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Change in pericardial fat volume in postmenopausal women with papillary thyroid cancer undergoing thyrotropin suppressive therapy

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Abstract

Background Despite TSH suppressive therapy improve the prognosis for the patient with differentiated thyroid cancer (DTC), there is an increasing concern regarding the potentially harmful effects of lifelong TSH suppression. Therefore, we aimed to examine the changes in body composition under TSH suppression in postmenopausal women with DTC.

Methods The body composition was assessed by the volumes as following; fat tissues of the epicardium and abdominal visceral and subcutaneous areas; bilateral psoas muscle or thigh muscle. Each volumetric measurements were performed using computed tomography (CT) scans using baseline and follow-up fluorine-18 fluorodeoxyglucose positron emission tomography/CT (^{18}F-FDG PET/CT)s for 2-year follow up period in Pusan National University Hospital, South Korea.

Results The 43 patients' median age was 50.0 years, and median body mass index (BMI) was 23.53 (interquartile range[IQR]: 22.19- 24.92) at the initial ^{18}F-FDG PET/CT. The median follow-up period was 19.24 months (IQR: 17.24–21.79). No significant change in weight or BMI were observed during follow-up. Volumes of fat and muscles was not changed significantly except epicardial fat volume. The epicardial fat volume significantly increased during the follow-up period. The epicardial fat volumes were correlated with visceral fat volume, respectively, however, the changing ratio was only correlated with TSH suppression on multiple regression analysis.

Conclusion Both skeletal muscle and abdominal fat volumes did not change, whereas epicardial fat volume increased over less than 2 years of observation under TSH suppressive therapy. Further research is needed for the harmonization of benefits or losses with the optimal TSH concentration in postmenopausal women.

Keywords Differentiated thyroid cancer, TSH suppressive therapy, Epicardial fat, Menopause, Body composition, F-18 FDG PET/CT

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Introduction

Thyroid carcinoma, especially differentiated thyroid cancer (DTC) is the most common endocrine malignancy and the most rapidly increasing malignancy in recent decades [1]. The prognosis is favorable, with an overall 10-year survival rate of 80% to 95% [2]. Initial total thyroidectomy and radioiodine ablation using iodine-131, followed by suppression of TSH with exogenous levothyroxine (LT4), is the traditional treatment for DTC [3–5]. Eliminating the TSH stimulus is theoretically viable because it inhibits the growth of residual neoplastic tissue [6–8]. In the clinical setting, endogenous or exogenous increases in TSH levels may occasionally induce disease progression in patients with thyroid cancer [9, 10].

As DTC is generally an indolent tumor and its cancer-specific mortality is very low, TSH suppression therapy has recently been reconsidered due to concern about the potentially harmful effects of lifelong TSH suppression [1]. Serious adverse effects of long-term TSH suppressive therapy have been reported, including thyrotoxicosis, cardiovascular disease, and osteoporosis [1, 11–14]. Although TSH suppression reduces the risk of tumor recurrence and improves patient survival [6, 15], insufficient evidence is currently available regarding the optimal TSH concentration to reduce tumor recurrence while ensuring minimal adverse effects from subclinical hyperthyroidism.

Thyroid hormones regulate energy metabolism and show correlations with body weight and energy expenditure [16, 17]. Hyperthyroidism is a high metabolic state characterized by weight loss and increased resting energy expenditure, lipolysis, and gluconeogenesis [17, 18]. Hyperthyroidism is also accompanied by hemodynamic changes, such as an increased heart rate, cardiac contractility, cardiac output [18], and increased stroke volume, which may harm arterial distensibility and imply vascular stiffness [19]. Hypothyroidism is related to weight gain, obesity [20], and increased fat volume at various sites, such as visceral and epicardial fat [21]. However, few studies have investigated the relationship between thyroid hormone levels and body composition in hyperthyroidism, especially in patients with subclinical hyperthyroidism undergoing TSH suppression therapy.

