J Endocrinol Invest
DOI 10.1007/s40618-014-0199-x

ORIGINAL ARTICLE

Evaluation of epicardial fat tissue thickness as a marker of cardiovascular risk in patients with subclinical hypothyroidism

O. C. Santos · N. A. O. Silva · M. Vaisman · M. D. Turano · M. G. Dytz · G. A. Huber · V. B. Braulio · P. F. S. Teixeira

Received: 2 August 2014 / Accepted: 14 October 2014

Abstract
Background Epicardial fat thickness (EFT) has been evaluated as a marker of cardiovascular disease, with good correlation with classical cardiovascular risk factors in the general population. The aim of this study was to evaluate the EFT in subclinical hypothyroidism (SCH), in comparison to a group without thyroid dysfunction.
Methods A cross-sectional study was performed with 100 participants, including 52 SCH patients and 48 individuals without any thyroid dysfunction (euthyroid group-EU). Transthoracic echocardiography (TE), thyroid hormone levels, lipid profile, and assessment of body composition by bioelectrical impedance (BIA) and anthropometry were measured in all subjects.
Results The SCH and EU groups were comparable with respect to age, gender, and Framingham risk scores. Serum thyroid-stimulating hormone (TSH) was 6.7 ± 1.4 mIU/L in the SCH group and 2.0 ± 0.84 mIU/L in the control group. EFT was similar in both groups (SCH 3.5 ± 1.3 mm, EU 3.5 ± 1.1 mm, $p = 0.43$). EFT showed a slight trend for a positive correlation with serum TSH in the SCH group ($r_s = 0.263$, $p = 0.05$). EFT correlated with the body fat percentage in the SCH group ($r_s = 0.350$, $p = 0.03$) and EU group ($r_s = 0.033$, $p = 0.04$). EFT in this cohort was not independently correlated to changes in TSH and Framingham risk score.
Conclusions EFT determination by TE does not seem to be a good marker of cardiovascular risk in SCH patients with serum TSH <10.0 mIU/L and no pre-existing cardiovascular morbidity.

Keywords Subclinical hypothyroidism · Epicardial fat tissue · Transthoracic echocardiogram · Cardiovascular risk

O. C. Santos · N. A. O. Silva · M. Vaisman · M. G. Dytz · G. A. Huber · V. B. Braulio · P. F. S. Teixeira
Medical School, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

O. C. Santos (✉) · M. Vaisman · P. F. S. Teixeira
Endocrinology Service, Clementino Fraga Filho University Hospital, Rua Rodolpho Paulo Rocco 255, Ilha do Fundão, Rio de Janeiro, RJ 21941-913, Brazil
e-mail: o1gacs@yahoo.com.br

M. D. Turano
Cardiology Service, Clementino Fraga Filho University Hospital, Rio de Janeiro, Brazil

V. B. Braulio
Nutrition and Metabolism Service, Clementino Fraga Filho University Hospital, Rio de Janeiro, Brazil

Introduction

Subclinical hypothyroidism (SCH) is defined biochemically when serum thyroid-stimulating hormone (TSH) concentration is elevated and serum thyroid hormone concentration is in the normal range [1].

This condition affects about 10 % of the adult population, with a higher prevalence in older women [2, 3]. Since patients with SHC frequently are oligo or asymptomatic, the clinical relevance of this condition remains controversial. However, SCH has been associated with increased serum total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels [4, 5], as well as with other cardiovascular risk factors, with a consequent increased risk for atherosclerotic disease [6–12]. Atherosclerosis was first related to the presence of SCH in women aged >55 years old and thereafter in different populations [3, 9, 13]. The exact mechanisms enrolled in the development of atherosclerosis in those patients are

Published online: 29 October 2014

still in debate with classical and non-classical cardiovascular risk factors being proposed [14–18]. Increased risk of coronary heart disease (CHD) events and CHD mortality and even by general mortality has been described as a consequence of SCH [9, 13, 19]. This association has been related to serum TSH >7.0 μUI/ml [9], especially in patients <65 years old [20].

Recently, noninvasive imaging methods have been used to assess subclinical atherosclerotic disease. Epicardial fatty tissue (EFT) directly surrounds the coronary arteries [21] and has been positively associated with the severity of coronary artery disease [21]. The thickness of the EFT may be assessed by transthoracic echocardiography (TE) [22, 23], magnetic resonance imaging, or computed tomography [24]. We proposed to evaluate the extent of epicardial fat tissue by TE in patients with SCH compared to individuals with normal thyroid function. Our second aim was to correlate the EFT of SCH patients with cardiovascular risk factors assessed by the Framingham risk score and with body adiposity.

