

Thickening of the epicardial adipose tissue can be alleviated by thyroid hormone replacement therapy in patients with subclinical hypothyroidism

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Abstract

Background: Subclinical hypothyroidism (SCH) is a common disorder which has adverse cardiovascular effects. Epicardial adipose tissue (EAT), a novel marker of cardiovascular risk, is increased in SCH.

Aim: We aimed to investigate whether L-thyroxine treatment can reverse the thickening of EAT in SCH.

Methods: Forty-four patients with SCH and 42 euthyroid control subjects were included. EAT thickness was measured using transthoracic echocardiography at baseline and after restoration of the euthyroid status with 3 months of L-thyroxine treatment.

Results: At baseline, mean EAT thickness was significantly greater in the SCH group when compared to the control group (6.3 ± 1.7 mm vs. 4.1 ± 0.9 mm, respectively, $p < 0.001$). There was a significant positive correlation between baseline serum thyroid stimulating hormone (TSH) level and EAT thickness in the SCH group. There was a significant reduction in mean EAT thickness in response to L-thyroxine treatment (6.3 ± 1.7 mm vs. 5.1 ± 1.4 mm, $p < 0.001$). The decrease in EAT thickness after L-thyroxine treatment when compared to baseline (Δ EAT) significantly correlated to the difference in TSH levels before and after treatment (Δ TSH; $r = 0.323$; $p = 0.032$).

Conclusions: Epicardial adipose tissue thickness is increased in patients with SCH. This thickening was alleviated with restoration of the euthyroid status with L-thyroxine treatment in our study population of predominantly male, relatively old subjects with greater baseline EAT thickness.

Key words: subclinical hypothyroidism, epicardial adipose tissue, L-thyroxine

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INTRODUCTION

Subclinical hypothyroidism (SCH) is defined as normal serum levels of free thyroxine (fT4) and increased serum levels of thyroid stimulating hormone (TSH) [1]. The prevalence of SCH has been reported to be between 3% and 18% in adults [1]. The prevalence increases with age and is higher in women [1]. The necessity of thyroid hormone replacement therapy (THRT) in patients with SCH is controversial [2]. SCH is an insidious disease in that it is generally asymptomatic, yet it is associated with deleterious effects on the cardiovascular system. Among these, arterial stiffness and cardiac diastolic dysfunction [3], endothelial dysfunction [4], increased carotid intima–media thickness [5], coronary

artery disease (CAD), and CAD related death [6] are the most prominent. Mechanisms linking SCH to cardiovascular disease include dyslipidaemia and oxidative stress [5, 7].

Epicardial adipose tissue (EAT), a specialised visceral adipose tissue, produces numerous proinflammatory and proatherogenic mediators that promote initiation and progression of coronary atherosclerosis [7]. Increased EAT is related to the presence and angiographic severity of CAD [8] and coronary plaque vulnerability [9], and independently predicts major adverse cardiovascular events (MACE) [10].

The reports concerning EAT thickness in patients with SCH are somewhat conflicting: while EAT thickness was pre-

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viously reported to be increased in patients with SCH when compared to euthyroid controls [11–13], a recent study did not find any such difference, and EAT thickness was not associated with cardiovascular risk in SCH patients [14].

To the best of our knowledge, there is only one published study that demonstrated reduction in EAT thickness in response to restoration of the euthyroid status with THRT in patients with SCH [15].

In this study, we aimed to test and verify the hypotheses that: (1) EAT thickness is increased in patients with SCH, when compared to healthy euthyroid controls; (2) the thickening of the EAT may be alleviated by restoring the euthyroid status with THRT in patients with SCH.

METHODS

Study population

In this study, 55 consecutive patients diagnosed with SCH, who were referred from the Endocrinology Department to the Cardiology Department, were screened. The study was performed in a single tertiary centre. All of the patients underwent transthoracic echocardiography as part of a clinical cardiovascular evaluation in order to rule out possible cardiac involvement of SCH. Eleven patients were excluded due to the presence of the following exclusion criteria: use of statins or any other lipid lowering drug ($n = 5$), pericardial effusion ($n = 2$), severe valvular pathology ($n = 2$), and poor echocardiographic imaging quality ($n = 2$). The remaining 44 patients constituted the patient group. The diagnostic criteria of SCH were the following: serum TSH level $> 5 \mu\text{IU/mL}$ with normal fT_4 and free triiodothyronine (fT_3), no medication effecting thyroid status (amiodarone, lithium, recombinant human TSH injections), and no disorder without hypothyroidism. ETA guidelines recommend repeating the thyroid function tests at least three months apart to make a firm diagnosis [16]. Eligible subjects ($n = 44$) entered a three-month run-in period, during which they did not receive L-thyroxine treatment or any other medications effecting thyroid status. At the end of the run-in period thyroid function tests (TFTs) were rechecked along with anti-TPO and anti-TG antibodies. The most common cause of SCH was considered to be chronic autoimmune thyroiditis (Hashimoto's thyroiditis) associated with anti-TPO antibodies in our patient group ($n = 40$, 90%). Another cause was considered to be subacute thyroiditis ($n = 4$, 10%). Forty-two age- and sex-matched healthy euthyroid subjects constituted the control group.

