Turkish Journal of Diabetes and Obesity / *Türkiye Diyabet ve Obezite Dergisi*
Original Article / Özgün Araştırma

The Relationship with Serum Heart Type Fatty Acid Binding Protein and Subclinical Atherosclerosis in Patients with Hypothyroidism

Gülsüm GÖNÜLALAN[1], Mustafa KULAKSIZOĞLU[2], Erkan TAŞYÜREK[3], Mustafa Sait GÖNEN[4]

[1]KTO Karatay University, Faculty of Medicine, Medicana Konya Hospital, Department of Endocrinology and Metabolic Diseases, Konya, Turkey
[2]Necmettin Erbakan University, Faculty of Medicine, Department of Endocrinology and Metabolic Diseases, Konya, Turkey
[3]Cihanbeyli State Hospital, Department of Biochemistry, Konya, Turkey
[4]İstanbul University, Cerrahpaşa Faculty of Medicine, Department of Endocrinology and Metabolic Diseases, İstanbul, Turkey

Cite this article as: Gönülalan G et al. The relationship with serum heart type fatty acid binding protein and subclinical atherosclerosis in patients with hypothyroidism. Turk J Diab Obes 2021;3: 333-339.

ABSTRACT

Aim: To investigate the variability of Carotid intima-media thickness (CIMT) and the relationship between CIMT and serum Heart-type fatty acid binding protein (H-FABP) levels in patients with overt and subclinical hypothyroidism. We also aimed to evaluate the effect of levothyroxine treatment on these markers.

Material and Methods: 40 patients with overt hypothyroidism (OH), 40 patients with subclinical hypothyroidism (SH) and 30 healthy individuals as control group were evaluated according to serum lipid and thyroid hormone panels, serum H-FABP levels and CIMT measurements. Serum H-FABP levels and CIMT of the patients in group OH were also evaluated following 6-months levothyroxine replacement treatment.

Results: The levels of serum total cholesterol, LDL cholesterol and H-FABP in group OH were significantly higher ($p<0.05$). CIMT in group OH was also significantly higher than other groups ($p<0.05$). There was an insignificant slight positive correlation between serum H-FABP and CIMT. The values of serum H-FABP levels and CIMT measurements after levothyroxine treatment significantly decreased in comparison with pre-treatment period ($p<0.05$).

Conclusion: The increased CIMT and H-FABP levels in overt hypothyroidism might be used as an indicator in determining subclinical atherosclerosis. Levothyroxine treatment might protect the patients with overt hypothyroidism in terms of cardiovascular risk by decreasing CIMT and serum H-FABP levels.

Keywords: *Atherosclerosis, Hypothyroidism, Heart-type fatty acid binding protein, Carotid intima-media thickness*

Hipotiroidizmli Hastalarda Serum Kalp Tipi Yağ Asit Bağlayıcı Protein ve Subklinik Ateroskleroz Arasındaki İlişki

ÖZ

Amaç: Çalışmamızda aşikar hipotiroidisi ve subklinik hipotiroidisi olan hastalarda Karotis intima media kalınlığı (KİMK) ölçümleri ve serum Kalp tipi yağ asidi bağlayıcı protein (K-YABP) düzeylerinin karşılaştırılması amaçlanmıştır. Ayrıca aşikar hipotiroidi hastalarında levotiroksin replasman tedavisinin bu parametreler üzerindeki etkisi araştırılmıştır.

Gereç ve Yöntemler: Çalışmamıza Endokrinoloji ve Metabolizma Hastalıkları Bilim Dalı polikliniğine başvuran 40 aşikar hipotiroidi, 40 subklinik hipotiroidi tanısı almış hastalarla 30 sağlıklı birey karşılaştırıldı. Gruplar demografik bulgular, serum lipid ve tiroid hormon panelleri, serum K-YABP ve KIMK ölçümleri açısından karşılaştırıldı. Ayrıca aşikar hipotiroidi nedeniyle 6 aylık levotiroksin replasman tedavisi alan hastaların tedavi öncesi ve sonrası serum K-YABP ve KIMK ölçümleri karşılaştırıldı.

