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Evaluation of Epicardial Adipose Tissue Thickness and Proinflammatory Cytokines in Subclinical Hypothyroidism: A Case Control Study

Subklinik Hipotiroidide Epikardiyal Yağ Doku Kalınlığı ve Proinflamatuar Sitokinlerin Değerlendirilmesi: Bir Vaka Kontrol Çalışması

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ABSTRACT Objective: Epicardial adipose tissue (EAT) is an adipose tissue located between the myocardial surface and the visceral layer of the pericardium. Epicardial adipose tissue thickness (EATT) is a sign of atherosclerosis. It has been reported that EATT is increased in patients with subclinical hypothyroidism (SCH). It is suggested that EAT may cause coronary atherosclerosis through paracrine and vasocrine pathways mediated by adipokines / cytokines. In this study, it was aimed to evaluate the relationship of EATT in SCH with proinflammatory cytokines (interleukin-6 (IL-6), highly sensitive C-reactive protein (hsCRP), monocyte chemo attractant protein-1 (MCP-1) and tumor necrosis factor-alpha (TNF-alpha)). **Material and Methods:** A total of 32 cases of SCH and 27 healthy volunteers were prospectively included in the study. EATT were measured by echocardiography. IL-6, hsCRP, MCP-1 and TNF-alpha were measured through simultaneously taken serum samples. **Results:** EATT was significantly higher in SCH compared to the control group (p=0.05). Groups were similar in terms of age, BMI, total-cholesterol, LDL-cholesterol levels; but only HDL-cholesterol was found to be significantly higher in SCH group (p=0.034). There was no significant difference between the SCH and the control group in terms of IL-6, hsCRP, MCP-1 and TNF-alpha. **Conclusion:** EATT was found to be increased in SCH. But, serum levels of proinflammatory cytokines were similar between groups. In the SCH group, there was no relationship between EATT and proinflammatory cytokines. Although EATT is an indicator of atherosclerosis, it may have different control mechanisms in SCH in terms of proinflammatory bioactive molecule synthesis and secretion.

Keywords: Subclinical hypothyroidism; epicardial adipose tissue; monocyte chemo attractant protein-1; tumor necrosis factor-alpha

ÖZET Amaç: Epikardiyal yağ dokusu (EYD), miyokardiyal yüzey ileperikardın visseral tabakası arasında yer alan bir yağ dokusudur. Epikardiyal yağ doku kalınlığı (EYDK) aterosklerozun belirteçlerinden biridir. Subklinik hipotiroidili (SKH) hastalarda, EYDK'nin arttığı bildirilmektedir. EYD'nin adipokin/ sitokin aracılı parakrin ve vazokrin yolaklar ile koroner ateroskleroza neden olabileceği öne sürülmektedir. Ancak SKH'de proinflamatuar sitokinler ile EYDK'nin ilişkisi net değildir. Bu çalışmada, SKH'de EYDK'nin proinflamatuar sitokinler [interlökin (IL-6), yüksek hassasiyetli C-reaktif protein (high sensitivity C-reactive protein "hs-CRP"), monosit kemoatraktan protein-1 (monocyte chemo attractant protein-1 "MCP-1") ve tümö rnekrozis faktör-alfa (TNF-α)] ile ilişkisinin değerlendirilmesi amaçlandı. **Gereç ve Yöntemler:** SKH tanılı 32 olgu ve 27 sağlıklı gönüllü prospektif olarak çalışmaya dâhil edildi. Olguların EYDK'lari ekokardiyografiile ölçüldü. Eş zamanlı alınan serum örneklerinde IL-6, hs- CRP, MCP-1 ve TNF-α düzeyleri ölçüldü. **Bulgular:** SKH'li olgularda, EYDK kontrol grubuna göre anlamlı yüksekti (p=0,05). Gruplar yaş, beden kitle indeksi, total kolesterol, düşük yoğunluklu lipoprotein kolesterol düzeyleri açısından benzerdi; ancak yüksek yoğunluklu lipoprotein kolesterol SKH grubunda anlamlı olarak yüksek bulundu (p=0,034). Hasta grubu ve kontrol grubu arasında IL-6, hs-CRP, MCP-1 ve TNF-α açısından anlamlı farklılık saptanmadı. **Sonuç:** SKH olgularında, EYDK artmış olarak saptandı. Karşıt olarak serum proinflamatuar sitokinlerin düzeyleri kontrol grubundan farklı değildi. Proinflamatuar sitokinlerle EYDK arasında anlamlı ilişki bulunamadı. EYDK, aterosklerozun bir göstergesi olmasına rağmen proinflamatuar biyoaktif molekül sentezi ve salgılanması açısından SKH durumunda farklı kontrol mekanizmalarına sahip olabilir.