Postmenopausal women are the most common population to present WDTC. The menopause state, which involves a reduction of estrogen production, may cause major metabolic changes and induce modifications in body composition [22, 23]. Advancing age with menopause is characterized by a progressive decrease in lean mass and increase in fat mass, resulting in obesity and sarcopenia [22, 24] Therefore, condition with both menopause and hyperthyroidism could have additive effects on body composition including bone, muscle and fat.

This study aimed to evaluate changes in muscle quantity and ectopic fat accumulation in patients with DTC who underwent TSH suppressive therapy. We investigated whether the iatrogenic conditions of overt or subclinical hyperthyroidism induced by exogenous LT4 altered the body composition of postmenopausal women with DTC after total thyroidectomy.

Materials and methods

Study population

We retrieved data from 138 patients with thyroid cancer who underwent total thyroidectomy and were followed up with fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) between 2009 and 2017 in Pusan National University Hospital, Busan, South Korea. A flow diagram describing the eligible patients is shown in Fig. 1. We excluded 23 patients who did not present with DTC (medullary thyroid cancer, n = 11; anaplastic cancer, n = 5; lymphoma, n = 5; sarcoma, n = 2) or multiple distant metastases (n = 21). Forty-five patients were excluded due to a combination of other malignancies, including breast cancer (n = 31), colon cancer (n = 3), lung cancer (n = 5), renal cell carcinoma (n = 2), gastric cancer (n = 1), hepatocellular carcinoma (n = 1), and lymphoma (n = 2). Of the remaining patients, 37 who received radioiodine therapy between the two follow-up ^{18}F-FDG PET/CT scans were excluded. We cannot find any significant medication including metformin and DPP4 inhibitors or TZD or on the status of uncontrolled diabetes mellitus or hypertension of enrolled patients. In addition, serum fasting blood sugar (FBS) concentration levels were confirmed as less than 120 mg/dl before F-18 FDG administration. All image acquisition processes were standardized by following to the 2015 EANM guidelines [25]. In addition, all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The requirement of written informed consent from enrolled subjects was waived by the Institutional Review Board of Pusan National University Hospital due to the retrospective study design. (IRB No. 1809–018–071).

Quantification of body composition

Changes in body composition patterns were assessed by comparing muscle and fat areas measured on serial CT scans of ^{18}F-FDG PET/CT, which were performed to monitor the recurrence or disease progression of thyroid