Materials and methods

Study design and the studied population

A cross-sectional study, including SCH patients and healthy volunteers without thyroid dysfunctions, was conducted. Patients (SCH group) and controls [Euthyroid group (EU)] were recruited at the endocrinology outpatient clinic of the University Hospital of the Federal University of Rio de Janeiro (UFRJ), and gave assignment consent to participate in the study, which was approved by ethical local institution. SCH patients were referred to the endocrine clinic by other clinical staff, after explanation and promotion of the specific recruitment with research purpose. For the purpose of this study, SCH was diagnosed by elevated TSH levels (>4 μIU/mL), with free thyroxin (FT4) in the normal range [18, 25, 26]. All SCH patients had spontaneous elevations of serum TSH as a consequence of autoimmune thyroid disease, which was confirmed in a second measurement, 8 weeks apart from the first one. SCH patients with serum TSH >10 μIU/mL were excluded to guarantee a homogeneous group of patients with minimal thyroid dysfunction in which there is still doubt about its impact in different endpoints and consequently doubts about the benefits of levothyroxine replacement [18, 26]. The controls were recruited among patient's relatives and hospital employers with similar characteristics regarding demographic [age, Body Mass Index (BMI), gender, previous Hypertension or Diabetes diagnosis, smoke and sedentary life style] and also social economic aspects, which could influence cardiovascular risk. The inclusion criteria for the control group were demonstration of normal serum TSH and FT4, negative antithyroperoxidase antibodies, (Anti-TPO) and no past history of thyroid disease. None of the participants took any medication for thyroid disease. Patients with liver or renal disease, chronic pancreatitis, primary hyperlipidemia, and pregnancy were excluded from the study.

A specific anamnesis, physical examination, body composition, bloody pressure, and EFT measurements were performed in all participants, as well as laboratory analysis including thyroid function tests, fasting glucose levels, and lipid profile. Blood pressure was measured using a standard manual mercury sphygmomanometer for at least three measurements.

Body composition

Body composition was assessed using anthropometry and bioelectrical impedance analysis (BIA). Subjects were studied at least 4 h after their last meal, and had emptied their bladders before their body weight and height were recorded. BIA was undertaken with a tetrapolar bioanalyzer device (Model 310, Biodynamics Corp, Seattle, WA, USA). Measurements were undertaken as previously described [27]. Fat-free mass (FFM) and fat mass (FM) were calculated from the measurements of resistance made at 50 kHz, along with height, weight, and age in specific equations published by Segal et al. [28]. BMI was calculated as weight (in kg) divided by squared height (in m). Waist and hip circumferences (in cm) were measured at the midline between the lower rib margin and the iliac crest and as the widest diameter over the greater trochanters, respectively, while the participants were standing with their heels together.

Assessment of thyroid function

Serum TSH, FT4, and Anti-TPO were determined in all participants by a chemiluminescent immunometric assay (Diagnostic Products Corporation, Automatic Instrument Immulite 2000®), with reference values of 0.4–4.0 mIU/L, 0.8–1.9 ng/dL, and <35 UI/mL, respectively. A minimal interval no less than 8 weeks apart was necessary to confirm SCH in the selected patients [25].

Biochemical assays

Plasma glucose, TC, high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) concentrations were measured using enzymatic kits (Dimension®, Dade Behring). The LDL-C level was calculated according to the Friedewald formula: LDL-C = TC − HDL-C − TG/5.

Echocardiographic study

Subjects underwent a complete TE. A single cardiologist, who had expertise in echocardiography and was blinded to the clinical data, obtained all of the TE. The exam was done with subjects in the left lateral decubitus position, using a GE Model G6 transducer (1.7–4.4 MHz frequency) and an Acuson X300 transducer (1–5 MHz frequency). Images were recorded to a computerized database. EFT was measured on the free wall of the right ventricle from the parasternal long-axis views, as previously described and validated [22]. EFT was identified as an echo-free space in the pericardial layers on the two-dimensional echocardiography. Its thickness was measured perpendicularly on the free wall of the right ventricle at end-diastole (QRS complex) for three cardiac cycles. The measurement was performed at a point on the free wall of the right ventricle along the midline of the ultrasound beam, perpendicular to the aortic annulus. The EFT was evaluated as a continuous variable, which was compared between groups or correlated with other continuous variables. Furthermore, it was considered abnormal when $\geq$9.5 mm in males and $\geq$7.5 mm in females according to Iacobellis [29].