Anahtar Kelimeler: Subklinik hipotiroidi; epikardiyal adipoz doku; monosit kemoatraktan protein-1; tümör nekrozis faktör-alfa

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In subclinical hypothyroidism (SCH), which is one of the thyroid dysfunctions, serum levels of triiodothyronine (fT3) and free thyroxine (fT4) levels are normal, while serum thyroid-stimulating hormone (TSH) level is high.[1] There are studies showing that the risk of mortality due to cardiovascular events increases in patients with SCH.[2,3] It has also been reported that factors causing cardiac and endothelial dysfunction may increase the risk of cardiovascular disease (CVD) in SCH.[4] It is not known whether or not proinflammatory cytokines (interleukins, transforming growth factors, chemokins etc.), which are widely accepted in the etiopathogenesis of atherosclerosis, affect the susceptibility to atherosclerosis in patients with SCH.

Adipose tissue is an endocrine organ that plays a role in metabolic and inflammatory processes and can secrete polypeptidic cytokines and hormone-like molecules.[5] Epicardial adipose tissue (EAT) is an adipose tissue located between myocardial and visceral pericardium. Adipokines are from the family of hormones and cytokines secreted by adipose tissue both with pro-inflammatory and anti-inflammatory effects. Although EAT is important for the protective regulation of vascular functions and energy needed in healthy conditions, the increase in EAT thickness (EATT) transforms it into a lipolytic, prothrombotic and proinflammatory structure.[6] It is stated that EAT may result in coronary atherosclerosis through paracrine and vasocrine pathways mediated by adipokines and cytokines.[7,8]

It has been reported that there is an increase in EATT in patients with SCH, which may cause a greater risk of CVD.[9,10] However, the relationship between increased EATT and inflammation in SCH is not clearly known. It is hypothesized that evaluating EATT increase along with inflammatory markers will yield more accurate results.[11] The aim of current study was to explore the relationship of EATT with serum inflammatory markers in SCH.

MATERIAL AND METHODS

STUDY GROUP

Patients diagnosed with SCH and healthy volunteers in our internal medicine outpatient clinics between October 2010-February 2011 were included in the prospective cohort study. Exclusion criteria were determined as following: 1) Patients with CVD, diabetes mellitus, chronic renal failure or psychiatric disease, 2) Being pregnant, 3) Using drugs that may affect thyroid hormone levels, 4) Smoking. The Gazi University Medical Faculty Institutional Review Committee was approved this study (decision number: 169, date: September 29, 2010). The informed consent forms were signed by the all participants. The study was planned in accordance with the Declaration of Helsinki.

Diagnosis of SCH

Cases with TSH levels above 5 mIU/mL, and free T3 (2.3-4.2 pg/mL) and free T4 (0.89-1.76 ng/dL) levels in the normal range were accepted as SCH.

Eat Measurement

EATT was measured with the Vivid 7 Dimension (GE Ultrasound, Horten, Norway) device using 2-D and M-mode techniques. EATT simultaneous with both ventricular collapse from the right ventricular free wall was measured using parasternal long-axis images. Cases that could not be measured due to poor echogenicity were not included in the study.

High-Sensitivity C-Reactive Protein, Interleukin-6, Tumor Necrosis Factor-Alpha and Monocyte Chemo Attractant Protein-1 Measurement

High-sensitivity C-reactive protein (hs-CRP) levels were determined by the nephelometric method (BN prospec®, DadeBehring Marburg, Germany). The serums were studied promptly after blood collection.

Interleukin-6 (IL-6) was studied in stored serum samples by the immunoenzymetric method (DIAsource IL-6 EASIA kit, KAP1261, DIAsource ImmunoAssays S.A, Belgium). All samples and calibrators were added to microplates coated with monoclonal antibodies bound to IL-6 epitopes. After one hour of incubation and washing at room temperature, the anti-IL-6-HRP conjugate was added. Afterwards chromogenic solution was added and incubated for 15 min away from sunlight. Finally, after adding the stop solution, the resulting product was measured colorimetrically at wavelengths of 450 nm and 490 nm.

Tumor necrosis factor-alpha (TNF-α) was studied in stored serum samples by the immunoenzymetric method (DIAsource TNF-α EASIA kit, KAP1751, DIAsource ImmunoAssays S.A, Belgium). All samples and calibrators were added to microplates coated with monoclonal antibodies bound to TNF-α epitopes. After two hours of incubation and washing at room temperature, anti-TNF-α-HRP conjugate and chromogenic solution were added respectively and incubated for 30 min protected from sunlight. Finally, after adding the stop solution, the resulting product was measured colorimetrically at wavelengths of 450 nm and 490 nm.