This study was conducted in accordance with the recommendations of the Declaration of Helsinki on Biomedical Research involving human subjects. The study protocol was approved by the institutional ethics committee. Written informed consent was obtained from each participant.

Baseline characteristics

Baseline characteristics including age, sex, past medical history, and concomitant medications were recorded. An-



Figure 1. Measurement of epicardial adipose tissue (EAT) thickness; PAT — pericardial adipose tissue; Ao — aorta; LA — left atrium; LV — left ventricle; RV — right ventricle

thropometric measurements included height in metres [m], body weight in kilograms [kg], and waist circumference (WC) in centimetres. WC was measured at the midpoint of the distance from the lowest rib to the iliac crest. Body mass index (BMI) was calculated as body weight [kg] divided by height [m] squared.

Laboratory assessment

Fasting blood samples were obtained before baseline echocardiography. Complete blood count (Cell-Dyn 3700, Abbott Diagnostics, USA), serum biochemistry, and lipid parameters (UniCell Dx C 800, Beckman Coulter, USA) were evaluated. Serum fT_3 , fT_4 , and TSH levels were determined using the ELISA method (Architect i2000sr, Abbott Diagnostics, USA). Serum fT_3 , fT_4 , and TSH levels were determined before, during, and after THRT in the SCH group. The normal level of fT_4 was taken to be 0.8–1.8 ng/dL, fT_3 — 1.71–4.0 pg/mL and that of TSH — 0.35–5.0 $\mu\text{IU/mL}$.

Echocardiography

All echocardiographic measurements were performed by the same cardiologist, who was blinded to the patient's biochemical results and clinical information, using a VIVID 7 Pro system (GE, Horten, Norway) with a 2.5–3.5 MHz transducer. Parasternal and apical views were obtained according to the recommendations of the American Society of Echocardiography [17]. EAT thickness was measured from the standard parasternal long axis view on the free wall of the right ventricle perpendicular to the aortic annulus at end-systole [18]. EAT was identified as the echo free space between the outmost border of the myocardium and the visceral layer of the pericardium. The thickest point of EAT was measured in each cycle and the average value of measurements obtained at three cardiac cycles was calculated (Fig. 1). Left ventricular

Table 1. A comparison of demographic and clinical characteristics between the subclinical hypothyroidism (SCH) and the control groups

	SCH group (n = 44)	Control group (n = 42)	P
Age [years]	41.2 ± 15.9	42.1 ± 13.5	0.23
Male	32 (72.7%)	29 (69.1%)	0.17
Body mass index [kg/m ²]	27.1 ± 5.2	26.4 ± 4.9	0.11
Waist circumference [cm]	88.4 ± 14.6	87.1 ± 13.8	0.09
Type 2 diabetes mellitus	5 (11.4%)	5 (12%)	1
Hypertension	14 (32%)	12 (29%)	0.48
Systolic blood pressure [mm Hg]	125.8 ± 16.6	126.2 ± 16.8	0.9
Diastolic blood pressure [mm Hg]	84 ± 4.8	78 ± 13.6	0.128
History of smoking	6 (14%)	10 (24%)	0.32
Total cholesterol [mg/dL]	211.2 ± 37.5	174.6 ± 28.2	0.001
Triglycerides [mg/dL]	165 ± 38.8	96.6 ± 21.4	0.001
HDL cholesterol [mg/dL]	33.2 ± 5.4	47.1 ± 8.6	< 0.001
LDL cholesterol [mg/dL]	116.4 ± 31.4	107.1 ± 18.7	0.189
Left ventricular mass index [g/m ²]	102 ± 24	94 ± 26	0.28
Thyroid stimulating hormone [μIU/mL]	10.8 ± 12.1	2.7 ± 3.0	< 0.001
Free triiodothyronine [pg/mL]	1.2 ± 1.0	2.3 ± 1.3	0.03
Free thyroxine [ng/dL]	1.2 ± 0.4	1.6 ± 0.6	0.04

Data one presented as mean ± standard deviation or number and percentage; HDL — high-density lipoprotein; LDL — low-density lipoprotein

mass index (LVMI [g/m²]) was calculated using the Devereux formula [19]. Intraobserver variability for EAT thickness was computed as 3.9%.