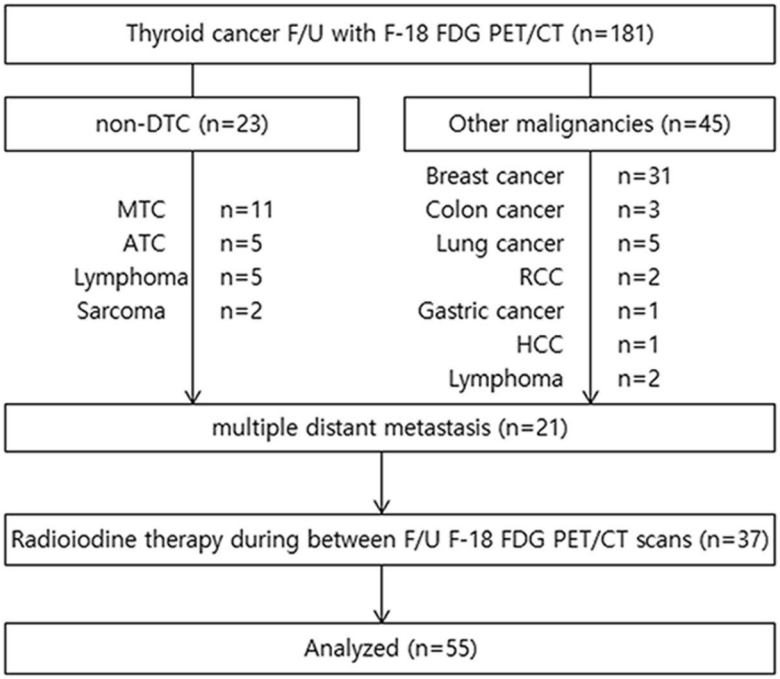

Fig. 1 Flow diagram for selection of the study subjects

cancer in patients undergoing TSH suppressive therapy after total thyroidectomy. CT images from ^{18}F-FDG PET/CT were used to quantify adiposity and muscle mass. The CT images were acquired using two types of scanners (Somatom Definition, Siemens Healthcare, Forchheim, Germany, and Gemini, Philips, MA,, USA). Oral or intravenous contrast agents were not administered. Scans were performed using a standard abdominal and pelvic viewing protocol at 120 kV, 99–320 mA, and a section thickness of 4 mm. The scan area extended from the level of the diaphragm to the pubic symphysis.

The fat tissue and muscle volumes were reconstructed and calculated using CT software (Siemens, syngo.CT basic evaluation). The adipose tissue volume in the epicardium and visceral and subcutaneous fat of the abdomen was examined. For the epicardial adipose tissue (EAT), the superior limit was determined as the point at which the main pulmonary artery began to divide and was inferiorly segmented by manually tracing the epicardium in the axial view every 3 or 4 mm from top to bottom. Abdominal visceral fat tissue boundaries were defined as intra-abdominal fat bound by the parietal peritoneum or transverse fascia. After segmentation, the fat tissue volume of the epicardium and viscera was calculated from the threshold of −250 to −50 hounsfield unit (HU) to isolate the adipose tissue containing voxels. For muscular quantitative assessment, the bilateral psoas muscle area at the mid-level of L5 and the bilateral mid-thigh area were compartmentalized into areas of normal-density muscle from a threshold of + 30 to + 100 HU. The summed values of the bilateral psoas muscle or thigh muscle were used as quantified values for the skeletal muscle. The changes of the pericardial fat volumes were assessed by ratio of the volume of the second scan to the that of the first scan.

Statistical analysis

Values of all normally distributed variables were expressed as mean ± standard deviation, and values of variables with non-normal distribution were expressed as medians and interquartile ranges (IQRs). Continuous variables between baseline and follow-up within each patient were compared using rank-sum tests because of the non-normality of the data. Associations among regional fat quantity, clinical parameters, and thyroid hormone levels were identified using Pearson's correlation. To evaluate the relationship between fat volumes and other clinical parameters, we conducted a stepwise multiple linear regression by considering a set of potential variables. The statistical analyses were performed using the R software version 4.2.0 (https://www.R-project.org/) and the MedCalc® for Windows version 16.4.3, and a *P*-value of less than 0.05 was regarded as significant.

Results

Patients' characteristics

We identified 43 patients with papillary thyroid cancer who underwent TSH suppressive therapy after total thyroidectomy. The median age of the patients was 50.00 (44.00–57.00) years. The body mass index (BMI) ranged from 18.98 to 32.67 with a median value of 23.5 (IQR: 22.2–23.9). The median value of FBS was 98 (IQR: 85.3–112.3) mg/dL. The first follow-up ^{18}F-FDG PET/CT was performed at 22.32 months (IQR: 19.18–28.12) after total thyroidectomy, and the median follow-up period was 19.24 months (IQR: 17.24–21.79). between the first and second ^{18}F-FDG PET/CT. According to the American Joint Committee on Cancer 8th Edition, all patients were classified as having stage I or II cancer. Thirty three patients (58.18%) who were in the low-risk group did not receive radioiodine therapy. The baseline clinical characteristics of the patients at the time of the first follow-up ^{18}F-FDG PET/CT are summarized in Table 1.