Statistical analysis

SPSS 10.0 was used for statistical analysis. A p value <0.05 was considered statistically significant. Continuous variables were expressed as means $\pm$ standard deviations (medians), and categorical variables were expressed as percentages. For continuous variables, the normality of the data distribution was assessed using the Kolmogorov–Smirnov test. Student's t test or the Mann–Whitney U test was selected to compare variables between two groups with a normal or non-normal distribution, respectively. Proportions were compared by a Chi-squared or Fisher's exact test. Correlations between two continuous variables were investigated by Pearson's (r_p) or Spearman's correlation coefficient (r_s). Stratified analysis was used to evaluate the influence of a confounding variable on the results.

Results

Table 1 shows the demographic and clinical characteristics for the SCH and controls. The EFT in the SCH group was not higher than that in the EU group and was within the normal range. There were no significant differences in body composition and CHD risk factors between both groups.

As shown in Table 2, EFT was positively correlated with body adiposity (BF % and FM) in both the groups (SCH and EU groups). A tendency toward a positive correlation between EFT and TSH was observed in SCH group ($p = 0.05$) as demonstrated in Table 2 and Fig. 1.

EFT was positively correlated with age and waist circumference in the group without thyroid dysfunction. Also, we only detected a significant correlation between EFT and the absolute risk of cardiovascular event in 10 years in this control subgroup.

Multivariate linear regression results can be found in Table 3. EFT in this cohort was not independently correlated to changes in TSH and Framingham risk score. However, it was directly associated with body adiposity.

Discussion

To the best of our knowledge, this is the first study to combine body fat measurement to the assessment of EFT in patients with SCH. In addition to serving as a cardiovascular risk marker, the EFT is associated with an increase in the amount of body fat, which may be associated with increased serum TSH, even in the normal range [30, 31]. This positive association between body fat and serum TSH has been described by several authors [30, 31], despite postulations about the cause–consequence effect. Knudsen et al. [31] investigated the association between thyroid function, BMI, and obesity in a cross-sectional study and showed positive correlations between serum TSH and BMI and between weight gain and a progressive increase in TSH.

We did not observe a correlation between EFT and the absolute risk of a cardiovascular event at 10 years in the SCH group. This finding may support the hypothesis that other non-classical cardiovascular risk factors are associated with atherosclerotic development in this specific population. In the last decade, there are a number of studies that have associated SCH with increased cardiovascular disease risk and mortality [8–10, 13, 32]. Despite these evidences, there is no conclusive evidence (e.g., from prospective randomized, double-blind trials) about the potential benefits of levothyroxine replacement in the mild SCH group [33]. Moreover, the pathway(s) responsible for the cardiovascular risk increment in SCH remain unclear; authors disagree as to whether reported classical or non-classical risk factors are more important, as was first suggested in the Framingham study [4–11].

In the EU subgroup, we observed clear correlations between EFT and the absolute risk of a cardiovascular event by 10 years, as described in different studies with nonspecific populations. The EFT has been the subject of many studies of metabolic syndrome, cardiovascular disease, and cardiovascular mortality in general populations and some specific groups. Most of these groups have had classical cardiovascular risk factors, such as diabetes, metabolic syndrome, or obesity, among others [24, 29, 34, 35]. However, the present report is one of the few studies