Thyroid hormone replacement therapy

At the end of run-in period TFTs rechecked along with anti-TPO and anti-TG antibodies. Patients with persistent SCH with TSH > 10 μIU/mL and SCH with TSH between 5 and 10 μIU/mL but who had progressive TSH increase, goitre, antithyroid antibodies positivity, and clinical symptoms of hypothyroidism were initiated L-thyroxine treatment (Levotiron 0.1 mg, Abdi Ibrahim, Istanbul, Turkey). The dose was titrated up every 15 days to a level that achieved and maintained a normal TSH level. The mean L-thyroxine dosage was 31.3 ± 14.4 μg. After three months of THRT, thyroid status was reassessed and it was confirmed that the euthyroid status was maintained. Transthoracic echocardiography was also performed again in order to measure the EAT thickness after restoration of the euthyroid status.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation; categorical variables were defined as numbers and percentages. The data were tested for normal distribution using the Kolmogorov-Smirnov test. For continuous variables, mean values were compared with the ANOVA test among different groups. The χ² test was used for the comparison of categorical variables among the groups.

An optimal cut-off value of serum TSH level for the detection of increased (i.e. greater than median value) EAT thickness was determined by receiver operating characteristics (ROC) analysis, and area under curve (AUC) values were calculated. All tests of significance were two-tailed. Statistical significance was defined as p < 0.05. The SPSS statistical software (SPSS 20.0 for Windows, Inc., Chicago, IL, USA) was used for all statistical calculations.

RESULTS

There were no significant differences between the SCH group and the control group with respect to sex, age, and anthropometric measurements including WC and BMI. As expected, mean serum TSH level was higher and fT3 and fT4 levels were lower in the SCH group. Mean serum total cholesterol and triglyceride levels were higher and HDL cholesterol level was lower in the SCH group. Baseline characteristics are presented in Table 1.

At baseline, mean EAT thickness was significantly greater in the SCH group when compared to the control group (6.3 ± 1.7 mm vs. 4.1 ± 0.9 mm, respectively (p < 0.001; Fig. 2). Age, BMI, WC, and serum TSH level were significant correlates of baseline EAT thickness in the SCH group (Table 2). There was a significant positive correlation between baseline serum TSH levels and EAT thickness in the SCH group (Fig. 3). EAT thickness was positively correlated with LVMI (r = 0.356, p = 0.18). However, we found no correlation between EAT thickness with ejection fraction (r = 0.005, p = 0.974) and diastolic dysfunction (p = 0.197).

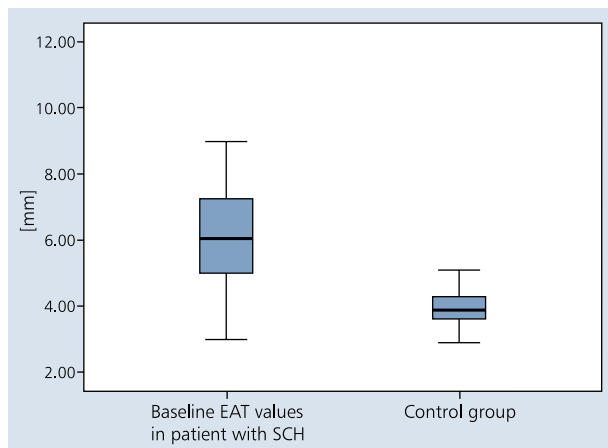


Figure 2. Baseline epicardial adipose tissue (EAT) thickness was significantly greater in the subclinical hypothyroidism (SCH) group when compared to the euthyroid controls.