Changes in clinical and biochemical parameters

TSH levels were suppressed; however, no significant change was observed during the follow-up period. T4 and T3 serum levels and lipid profiles, including triglycerides, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, and aspartate transaminase/alanine transaminase ratios, did not change during the observed follow-up period. Additionally, no significant change was observed in weight (median value 62.34 [IQR: 58.20—65.90] vs. 62.78 [58.43 – 66.28]; $P=0.13$) and BMI (median value 23.83 [22.45—26.19] vs. 23.94 [22.87—25.74]; $P=0.36$) (Table 2).

Table 1 Clinical and pathological characteristics of patients at the baseline

Characteristics			%
No. of patients		55	
Age (years)		50.00 (44.00–57.00)	
Tumor size (cm)		1.73 (0.40–6.10)	
Microcarcinoma		25	45.45
Microscopic extrathyroidal extension	Yes	32	58.18
	No	23	41.82
T stage	T1	29	52.73
	T2	22	40.00
	T3	2	7.27
N stage	N0	21	38.18
	N1a	22	20.00
	N1b	12	21.82
AJCC TNM	I	32	58.18
	II	23	41.82
Ablation RAI dose	None	22	38.18
	30 mCi	18	32.73
	100 mCi	20	36.36
	150 mCi	17	30.91

American Joint Committee on Cancer 8th Edition

Data reported as median (interquartile range)

RAI radioactive iodine

Changes in quantity of body composition

During the follow-up period between the first and second PET/CT scans, EAT volume (median value 147.96 [131.39—165.42] vs. 166.30 [146.73—187.28]; $P<0.01$) significantly increased. The representative example of patient who showed the prominent increased EAT area during the follow-up period (Fig. 2). Visceral fat volume (median value 214.77 [196.48- 233.38]vs. 217.57 [197.30—237.85); $P=0.57$) did not change significantly. The summed area of the bilateral psoas muscle (median value 14.51 [13.50—15.51] vs. 14.21 [13.34—15.08); $P=0.57$) and that of the bilateral thigh muscle (median value 24.46 [23.98 – 27.49] vs. 24.38 [23.38 – 25.94]; $P=0.93$) did not show significant differences between the first and second images (Fig. 3).

Multiple regression analysis between adiposity indices and insulin resistance

In the regression analysis, pericardial fat volume were associated with all metabolic related factors of BMI and fat volumes of visceral and total abdominal areas. The thyroid function test were not correlated with the absolute volume of the pericardial fat (Table 3). However, the changing ratio of pericardial fat was only correlated with TSH level and multiple regression analyses showed that serum TSH level ($\beta=-5.91$, $P=0.02$) remained an independent predictor of changing pericardial fat in postmenopausal women with TSH suppressive therapy (Table 4).

Discussion

In this study, we showed that postmenopausal women who underwent TSH suppression therapy after total thyroidectomy had significantly increased epicardial fat deposition; however, no change in visceral fat volume or muscle mass was observed.Epicardial fat is the adipose tissue between the epicardial surface of the heart and the visceral surface of the epicardium, which is enclosed by the epicardial sac and directly surrounds the coronary arteries [26]. The physiological function of EAT is to serve as an energy source for the myocardium [27], thermoregulation, and a buffer between the myocardium and local vasculature to protect the heart from lipotoxicity [28]. However, the EAT is also a visceral fat deposit that secretes biologically active adipokines. Adipokines

Table 2 Comparison of clinical and laboratory data between 1st and 2nd F-18 FDG PET/CT scans

