversely correlated with BMI and LDL-C, and fT_4 level was inversely correlated with waist circumference and BMI.

This is the first study to investigate the associations between thyroid function and regional fat quantity and show significant associations between fT_3 and fT_4 levels and pericardial fat volume in euthyroid men, after adjustment for age. We used relatively objective and accurate methods for quantifying regional fat. Specifically, we achieved the optimal measurement of pericardial fat by measuring the volume of the total fat depot from the starting division of the main pulmonary artery through the whole pericardium. To our knowledge, this is the first report describing the relationship between thyroid function and pericardial fat volume.

Thyroid hormones regulate the basal metabolic rate of all cells, thereby modulating all metabolic process in the body. Changes in thyroid status can alter metabolic processes and lead to metabolic syndrome, comprising abdominal obesity, dyslipidemia, hypertension, and

Table 3 Associations between thyroid hormone levels and regional fat accumulation by multiple linear regression analysis.

	B (95% CI)	***P***	R^2 **for model** (*P* for model)
Pericardial fat volume			
TSH	0.007 (−0.076 to 0.090)	0.865	0.083 (0.016)
Free T_3	−0.079 (−0.142 to −0.017)	0.013	0.093 (0.015)
Free T_4	−0.411 (−0.780 to −0.042)	0.030	0.121 (0.002)
Abdominal visceral fat area			
TSH	−0.043 (−0.120 to 0.034)	0.271	0.016 (0.477)
Free T_3	−0.043 (−0.103 to 0.017)	0.154	0.025 (0.357)
Free T_4	−0.355 (−0.705 to −0.005)	0.047	0.046 (0.122)
Abdominal subcutaneous fat area			
TSH	−0.004 (−0.083 to 0.075)	0.926	0.019 (0.403)
Free T_3	−0.036 (−0.097 to 0.026)	0.250	0.041 (0.177)
Free T_4	−0.324 (−0.679 to 0.031)	0.073	0.059 (0.064)
Intramuscular fat area			
TSH	−0.031 (−0.098 to 0.037)	0.367	0.025 (0.310)
Free T_3	−0.059 (−0.106 to −0.011)	0.016	0.078 (0.032)
Free T_4	−0.304 (−0.612 to 0.004)	0.053	0.056 (0.074)
Hepatic fat (LS difference)			
TSH	0.008 (−0.284 to 0.300)	0.955	0.032 (0.499)
Free T_3	−0.237 (−0.441 to −0.033)	0.024	0.168 (0.031)
Free T_4	−0.816 (−2.039 to 0.406)	0.185	0.072 (0.208)

B, unstandardized coefficient. *P* from multiple linear regression analysis after adjusting for age. LS difference, liver-spleen Hounsfield unit difference.

glucose intolerance. Thus, efforts have been made to demonstrate the association between thyroid status and metabolic syndrome. Metabolic syndrome is a cluster of several cardiovascular risk factors; thus, it is an important problem because it poses a serious risk of cardiovascular diseases.

The association of thyroid disease with atherosclerotic cardiovascular disease may in part be explained by thyroid hormone's regulation of lipid metabolism and its influence on systemic vascular resistance, diastolic and systolic function, and blood pressure (15). However, the impact of various degrees of thyroid dysfunction on these factors continues to be debated.

The association of cardiovascular diseases with overt hypothyroidism is undoubted, but there is controversy as to whether a similar association exists with subclinical hypothyroidism. However, many recent studies have shown that subclinical hypothyroidism was also associated with an increased risk of coronary heart disease (16), and low fT_4 levels in euthyroid subjects were a risk factor for carotid atherosclerosis (17). We and others previously reported that increased pericardial fat volume was an independent risk factor for CAD, possibly because it aggravated vessel wall inflammation (7, 8, 9). On the basis of these findings, we can postulate that a low level of fT_3 or fT_4 plays a role in pericardial fat deposition and aggravates vessel wall inflammation and atherosclerosis. Our result is also consistent with previous reports addressing the concept that low fT_3 levels were associated with the presence and severity of CAD in the euthyroid subjects (3, 4, 5).

Interestingly, in this study, fT_3 and fT_4 levels were inversely correlated with BMI or waist circumference, which are common parameters for obesity. Overt hypothyroidism is associated with weight gain and adiposity, with weight gain commonly occurring after treatment of Graves' disease. Indeed, a great deal of research has been conducted to elucidate the association between thyroid function and obesity or BMI. However, data conflict with regard to whether mild hypothyroidism, subclinical hypothyroidism, or both are associated with obesity (18). Although the studies showing positive relationships mostly involved morbidly obese subjects (19, 20, 21, 22, 23), we were able to demonstrate a significant relationship between thyroid function and regional fat accumulation in nonobese, euthyroid men, in spite of a relatively small sample.

In this study, serum fT_3 level was also inversely correlated with intramuscular fat area and hepatic fat quantity. Ectopic fat in insulin-sensitive tissue, such as liver and muscle, is associated with IR, so we analyzed its association with HOMA-IR (IR index) and thyroid function parameters. However, we did not identify any significant association. Our analysis may have been confounded by the fact that we were unable to measure the entire volume of hepatic or intramuscular fat, as we did with pericardial fat, because precise measurement in these regions was not possible with MDCT.

We found no significant association between thyroid hormone levels and abdominal visceral fat, which is also considered a metabolic organ. The design of our study was cross-sectional, and hence, we cannot explain exactly why thyroid hormone levels were associated with pericardial fat volume but not abdominal visceral fat area. However, fT_4 level was inversely correlated with abdominal visceral fat area. Therefore, abdominal visceral fat area could have an association with thyroid hormone similar to that of pericardial fat volume. One of the main reasons for more significant results with pericardial fat is that we were able to measure pericardial fat volume more exactly than abdominal visceral fat volume. We measured whole pericardial fat volume from the starting division of the main pulmonary artery to the cardiac apex using MDCT. However, for abdominal visceral fat, we evaluated just one section. So, our measurement of pericardial fat volume was more precise than our measurement of abdominal visceral fat area.

We found no association between serum TSH level and body fat distribution. This result suggests that fT_3 or fT_4, rather than TSH, plays a more sensitive role in controlling metabolic parameters. This is in accordance with the reports that fT_4, but not TSH, was related to plasma LDL-C, HDL-C, and HOMA-IR (24, 25).

The limitations of our study are its small sample size and cross-sectional design. We cannot determine whether this association is a cause-and-effect relationship. Further longitudinal studies are needed to solve this problem. In addition, we measured thyroid hormone levels only once. All the participants in this study were visiting our hospital for routine health screening and had no acute health problems. Therefore, even though transient thyroid hormonal change cannot be completely ruled out, there were likely very few cases of persistent thyroid dysfunction influencing our results.

In conclusion, fT_3 level and fT_4 level were each significantly associated with pericardial fat volume and BMI. Thyroid hormone levels can affect cardiovascular risk through regulation of pericardial fat deposition, in addition to other known mechanisms.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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