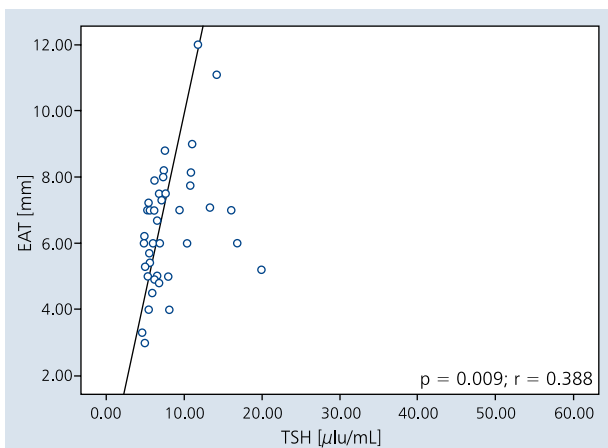


Figure 3. There was a significant positive correlation between baseline thyroid stimulating hormone (TSH) levels and epicardial adipose tissue (EAT) thickness in the subclinical hypothyroidism group

Age ($p < 0.01$, $r = 0.511$), BMI ($p = 0.001$, $r = 0.472$), and WC ($p < 0.01$, $r = 0.511$) were correlated positively with baseline EAT thickness in the control group. However, TSH level ($p = 0.09$, $r = 0.382$) was not correlated with baseline EAT thickness in the control group (Table 3).

L-thyroxine was administered in cases of SCH for three months and differences in serum TSH, fT4, and fT3 levels following treatment were assessed. A decrease was observed in serum TSH levels and this was statistically significant ($p = 0.04$) compared with pre-treated values. After levothyroxine treatment all serum TSH, fT4, and fT3 levels were within the reference values in the SCH group.

Table 2. The correlates of baseline epicardial adipose tissue thickness in the subclinical hypothyroid group

	r	p
Age	0.381	0.011
BMI [kg/m ²]	0.620	< 0.001
WC [cm]	0.552	< 0.001
bTSH [μIU/mL]	0.388	0.009
bfT3 [pg/mL]	-0.146	0.343
bfT4 [ng/dL]	-0.188	0.222

BMI — body mass index; WC — waist circumference; bTSH — baseline thyroid stimulating hormone; bfT3 — baseline free triiodothyronine; fT4 — baseline free thyroxine

Table 3. The correlates of baseline epicardial adipose tissue thickness in the control group

	r	p
Age	0.540	< 0.001
BMI [kg/m ²]	0.472	0.001
WC [cm]	0.511	< 0.001
bTSH [μIU/mL]	0.382	0.09

BMI — body mass index; WC — waist circumference; bTSH — baseline thyroid stimulating hormone

Table 4. Comparison of baseline and post treatment epicardial adipose tissue (EAT) thickness and thyroid hormone profiles

	Baseline	Post treatment
Thyroid stimulating hormone [μIU/mL]	6.6 (5.5–9.0)	2.2 (1.9–4.3)
Free triiodothyronine [pg/mL]	0.8 (0.3–2.1)	1.8 (1.1–3.0)
Free thyroxine [ng/dL]	1.5 (0.9–1.2)	1.7 (1.0–2.1)
EAT thickness [median (25 th –75 th)] [mm]	6.1 (6.1–7.3)	5.0 (3.5–6.9)

There was a significant reduction in mean EAT thickness in response to restoration of the euthyroid status with L-thyroxine treatment according to the Wilcoxon signed ranks test (6.3 ± 1.7 mm vs. 5.1 ± 1.4 mm, $p < 0.001$). Baseline and post-treatment serum TSH, fT3, fT4 levels, and EAT thickness in the SCH group are given in Table 4. Following three months of L-thyroxine an increase of EAT thickness was observed in one (2.3%) patient. In five (11.4%) patients EAT thickness did not change.

The decrease in EAT thickness after L-thyroxine treatment as compared to baseline (Δ EAT) displayed a significant and positive correlation with the difference in serum

TSH level before and after treatment (Δ TSH; $r = 0.323$, $p = 0.032$).

Despite the significant reduction achieved with L-thyroxine treatment, post-treatment EAT thickness in the SCH group remained significantly higher than that of the euthyroid control group (5.1 ± 1.4 mm vs. 4.1 ± 0.9 mm, $p < 0.001$).

The median value for EAT thickness was 6.0 mm in the SCH group. ROC analysis revealed the optimal cut-off value for serum TSH level to predict an EAT thickness greater than 6.0 mm as $6.51 \mu\text{IU/mL}$. A serum TSH level above this cut-off value predicts a greater than median EAT thickness with a sensitivity of 68% and a specificity of 64% (AUC: 0.670, 0.508–0.833, $p = 0.043$).