	F/U PET/CT #1	F/U PET/CT #2	*p*-value
Body weight (kg)	62.34 (58.20—65.90)	62.78 (58.43 – 66.28)	0.13
BMI (kg/m^2)	23.83 (22.45—26.19)	23.94 (22.87—25.74)	0.36
Dose of L-thyroxine administration(mg)	0.15 (0.13 – 0.15)	0.15 (0.13 – 0.15)	0.94
Dose of L-thyroxine per body weight (mg/kg)	2.20*10^{-3} (1.97*10^{-3} – 2.60*10^{-3})	2.26*10^{-3} (2.20*10^{-3}– 2.60*10^{-3})	0.82
TSH (uIU/mL)	0.08 (0.01 – 0.21)	0.13 (0.01 – 0.38)	0.41
freeT4 (ng/dL)	1.49 (1.37 – 1.73)	1.54 (1.33 – 1.64)	0.64
T3 (ng/dL)	127.24 (114.11 – 138.32)	117.01 (109.46 – 127.68)	0.27
Total cholesterol (mg/dL)	186.12 (171.21—198.24)	185.18 (171.26—194.63)	0.87
Triglyceride (mg/dL)	155.13 (103.87—201.97)	131.34 (101.34 –187.12)	0.15
LDL-cholesterol (mg/dL)	122.12 (104.42—141.15)	121.46 (104.81—131.98)	0.68
HDL-cholesterol (mg/dL)	52.12 (48.12—58.32)	51.12 (46.12—55.79)	0.49
AST (U/L)	24.32 (21.32—27.38)	24.23 (21.81—28.23)	0.12
ALT (U/L)	24.71 (19.73—27.22)	25.12 (21.72—29.01)	0.59
Area of thigh muscle (cm^2)	24.46 (23.98 – 27.49)	24.38 (23.38 – 25.94)	0.93
Area of psoas muscle (cm^2)	14.51 (13.50—15.51)	14.21 (13.34—15.08)	0.18
Volume of visceral fat (cm^3)	214.77 (196.48- 233.38)	217.57 (197.30—237.85)	0.57
Volume of epicardial fat (cm^3)	147.96 (131.39—165.42)	166.30 (146.73—187.28)	< 0.01

Variables were expressed by median (interquartile range)

TSH thyroid stimulating hormone, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *BMI* body mass index

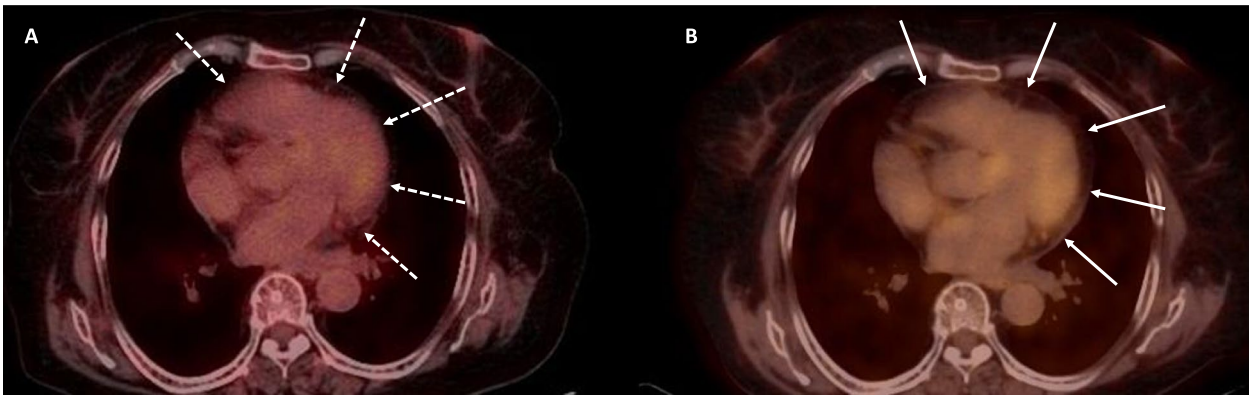

Fig. 2 Representative examples of A 65-year-old woman at the time of diagnosis of differentiated thyroid cancer (T2N0M0) who showed increased epicardial fat volume during 2-year follow-up. **A** The epicardial fat area (white dotted arrow) was scares at the first scan of F-18 FDG PET/C with volume of 127cm^3. **B** On the second scan of F-18-FDG PET/CT, there was widening of epicardial fat areas (white solid arrows) with increased volume of 251 cm.^{3}