Table 1 Summary statistics for the studied variables in SCH and EU groups

Variables	SCH group ($n = 52$)				Euthyroid group ($n = 48$)				p
	Mean ± SD	Median	Interquartil range	n (%)	Mean ± SD	Median	Interquartil range	n (%)	
Female, n (%)				49 (94.2)					0.92
Age, (years)	51.0 ± 8.5	52.5	43.2–57.7		48.0 ± 6.9	47.5	43.0–53.0	45 (93.8)	0.05
Body mass index, (kg/m^2)	28.5 ± 5.7	27.5	23.9–32.3		28.8 ± 6.4	28.8	24.8–32.3		0.85
Waist circumference, (cm)	91.7 ± 11.7	91.2	82.6–100.0		93.2 ± 14.2	95.7	84.2–101.0		0.58
Body fat, (%)	37.7 ± 8.1	39.7	34.6–43.4		37.1 ± 9.4	40.1	34.8–42.9		0.72
Fat mass, (kg)	27.5 ± 10.2	27.5	19.2–35;8		28.9 ± 11.7	28.5	19.9–35.5		0.56
Thyroid-stimulating hormone, (mIU/L)	6.7 ± 1.4	6.5	5.6–7.9		1.7 ± 0.9	1.5	0.9–2.1		<0.01
Free thyroxin, ng/(dL)	0.9 ± 1.2	0.9	0.9–1.1		1.0 ± 0.1	1.0	1.0–1.1		0.16
Anti-TPO positive, (%)				23 (44.2)					<0.01
Fasting plasma glucose, (mg/dL)	95.0 ± 13.4	93.0	85.5–99.0		91.1 ± 12.6	90.0	85.0–97.0	0 (0.0)	0.15
Total cholesterol, (mg/dL)	211.2 ± 41.7	204.0	179.5–233.2		205.2 ± 36.0	199.5	176.0–233.2		0.46
HDL cholesterol, (mg/dL)	48.7 ± 14.8	46.0	38.0–57.0		52.5 ± 17.2	54.0	39.0–63.2		0.27
LDL cholesterol, (mg/dL)	130.9 ± 39.5	129.0	105.0–151.0		124.9 ± 32.9	126.0	103.0–152.0		0.44
Triglyceride, (mg/dL)	153.2 ± 115.7	122.0	89.0–171.0		122.1 ± 71.0	98.5	81.5–136.7		0.13
Absolute risk of cardiovascular event in 10 years, (%)	3.1 ± 4.3	2.0	1.0–3.7		2.5 ± 5.0	1.0	0.0–2.0		0.54
Epicardial fat thickness, (mm)	3.5 ± 1.3	3.5	3.0–4.0		3.5 ± 1.2	3.6	3.0–4.0		0.96
Abnormal epicardial fat thickness, n (%)				1 (1.9)					0.34
Hypertension, n (%)				17 (32.7)				0 (0.0)	0.93
Diabetes mellitus, n (%)				3 (5.8)				15 (31.9)	0.90
Low Framingham risk score, n (%)				47 (90.4)				3 (6.4)	0.64
								40 (93.0)	

Table 2 Correlations of EFT with thyroid related hormones, body composition, and CHD risk variables

Correlated variables	SCH group		EU group	
	r	*p*	*r*	*p*
Age, (years)	0.250	0.07	0.322	0.02
Thyroid-stimulating hormone, (mIU/L)	0.263	0.05	0.223	0.16
Free thyroxin, (ng/dL)	0.072	0.61	−0.195	0.25
Waist circumference, (cm)	0.202	0.16	0.323	0.02
Body fat percentage, (%)	0.350	0.03	0.033	0.04
Fat mass, (kg)	0.408	0.01	0.283	0.08
Absolute risk of cardiovascular event in 10 years, (%)	−0.116	0.41	0.311	0.04

EFT epicardial fat thickness, *CHD* coronary heart disease

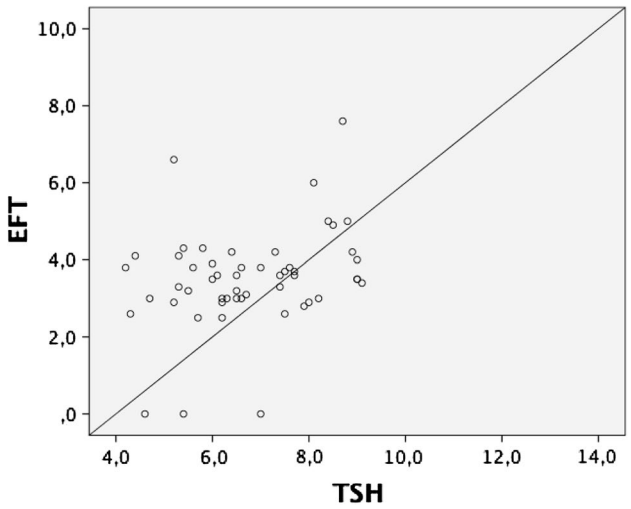

Fig. 1 Scatterplot showing correlation between EFT and TSH

to assess the relationship between EFT and serum TSH elevations.