There was a significant decrease in BMI from pre-treatment mean levels of 27.1 ± 4.8 kg/m² to 26.8 ± 4.6 kg/m² ($p = 0.01$). There was a mild increase in ejection fraction from mean pre-treatment levels of $64.9 \pm 2.1\%$ to $65 \pm 1.9\%$. However, it was not statistically significant ($p = 0.573$). LVMI did not change statistically significantly ($p = 0.163$).

DISCUSSION

Subclinical hypothyroidism is a relatively common condition affecting 3% to 18% of the adult population. SCH is frequently a laboratory diagnosis since the majority of patients are asymptomatic, and the condition is often diagnosed incidentally. Nevertheless, it has been previously reported that SCH is related to various cardiovascular conditions, including cardiac diastolic dysfunction [3], endothelial dysfunction [4], increased carotid intima-media thickness [5], CAD, and CAD related death [6].

Epicardial adipose tissue thickness has gained widespread acceptance as a non-invasive surrogate of atherosclerotic cardiovascular disease. Increased EAT is independently related to the presence and angiographic severity of CAD [8], as well as MACE [10]. Inflammatory infiltrations have been found in EAT in the areas near coronary lesions. Perivascular adipose tissue (PVAT) was previously evaluated in some studies. PVAT thickness surrounding the left anterior descending artery positively correlated to vessel stenosis [20]. The proinflammatory potential of PVAT has been previously stated [21]. Mazurek et al. [22] hypothesised that a higher level of local inflammatory burden in PVAT may lead to necrotic core formation and may result in plaque destabilisation. Kiriş et al. [23] found that EAT thickness and LVMI were significantly higher in patients with ventricular premature beat (VPB) than in controls. VPBs can lead to some adverse cardiovascular effects [24]. EAT thickness may be a new mechanism to explain the pathogenesis of VPBs.

The findings of our study demonstrated that echocardiographic EAT thickness is increased in patients with SCH when compared to healthy euthyroid subjects. This observation is in line with the majority of previous studies of EAT thickness in SCH [10–13]. These data suggest that increased EAT thickness in SCH is not just an observational coincidence, but mostly re-

lated the effects of thyroid hormones on the heart and adipose tissue [11–13]. An important discriminating aspect of our study is that the baseline EAT thickness is numerically greater than those observed in the previous studies. We speculate that our relatively older, predominantly male patient population may be an explanation for this discrepancy. Relatively advanced age may have brought about longer duration of SCH, and thus may have allowed more time for the thickening effect on the EAT to occur. Nevertheless, this is merely a speculation and this issue needs to be elucidated with further studies of EAT in SCH.

We demonstrated a significant positive correlation between baseline EAT thickness and baseline serum TSH levels, suggesting a direct causal relationship between SCH and EAT thickening. In particular, a serum TSH level greater than the cut-off value of $6.51 \mu\text{IU/mL}$ seems to predict a relatively thick (i.e. above the median thickness) EAT. This cut-off value is in line with the literature, as the risk of cardiovascular events is not increased in SCH subjects with a TSH level below $7.0 \mu\text{IU/mL}$ [6], a level that is quite close to the cut-off value that we have found. Considering that EAT is a marker and/or mediator of cardiovascular risk, it seems logical that the cut-off value for TSH that predicts a relatively thicker EAT is close to the one that predicts increased cardiovascular risk in SCH.

We also demonstrated that thickening of the EAT can be alleviated by restoration of the euthyroid status with THRT. We aimed to eliminate a possible confounding effect by excluding patients on statins or any other lipid-lowering treatment because statin treatment has been reported to induce regression of the EAT, regardless of the low-density lipoprotein-cholesterol lowering effect [25]. The reduction in EAT thickness (Δ EAT) achieved with THRT correlated significantly with the decrease in serum TSH levels (Δ TSH). We interpret this observation as further proof supporting our hypothesis that SCH per se causes thickening of the EAT and thus restoration of the euthyroid status has a direct effect in reversal of EAT thickening.

In line with our findings, a recent study showed that L-thyroxine treatment can decrease EAT thickness in patients with SCH: In their study, Yazıcı et al. [15] demonstrated that EAT thickness is greater in patients with SCH when compared to euthyroid controls. Restoration of the euthyroid status with L-thyroxine treatment resulted in a significant reduction in EAT thickness in their patient group.