produced by EAT influence the underlying atherosclerotic plaque by paracrine signaling directly through the vessel wall, which initiates inflammation, and by vasocrine signaling by directly entering the lumen of the closely opposed adventitial vasa vasorum enclosed by the EAT [26]. EAT is involved in the initiation of inflammation and the inflammatory process within and around atherosclerotic plaques [27]. The inflammatory response plays a fundamental role in mediating all stages of atherosclerosis, from initiation to progression and, ultimately, the thrombotic complications of atherosclerosis [29]. Coronary calcification is closely related to vascular damage and atherosclerotic plaques and is used to diagnose coronary atherosclerosis [30]. Several studies have shown a link between epicardial fat volume and coronary artery disease as estimated by coronary artery calcifications [31–33], plaque [34–36], or coronary events [37–39]. However, some studies have reported that the

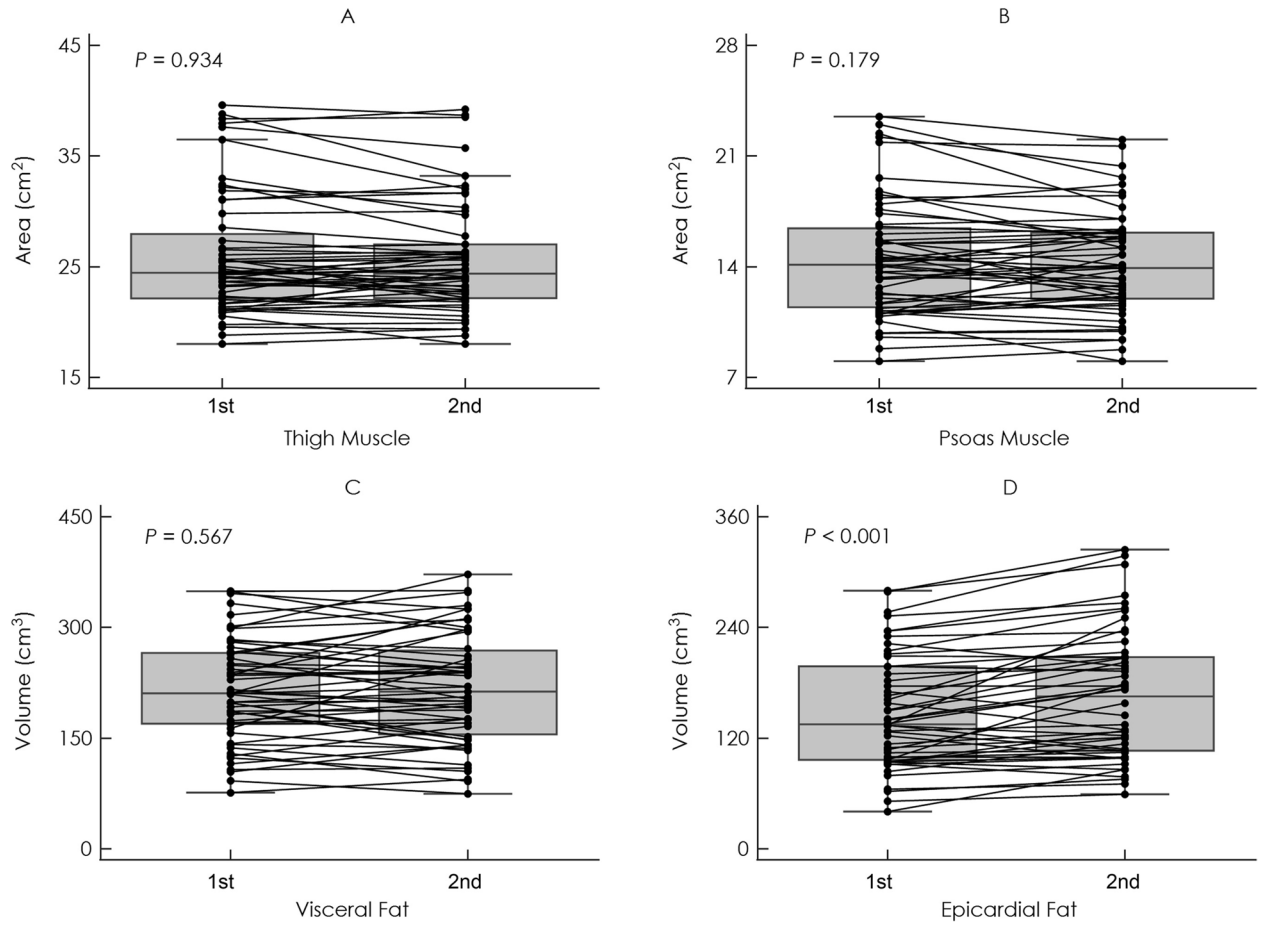

Fig. 3 Differences in area of thigh muscle (**A**), psoas muscle (**B**), volume of visceral fat (**C**) and epicardial fat (**D**) during follow up period between first and second PET/CT scan under TSH suppression therapy

Table 3 Pearson correlation coefficients between clinical parameters and thyroid function at the 2nd F/U F-18 FDG PET/CT

	Total fat	Visceral fat	Subcutaneous fat	Pericardial fat
Total fat	-	-	-	-
Visceral fat	0.78 (< 0.01)	-	-	-
Subcutaneous fat	0.83 (< 0.01)	0.42 (< 0.01)	-	-
Epicardial fat	0.65 (< 0.01)	0.72 (< 0.01)	0.38 (< 0.01)	-