Monocyte chemo attractant protein-1 (MCP-1) was studied in stored serum samples by ELISA method (BioVendor, Human MCP-1 ELISA, RBMS281R, Biovendor Laboratorni Medicina, Czech Republic). All samples and calibrators were added to microplates coated with anti-human MCP-1. After two hours of incubation and washing at room temperature, HRP conjugate was added and incubated for another 2 hours at room temperature. After washing, chromogenic solution was added and incubated for 30 min protected from sunlight. When the mixture turned dark blue, the enzyme reaction was terminated by addition of the stop solution. The absorbance of each microplate was measured with spectrophotometry at a wavelength of 450 nm.

STATISTICAL ANALYSIS

All results were presented as mean±standard deviation or median (minimum-maximum). Mann-Whitney U test was used to compare the categorical variables between groups. Spearman correlation test was used to analyze the correlation between variables. p value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 21.0 (SPSS, Chicago, IL).

RESULTS

A total of 32 patients with SCH (Group 1) and 27 healthy volunteers (Group 2) were included. The Group 1 and 2 consisted of 28 women (87.5%) and 4 (12.5%) men; 22 women (81.5%) and 5 men (18.5%), respectively. As expected, TSH level was significantly higher in the Group 1 (p<0.01). fT3 and fT4 levels were similar across the groups (p>0.01). Age, body mass index, total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels were similar between the groups, while high-density lipoprotein cholesterol (HDL-C) was significantly higher in SCH patients (p=0.034) (Table 1).

EATT was increased in the SCH group (p<0.001). hs-CRP, IL-6, TNF-α and MCP-1 levels were not different between the groups (p=0.067 p=0.891, p=0.095, p=0.196, respectively). EATT and inflammatory marker levels are shown in Table 2. When SCH and the control group were evaluated separately, no correlation was found between EAT and TSH, total cholesterol, LDL-C, HDL-C, MCP-1, TNF-α, IL-6 and hs-CRP levels (p>0.05).

DISCUSSION

In this study, EATT was found to be increased in patients with SCH compared to healthy volunteers. It was observed that the proinflammatory cytokines involved in the etiopathogenesis of atherosclerosis did

TABLE 1: Comparison of some demographic and laboratory values of the cases.

	SCH (n=32)	Control (n=27)	p value
Age (years)	37.12±11.2	35.7±10.2	0.642
BMI (kg/m^2)	25.2±4.4	26.5±5.3	0.267
LDL-C (mg/dL)	107±33.7	105.1±34.3	0.988
HDL-C (mg/dL)	50.03±13.4	43.4±11.9	0.034
Total cholesterol (mg/dL)	185.1±42.6	172.7±36.6	0.312
TSH (mIU/mL)	7.6±3.2	1.74±0.9	<0.001

SCH: Subclinical hypothyroidism; BMI: Body mass index; LDL: Low-density lipoprotein cholesterol; HDL: High-density lipoprotein cholesterol; TSH: Thyroid-stimulating hormone.

TABLE 2: Comparison of the hs-CRP, IL-6, TNF-α, MCP-1 levels and EATT.

	SCH (n=32)	Control (n=27)	p value
hs-CRP (mg/L)	0.20±0.25	0.31±0.37	0.637
IL-6 (pg/mL)	10.05±8.69	9.72±5.78	0.891
TNF-α (pg/mL)	7.63±3.2	6.14±2.54	0.095
MCP-1 (pg/mL)	165.06±138.8	132.2±69.2	0.196
EATT (mm)	5.34±0.63	4.16±0.61	<0.001

hs-CRP: High-sensitivity C-reactive protein; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-alpha; MCP-1: Monocyte chemo attractant protein-1; EATT: Epicardial adipose tissue thickness.

not differ between the groups and there was no statistically significant relationship between increased EATT and proinflammatory cytokines.

In the literature, there are studies indicating that SCH causes a risk of increased CVD. However, the underlying pathophysiological mechanism has not been fully clarified. The suggested mechanisms are increase in lipid levels, increase in arterial stiffness, and deterioration in endothelium-dependent vasodilation.[12-14] In a meta-analysis evaluating non-invasive cardiovascular risk markers in patients with SCH, it was reported that endothelial dysfunction, arterial wall thickening and hardening are significantly associated with SCH.[15] In another meta-analysis including 7 prospective studies, an increased risk of CVD was reported especially in cases with TSH>10 mIU/mL. It was also indicated that the increase in risk is independent of age, gender and the presence of autoantibodies.[16,17] In a study evaluating the effect of SCH on clinical outcomes after percutaneous coronary intervention (PCI), it was reported that SCH adversely affected the clinical course after PCI.[18] It could not be clearly demonstrated that normalizing TSH with levothyroxine replacement leads to CVD risk reduction.[19,20] The effect of SCH on serum lipid levels has not been clarified. While lipid levels were found to be high in some studies, either no change or low lipid levels were found in others. Contradictory results may be caused by the differences in factors such as age, gender, duration and degree of SCH, smoking and insulin resistance. In the current study total cholesterol and LDL levels were not different in entire the groups, while HDL levels were significantly higher in the SCH group (p=0.016).[21-23] The fact that the duration of the disease and the presence of insulin resistance were not known may have caused these results.