ORCID: Gülsüm Gönülalan / 0000-0001-5465-944X, Mustafa Kulaksızoğlu / 0000-0001-9908-7449, Erkan Taşyürek / 0000-0003-0244-5655, Mustafa Sait Gönen / 0000-0002-1089-623X

Correspondence Address / Yazışma Adresi:
Gülsüm GÖNÜLALAN
KTO Karatay Üniversitesi, Tıp Fakültesi, Medicana Konya Hastanesi, Endokrinoloji ve Metabolizma Hastalıkları Bilim Dalı, Konya, Turkey,
Phone: +90 (505) 515 19 58 • E-mail: gselcuklu@gmail.com

DOI: 10.25048/tudod.937670

Received / *Geliş tarihi* : 15.05.2021
Revision / *Revizyon tarihi* : 03.12.2021
Accepted / *Kabul tarihi* : 06.12.2021

Bulgular: Aşikar hipotiroidili hastaların serum total kolesterol, LDL kolesterol ve K-YABP düzeyleri diğer gruplara göre anlamlı olarak yüksekti (p<0,05). KIMK ölçümleri de aşikar hipotiroidili hastalarda diğer gruplara göre anlamlı olarak yüksek bulundu (p<0,05). Aşikar hipotiroidi hastalarında serum K-YABP ile KIMK ölçümü arasında hafif düzeyde pozitif korelasyon saptanmasına rağmen istatistiksel olarak anlamlı değildi. Aşikar hipotirodili hastalarda 6 aylık levoritoksin tedavisi sonrası serum K-YABP değerleri ve KIMK ölçümleri tedavi öncesi değerlere göre anlamlı olarak azalmaktaydı (p<0,05).

Sonuç: Bu çalışma aşikar hipotiroidi hastalarında ateroskleroz gelişimine yatkınlık olduğunu ve K-YABP yüksekliğinin subklinik aterosklerozu belirlemede bir belirteç olarak kullanılabileceğini düşündürmektedir. Altı aylık levotiroksin tedavisi aşikar hipotirodi hastalarında K-YABP düzeylerini ve KIMK'nı azaltarak kardiyovasküler risk açısından koruyucu bir tedavi olabilir.

Anahtar Sözcükler: *Ateroskleroz, Hipotiroidizm, Kalp tipi yağ asidi bağlayıcı protein, Karotis intima media kalınlığı*

INTRODUCTION

Hypothyroidism which is a thyroid hormone deficiency is commonly seen in population (1). The symptoms of hypothyroidism include mild symptoms such as tiredness, skin dryness, constipation, cold intolerance, weight gaining, or severe symptoms in which many organs are affected as a result of disease progression (2).

The most common cardiovascular symptoms and findings in overt hypothyroidism are bradycardia, systemic hypertension with low pulse pressure, an increase in mean arterial pressure, a decrease in exercise tolerance, prolonged QT and flattened or inverted T wave (3,4). Deficiency in parasympathetic nervous system and increased frequency of systemic hypertension were reported in subclinical hypothyroidism (5,6). Atherogenic risk factors in patients with overt hypothyroidism are the increased levels of low-density lipoprotein (LDL), C-reactive protein (CRP), hyperhomocysteinemia, plasminogen activator inhitor-1(PAI-1), D-Dimer and hypertension (7,8).

Carotid intima media thickness (CIMT) is used as a non-invasive indicator in the development of atherosclerosis (9). Lorenz et al. reported that myocardial infarction and stroke was frequently seen in patients with increased CIMT (10).

Heart-type fatty acid binding protein (H-FABP) was first detected from damaged myocardium in 1988 and it is widely used as a biochemical indicator for myocardium damage (11). H-FABP is one of the early indicators of myocardium damage (12). It has been reported that H-FABP has a positive correlation with the increased risk of cardiac mortality after acute coronary syndrome (13).