TSH	0.04 (0.68)	0.19 (0.45)	0.13 (0.42)	0.24 (0.22)
fT4	0.41 (0.15)	0.21 (0.53)	0.11 (0.29)	−0.21 (0.72)
T3	0.21 (0.24)	−0.02 (0.53)	0.23 (0.42)	0.22 (0.28)
BMI	0.85 (< 0.01)	0.72 (< 0.01)	0.69 (< 0.01)	0.62 (< 0.01)
Total cholesterol (mg/dL)	0.61 (0.09)	0.73 (0.12)	0.40 (0.16)	0.45 (0.43)
Triglyceride (mg/dL)	0.35 (0.39)	0.62 (0.07)	0.12 (0.09)	0.32 (0.45)
LDL-cholesterol (mg/dL)	−0.11 (0.12)	−0.17 (0.69)	0.54 (0.14)	0.57 (0.43)
HDL-cholesterol (mg/dL)	0.19 (0.08)	0.21 (0.09)	−0.11 (0.18)	- 0.20 (0.18)

TSH thyroid stimulating hormone, *BMI* body mass index, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein

P-values are expressed in the parentheses

Table 4 Multiple Regression Analysis between changing ration of pericardial fat volume and other clinical parameters

Variable	Changing ration of Pericardial fat volume (cm^3)			
	Univariate analysis		Multivariate analysis	
	β	*P*-value	*β*	*P*-value
BMI (kg/m^2)	−0.29	0.09		
TSH	−0.48	0.03	−5.91	0.02
freeT4	0.14	0.68		
T3	−0.11	0.72		
Total cholesterol (mg/dL)	−0.48	0.08		
Triglyceride (mg/dL)	0.22	0.43		
LDL-cholesterol	0.35	0.88		
HDL-cholesterol	−0.12	0.71		
Volume of visceral fat (cm^3)	0.63	0.81		

BMI body mass index, *TSH* thyroid stimulating hormone, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein

volume of epicardial fat has a weak relationship with cardiovascular disease, depending on cardiovascular risk factors or plaque characteristics [40, 41]. Nonetheless, epicardial fat accumulation is generally considered a leading factor in plaque calcification and the development of mature atherosclerotic plaques [42, 43].