Rather than being a simple fat storage site, EAT is classified as an endocrine organ. Besides adipocytes, it also contains inflammatory, vascular, stromal and immune cells. Under physiological conditions, it provides energy for the myocardium, takes part in thermogenesis and mechanically protects the coronary artery. EAT is a metabolically-active organ and is the source of many pro-inflammatory, proatherogenic, anti-inflammatory, thermogenic molecules, cytokines and adipokines.[24] In EAT secretagogues under pathological stress, hypertrophy develops, triglyceride storage decreases, lipolysis and inflammation increase. EAT, which is very important in the formation of atherosclerotic plaque, causes vasocrine or paracrine release of IL-6, IL-1b, MCP-1 and TNF-α. There are cross-sectional studies showing that increased EAT is associated with atherosclerosis.[25,26] Eiras et al. conducted a study on of 22 patients who had undergone some type of cardiac surgery, 11 of which had coronary heart disease and 11 of which did not. In it, they evaluated adipocyte volume, IL-10, MCP-1 and TNF-α levels in heart biopsy samples taken from the right ventricle, and serum IL-10, MCP-1 and TNF-α levels. Serum and EAT, MCP-1, IL-10, TNF-α levels were not different between groups. A positive correlation was found between plasma MCP-1 levels and EAT adipocyte volume. However, there was a negative correlation between EAT adipocyte volume and adipocyte MCP-1. A positive correlation was found between subcutaneous adipose tissue and MCP-1, TNF-α and IL-10 levels.[27] Due to the different and complex relationship between stromal cells in EAT, the inflammatory cytokine levels may contrast EAT and subcutaneous adipose tissue. Furthermore, the history of cardiovasculary risk factors in the cases included in the study affects the levels of inflammatory cytokines, and makes it difficult to evaluate the interaction of EAT mass and inflammatory cytokine levels. EATT has been previously shown to increase in SCH.[9,10] However, there are few studies about the relationship of EATT with inflammatory markers in SCH. According to Kokkotou et al. study, consisting of 32 euthyroid patients with chronic autoimmune hypothyroidism and 2 different control groups including 23 healthy volunteers and 43 euthyroid women with cold nodules, it has been shown that MCP-1 is increased in patients with chronic autoimmune thyroiditis.[28] The inclusion of euthyroid patients in the study cannot show the exact relationship between TSH level and MCP-1. In our study, in which SCH cases were included, no statistically significant difference was found between MCP-1 levels between SCH and the control group (p=0.171). The reason for the similarity of

MCP-1 levels may be the inclusion of patients with different characteristics compared to previous studies.

In our study, no direct relationship was found between EATT and other proinflammatory-proatherogenic parameters in SCH. Accordingly, EAT may have different control mechanisms in terms of molecule synthesis and secretion in SCH.

The limitations of our study can be determined as the small number of patients, the unknown duration of SCH, and the inability to evaluate inflammatory markers at the molecular level. Despite these, it is valuable for being a study that sheds light on the relationship between EATT and inflammatory cytokines in SCH, and is a precursor to future studies that will evaluate this relationship more comprehensively.

CONCLUSION

Although EATT was significantly increased in SCH compared to the healthy volunteers, statistically significant relationship could not be found between EATT and inflammatory cytokines. In order to evaluate this relationship clearly, more comprehensive studies are required.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Gözde Tahtacı, Mehmet Ayhan Karakoç;* ***Design:*** *Gözde Tahtacı, Mehmet Ayhan Karakoç;* ***Control/Supervision:*** *Gözde Tahtacı, Mehmet Ayhan Karakoç;* ***Data Collection and/or Processing:*** *Gözde Tahtacı;* ***Analysis and/or Interpretation:*** *Gözde Tahtacı, Mehmet Ayhan Karakoç;* ***Literature Review:*** *Gözde Tahtacı, Mehmet Ayhan Karakoç;* ***Writing the Article:*** *Gözde Tahtacı, Mehmet Ayhan Karakoç;* ***Critical Review:*** *Mehmet Ayhan Karakoç, Gözde Tahtacı;* ***References and Fundings:*** *Gözde Tahtacı, Mehmet Ayhan Karakoç;* ***Materials:*** *Gözde Tahtacı.*

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