Two recently published studies reported increased EFT in SCH [36, 37]. Korkmaz et al. [36] studied 61 patients with newly diagnosed SCH and 24 controls matched for age, gender, and BMI without known cardiovascular disease. Patients with SCH (mean serum TSH = 9.3 ± 5.6 mIU/L) showed increased values for EFT (3.6 ± 0.9 mm) compared to the control group (2.8 ± 1.4 mm). SCH patients with serum TSH ≥10 mIU/L had a higher mean EFT (4.1 ± 0.8 vs. 3.5 ± 0.9 mm) compared to those with slightly high serum TSH (<10 mIU/L) although no differences were found between patients with TSH <10.0 mIU/L and the control group. Similar to our study, patients with mild SCH did not show a correlation between EFT and serum TSH levels. However, evaluating the whole group of SCH patients, there was a positive correlation between EFT and TSH ($r = 0.31$, $p = 0.014$). The

Table 3 Multiple linear regressions to assess independent factors associated with EFT results in the study groups

Group	Significant variable	*B*	SE	R^2	*p*
SCH ($n = 52$)	Fat mass	0.048	0.018	0.408	0.01
EU ($n = 48$)	Waist circumference	0.034	0.013	0.433	0.01

Multiple linear regression models with stepwise selection were performed to assess the factors associated with epicardial fat thickness. The variables age, STH, waist circumference, fat mass, body fat %, and risk of cardiovascular event in 10 years were included in the model. Only the significant variables that entered the model are presented in Table (variables with *p* value >0.05 are not reported)

weak correlation between EFT and serum TSH described in our study may be explained by the slight elevations in serum TSH of the SCH group.

Likewise, Asik et al. [37] showed that SCH patients ($n = 33$) had greater EFT than controls. However, this study also included patients with serum TSH >10 mIU/L (mean TSH 9.37 ± 3.91 mIU/L). In addition, there was a positive correlation between EFT and serum TSH levels in the whole group ($r = 0.31$, $p < 0.01$).

In the present study, despite the absence of differences regarding the amounts of EFT between SCH and euthyroid subjects, it demonstrated a trend toward positive correlation between EFT and serum TSH in SCH subjects, suggesting that EFT may increase with serum TSH elevations. This finding did not differ from the previously mentioned studies regarding this correlation [36, 37].

In our study, all SCH participants had serum TSH <10 mIU/L. Those with higher serum TSH levels had been treated with levothyroxine, according to Brazilian Consensus for SCH [33]. This specific characteristic from the included SCH subjects may also justify the absence of higher EFT among SCH patients in comparison to those with normal thyroid status, differing from the previously published data [36, 37]. However, it is important to notice that, in clinical practice, the majority of SCH patients present with minimal serum TSH elevations and questions regarding treated or non-treated SCH are focused on those people with serum TSH <10 mIU/L.

Another distinguishing feature which might have contributed for the negative result comparing SCH and euthyroid subjects, was the predominant inclusion of people with low cardiovascular risk, similar to the study conducted by Korkmaz et al. [36]. We evaluated other classical cardiovascular risk factors, such as high blood pressure and diabetes mellitus, which can act as confounding variables.

Adding new data to that previously reported, we demonstrated that the evaluation of EFT of an SCH group, with only slightly elevated serum TSH levels, in comparison to an EU subgroup with comparable Framingham risk scores,

did not show higher or abnormal values. The anthropometric parameters and body fat percentages of the population were also comparable between the two groups.

In our study, the same cardiologist who was blinded with respect to thyroid status measured the EFT (in mm) in all patients. Currently, there is no cutoff for a "normal" measurement of EFT. In a recent study, the average EFT that was associated with metabolic syndrome and cardiovascular risk was 9.5 mm for men and 7.5 mm for women [29]. As expected, in our group with low cardiovascular risk, we did not detect a higher prevalence of abnormal EFT, as categorized according to Iacobellis [29].

The major limitation of this study was the fact that the study population consisted of patients with low cardiovascular risk group. Another limitation was the fact that the SCH group comprised patients with TSH level <10 mUI/L and none of them had EFT greater than the limit for prediction of metabolic syndrome. Finally, the present results may not be extrapolated for SCH patients with a higher priori cardiovascular risk profile or patients with serum TSH >10 mUI/L.