Our findings confirm those of Yazıcı et al. [15]; however, there are some important differences with respect to the patient populations. While the vast majority of the patient population of Yazıcı et al. [15] were female (42 female patients and one male patient), our patient population were predominantly male (12 female patients and 32 male patients). Moreover, our patient population tended to be older when compared to that of Yazıcı et al. [15] (mean age 41.2 ± 15.9 years vs. 35.2 ± 10.7 years, respectively). Baseline EAT thickness

in our patient group was almost twice as great compared to that of Yazıcı et al. [15] (6.3 ± 1.7 mm vs. 3.2 ± 0.7 mm, respectively). Thus, we have demonstrated that restoration of the euthyroid status with THRT reduces EAT thickness in older, predominantly male SCH patients with greater baseline EAT thickness, as well.

Despite the significant reduction achieved with THRT, EAT thickness remained significantly higher in the SCH group when compared to that of the euthyroid controls. This observation may be attributed to the greater baseline EAT thickness of our study population. It may also be speculated that a longer follow-up period might have allowed complete normalisation of EAT thickness in SCH patients in response to THRT.

Limitations of the study

The most important limitation of this study is the relatively small sample size. The studied group consisted predominantly of men. The absence of a placebo group and lack of randomisation may have impact on the validity of our results due to possible investigator bias in analysing the results. Measurement of EAT thickness was performed by echocardiography. Although assessment of EAT volume by computed tomography is a more precise method, measurement of EAT thickness by transthoracic echocardiography is less costly and is a widely accepted method in the literature. However, computed tomography is not applicable for routine clinical use because of radiation. In addition, the short follow-up period is considered another limitation of the study.

CONCLUSIONS

Epicardial adipose tissue thickness, a novel surrogate of cardiovascular risk, is increased in patients with SCH. We have demonstrated that restoration of the euthyroid status with THRT decreases EAT thickness in SCH, and in addition to previous reports, this benefit seems to extend to older, predominantly male subjects with greater baseline EAT thickness. According to our findings, all SCH patients can be treated with THRT to reduce MACE. We propose that our findings warrant further research with longer follow-up, particularly in order to elucidate whether this reduction in EAT thickness with THRT translates into cardiovascular risk reduction in patients with SCH.

Conflict of interest: none declared

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Wpływ suplementacji hormonów tarczycy na ograniczenie przyrostu nasierdziowej tkanki tłuszczowej u chorych z subkliniczną niedoczynnością tarczycy

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Streszczenie

Wstęp: Subkliniczna niedoczynność tarczycy (SCH) jest częstym zaburzeniem niekorzystnie wpływającym na układ sercowo-naczyniowy. U chorych z SCH stwierdza się zwiększenie grubości nasierdziowej tkanki tłuszczowej (EAT) — nowego wskaźnika ryzyka sercowo-naczyniowego.

Cel: Badanie przeprowadzono w celu ustalenia, czy leczenie L-tyroksyną może zmniejszyć grubość EAT u tych chorych.

Metody: Do badania włączono 44 chorych z SCH i 42 osoby z eutyreozą, które stanowiły grupę kontrolną. Na początku badania i po przywróceniu eutyreozy w wyniku 3-miesięcznego leczenia L-tyroksyną zmierzono grubość EAT metodą echokardiografii przezprzełykowej.

Wyniki: Na początku badania średnia grubość EAT była istotnie większa w grupie SCH niż w grupie kontrolnej (odpowiednio $6,3 \pm 1,7$ mm vs. $4,1 \pm 0,9$ mm; $p < 0,001$). W grupie SCH stwierdzono istotną dodatnią korelację między początkowym stężeniem TSH w surowicy a grubością EAT. Po leczeniu L-tyroksyną nastąpiła istotna redukcja średniej grubości EAT ($6,3 \pm 1,7$ mm vs. $5,1 \pm 1,4$ mm; $p < 0,001$). Zmniejszenie grubości EAT po leczeniu L-tyroksyną w stosunku do wartości początkowych (Δ EAT) korelowało istotnie z różnicą stężeń TSH przed terapią i po jej zakończeniu (Δ TSH; $r = 0,323$; $p = 0,032$).

Wnioski: U chorych z SCH grubość EAT jest zwiększona. W populacji niniejszego badania, złożonej głównie z mężczyzn w starszym wieku z większą początkową grubością EAT, zmniejszono ilość nasierdziowej tkanki tłuszczowej dzięki przywróceniu eutyreozy poprzez leczenie L-tyroksyną.

Słowa kluczowe: subkliniczna niedoczynność tarczycy, nasierdziowa tkanka tłuszczowa, tyroksyna

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