One study has reported that epicardial fat thickness and carotid intima-media thickness (cIMT) are significantly increased in patients with overt hyperthyroidism, irrespective of confounding factors [44], while another study has shown that epicardial fat tissue volume is correlated with low TSH levels in Graves' disease [45]. Epicardial fat tissue volume is significantly positively associated with the intima-media thickness [21, 46, 47] and cIMT is significantly higher in patients with Graves' disease and reversed by treatment with propylthiouracil [48]. The American Thyroid Association management guidelines for DTC introduce cardiovascular risks, including atrial fibrillation and exacerbation of angina, as side effects of TSH suppression therapy after thyroidectomy [49]. We suggest that increased epicardial fat could be one of the reasons for the increased cardiovascular risk in patients receiving TSH suppression therapy for DTC.

Generally, patients with overt hyperthyroidism have low body weight, fat mass, fat-free mass and recover after treatment [50]. However, in subclinical hyperthyroidism induced by TSH suppression therapy after total thyroidectomy, ambiguous results have been observed. Some studies have reported that thyroxine therapy does not affect muscle mass or fat mass [51–53], but others have reported that muscle function is reduced in patients with subclinical hyperthyroidism after total thyroidectomy [54]. Our results are consistent with those of the former of these studies. Muscle mass estimated in the thigh and psoas did not change during TSH suppressive therapy after total thyroidectomy. This might be due to the relatively young age of the subjects and the short follow-up period. The lipid profiles were not correlated with the fat volume related factors in the current study. It might because that the enrolled individuals were metabolically healthy status of well controlled hypertension, diabetes mellitus or dyslipidemia.

The present study has several limitations. First, the number of participants at a single institution was relatively small. Therefore, we cannot conclude that these results apply to other populations. Second, given the potential limitations of information due to its nature of retrospective design of the study, determining a causal relationship between TSH suppression and epicardial fat volume is difficult. As the study participants were postmenopausal women, changes in inflammation or body composition could have been affected by hormonal changes or aging. Nonetheless, this study has some strengths. The study design was longitudinal, and other diseases that can affect body composition were excluded. All the participants were postmenopausal women with similar metabolic changes.

In conclusion, we showed that the epicardial fat volume increased over less than 2 years of observation in postmenopausal women undergoing TSH suppressive therapy after total thyroidectomy. Therefore, clinicians should be aware of the adverse effects of TSH suppression on the heart through atrial fibrillation and the accumulation of epicardial fat accompanying the inflammatory response. Generally, TSH suppression is recommended after total thyroidectomy in patients with thyroid cancer. Although our study suggests that TSH suppression did not affect on changes in psoas muscle mass and abdominal fat distribution, there were significant change in epicardial fat and the changing ratio was significantly correlated with serum TSH level. Therefore, caution should be exercised when considering the optimal TSH concentration for patients with DTC to compare the benefits or potential risks, especially in postmenopausal women. Further studies are needed to evaluate the causal relationship between TSH suppression and increased epicardial fat volume.

Abbreviations

DTC	Differentiated thyroid cancer
TSH	Thyroid stimulating hormone
^{18}F-FDG PET/CT	Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography
EAT	Epicardial adipose tissue
FBS	Fasting blood sugar
IQRs	Interquartile ranges

BMI Body mass index

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None.

Authors' contributions
K.K. and YKJ conceptualized the research question, designed the study, performed the statistical data analy-sis, and wrote the article. D.K. interpreted the results. J.K. searched the representative example for the additional figure. K.P, M.K and B.K revised the article for important intellectual content. All authors approved the final version of the article for publication.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and Consent to participate
This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by approved by the Institutional Review Board of the Pusan National University Hospital (No. H-1809–018-071). The requirement for written consent was waived because of the retrospective design.

Consent for publication
Not Applicable.

Competing Interests
The authors declare no competing interests.

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