Conclusions

In untreated SCH patients with serum TSH <10.0 mIU/L and no pre-existing cardiovascular morbidity, the EFT, a marker of the cardiovascular risk, was not different as compared to a healthy control group. Therefore, although the EFT measured by transthoracic echocardiography is related to the body fat, it does not seem to be a good marker of cardiovascular risk in the specific subgroup with serum TSH <10.0 mIU/L.

Conflict of interest Authors disclose no conflicts of interest regarding this manuscript.

References

1. Cooper DS (2001) Clinical practice. Subclinical hypothyroidism. N Engl J Med 345:260–265
2. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC (2000) The Colorado thyroid disease prevalence study. Arch Intern Med 160:526–534
3. Hak AE, Pols HA, Visser TJ, Drexhage HA, Hofman A, Witteman JC (2000) Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study. Ann Intern Med 132:270–278
4. Jung CH, Sung KC, Shin HS, Rhee EJ, Lee WY, Kim BS et al (2003) Thyroid dysfunction and their relation to cardiovascular risk factors such as lipid profile, hsCRP, and waist hip ratio in Korea. Korean J Intern Med 18:146–153
5. Asvold BO, Vatten LJ, Nilsen TI, Bjoro T (2007) The association between TSH within the reference range and serum lipid concentrations in a population-based study. The HUNT Study. Eur J Endocrinol 156:181–186
6. Maratou E, Hadjidakis DJ, Kollias A, Tsegka K, Peppa M, Alevizaki M et al (2009) Studies of insulin resistance in patients with clinical and subclinical hypothyroidism. Eur J Endocrinol 160:785–790
7. Cappola AR, Fried LP, Arnold AM, Danese MD, Kuller LH, Burke GL et al (2006) Thyroid status, cardiovascular risk, and mortality in older adults. JAMA 295:1033–1041
8. Walsh JP, Bremner AP, Bulsara MK, O'Leary P, Leedman PJ, Feddema P et al (2005) Subclinical thyroid dysfunction as a risk factor for cardiovascular disease. Arch Intern Med 165:2467–2472
9. Rodondi N, den Elzen WP, Bauer DC, Cappola AR, Razvi S, Walsh JP et al (2010) Subclinical hypothyroidism and the risk of coronary heart disease and mortality. JAMA 304:1365–1374
10. Rodondi N, Newman AB, Vittinghoff E, de Rekeneire N, Satterfield S, Harris TB et al (2005) Subclinical hypothyroidism and the risk of heart failure, other cardiovascular events, and death. Arch Intern Med 165:2460–2466
11. Ferreira MM, Teixeira PF, Mansur VA, Reuters VS, Almeida CP, Vaisman M (2010) Ambulatory blood pressure monitoring in normotensive patients with subclinical hypothyroidism. Arq Bras Cardiol 94:806–812
12. Liu D, Jiang F, Shan Z, Wang B, Wang J, Lai Y et al (2010) A cross-sectional survey of relationship between serum TSH level and blood pressure. J Hum Hypertens 24:134–138
13. Razvi S, Weaver JU, Vanderpump MP, Pearce SH (2010) The incidence of ischemic heart disease and mortality in people with subclinical hypothyroidism: reanalysis of the Whickham survey cohort. J Clin Endocrinol Metab 95:1734–1740
14. Meier C, Staub JJ, Roth CB, Guglielmetti M, Kunz M, Miserez AR et al (2001) TSH-controlled L-thyroxine therapy reduces cholesterol levels and clinical symptoms in subclinical hypothyroidism: a double blind, placebo-controlled trial (basel thyroid study). J Clin Endocrinol Metab 86:4860–4866
15. Danese MD, Ladenson PW, Meinert CL, Powe NR (2000) Clinical review 115: effect of thyroxine therapy on serum lipoproteins in patients with mild thyroid failure: a quantitative review of the literature. J Clin Endocrinol Metab 85:2993–3001
16. Silva N, Santos O, Morais F, Gottlieb I, Hadlich M, Rothstein T et al (2014) Subclinical hypothyroidism represents an additional risk factor for coronary artery calcification, especially in subjects with intermediate and high cardiovascular risk scores. Eur J Endocrinol 171:327–334
17. Momesso DP, Bussade I, Epifanio MA, Schettino CD, Russo LA, Kupfer R (2011) Increased epicardial adipose tissue in type 1 diabetes is associated with central obesity and metabolic syndrome. Diabetes Res Clin Pract 91:47–53
18. Cooper DS, Biondi B (2012) Subclinical thyroid disease. Lancet 379:1142–1154
19. McQuade C, Skugor M, Brennan DM, Hoar B, Stevenson C, Hoogwerf BJ (2011) Hypothyroidism and moderate subclinical hypothyroidism are associated with increased all-cause mortality independent of coronary heart disease risk factors: a PreCIS database study. Thyroid 21:837–843
20. Razvi S, Shakoor A, Vanderpump M, Weaver JU, Pearce SH (2008) The influence of age on the relationship between subclinical hypothyroidism and ischemic heart disease: a metaanalysis. J Clin Endocrinol Metab 93:2998–3007
21. Iacobellis G, Assael F, Ribaudo MC, Zappaterreno A, Alessi G, Di Mario U et al (2003) Epicardial fat from echocardiography: a new method for visceral adipose tissue prediction. Obes Res 11:304–310
22. Iacobellis G, Willens HJ (2009) Echocardiographic epicardial fat: a review of research and clinical applications. J Am Soc Echocardiogr 22:1311–1319 (quiz 1417–1318)

23. Jeong JW, Jeong MH, Yun KH, Oh SK, Park EM, Kim YK et al (2007) Echocardiographic epicardial fat thickness and coronary artery disease. Circ J 71:536–539
24. Ueno K, Anzai T, Jinzaki M, Yamada M, Jo Y, Maekawa Y et al (2009) Increased epicardial fat volume quantified by 64-multidetector computed tomography is associated with coronary atherosclerosis and totally occlusive lesions. Circ J 73:1927–1933
25. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH et al (2004) Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA 291:228–238
26. Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, Mechanick JI et al (2012) Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Endocr Pract 18:988–1028
27. Braulio VB, Furtado VC, Silveira M, Fonseca MH, Oliveira JE (2010) Comparison of body composition methods in overweight and obese Brazilian women. Arq Bras Endocrinol Metabol 54:398–405
28. Segal KR, Van Loan M, Fitzgerald PI, Hodgdon JA, Van Itallie TB (1988) Lean body mass estimation by bioelectrical impedance analysis: a four-site cross-validation study. Am J Clin Nutr 47:7–14
29. Iacobellis G, Willens HJ, Barbaro G, Sharma AM (2008) Threshold values of high-risk echocardiographic epicardial fat thickness. Obesity (Silver Spring) 16:887–892
30. de Moura Souza A, Sichieri R (2011) Association between serum TSH concentration within the normal range and adiposity. Eur J Endocrinol 165:11–15
31. Knudsen N, Laurberg P, Rasmussen LB, Bulow I, Perrild H, Ovesen L et al (2005) Small differences in thyroid function may be important for body mass index and the occurrence of obesity in the population. J Clin Endocrinol Metab 90:4019–4024
32. Imaizumi M, Akahoshi M, Ichimaru S, Nakashima E, Hida A, Soda M et al (2004) Risk for ischemic heart disease and all-cause mortality in subclinical hypothyroidism. J Clin Endocrinol Metab 89:3365–3370
33. Sgarbi JA, Teixeira PF, Maciel LM, Mazeto GM, Vaisman M, Montenegro Junior RM et al (2013) The Brazilian consensus for the clinical approach and treatment of subclinical hypothyroidism in adults: recommendations of the thyroid Department of the Brazilian Society of Endocrinology and Metabolism. Arq Bras Endocrinol Metabol 57:166–183
34. Baker AR, Silva NF, Quinn DW, Harte AL, Pagano D, Bonser RS et al (2006) Human epicardial adipose tissue expresses a pathogenic profile of adipocytokines in patients with cardiovascular disease. Cardiovasc Diabetol 5:1
35. Janik M, Hartlage G, Alexopoulos N, Mirzoyev Z, McLean DS, Arepalli CD et al (2010) Epicardial adipose tissue volume and coronary artery calcium to predict myocardial ischemia on positron emission tomography-computed tomography studies. J Nucl Cardiol 17:841–847
36. Korkmaz L, Sahin S, Akyuz AR, Ziyrek M, Anaforoglu I, Kose M et al (2013) Epicardial adipose tissue increased in patients with newly diagnosed subclinical hypothyroidism. Med Princ Pract 22:42–46
37. Asik M, Sahin S, Ozkul F, Anaforoglu I, Ayhan S, Karagol S et al (2013) Evaluation of epicardial fat tissue thickness in patients with Hashimoto thyroiditis. Clin Endocrinol (Oxf) 79:571–576