Our purpose in this study is to investigate the variability of CIMT as an indicator of atherosclerosis and the relationship between CIMT and serum H-FABP in patients with overt and subclinical hypothyroidism. These markers might be valuable predictors on cardiovascular morbidity in patients with hypothyroidism.

MATERIALS and METHODS

In our study, three groups of patients who applied to the Endocrinology and Metabolism Diseases department were included. The first group (OH group) consisted of 40 patients who had low serum free T4 and/or free T3 level and high TSH level (>10 mıu/l) and were diagnosed with overt hypothyroidism. The second group (SH group) consisted of 40 patients who had normal serum free T4 and free T3 levels, high TSH level (>4mıu/l) without any symptoms of hypothyroidism were diagnosed as subclinical hypothyroidism. The patients with SH did not treated with levothyroxine due to the absence of hypothyroidism symptoms and thyroid autoantibodies. 30 healthy individuals were included as the control group. Patients with positive thyroid autoantibodies in control group were excluded from the study. The patients with the diagnosis of acute coronary syndrome, hearth failure, stroke, pulmonary embolism, diabetes mellitus, renal failure, immunological disease, coronary artery disease were excluded. Patients who treated with levothyroxine for hypothyroidism were also excluded.

The age and gender of patients were evaluated. Anthropometric measurements included weight, height, waist and hip circumference of patients. Body Mass Index (BMI) was obtained by dividing body weight (kg) by the square of height (m2). Waist circumference was measured at the midpoint between iliac crests and the lowest rib while standing. Hip circumference was measured at the widest part of the hips. We also calculated the waist to hip ratios of all patients. The levels of serum total cholesterol, triglyceride, high-density lipoprotein (HDL), LDL were examined by the commercial kits in accordance with the routine method. The thyroid hormone (TSH, fT3 and fT4) and thyroid autoantibody (Anti-TPO, Anti-Tg) tests of patients in all groups were evaluated by chemiluminescent microparticle immunoassay and chemiluminescent competitive immunoassay methods.

Levothyroxine treatment with an initial dosage of 1.6 μg/kg/day was given to the all patients in OH group. The dosage of levothyroxine was adjusted according to the TSH levels of patients two months later.

In our study, demographic data, symptoms, physical examination findings, waist and hip circumferences, serum total cholesterol, triglyceride, HDL cholesterol, LDL cholesterol, thyroid function tests (TSH, fT3 and fT4), thyroid antibody levels of the patients in OH group, SH group and control groups were compared statistically. Similarly, serum H-FABP levels and ultrasonographic CIMT measurements in all groups were compared statistically. H-FABP levels and CIMT of the patients in OH group were measured and compared at the end of the 6-month levothyroxine treatment.

This study has been investigated and approved by Clinical Research Ethics Committee of our institute.

Measurement of Serum H-FABP Level

The blood samples of all patients were centrifuged and kept at -80^{0}C to measure the serum H-FABP levels in all groups. Serum H-FABP test was processed via Eastbiopharm kit using Sandwich Elisa method in serum samples. The study was conducted via BIO-TEK LX50 model ELISA DeviceTM by using Elisa washer and reader. H-FABP levels in the serum samples were measured using the concentration–absorbance graph according to the standards.

CIMT Measurement

IMT of common carotid artery of all patients were measured in first examination by the same person using LOGIQ P5 B-Mod Ultrasound DeviceTM. Three measurements were performed at the proximal first cm of the bifurcation of both common carotid arteries and the measurements were averaged as CIMT. The patients in OH group were treated with levothyroxine. Their CIMT measurements and serum H-FABP levels were re-evaluated in the control visit at the sixth months of treatment. All patients were euthyroid situation at control visit.

Statistical Analysis

"The Statistical Package for the Social Sciences" (22.0 for Windows, SPSS Inc., Chicago, Illinois, USA) software program was used in comparison of data. One-way ANOVA and chi-square tests were used to compare the data of patients at three groups. Paired-t test was also used to compare the data of the patients in OH group after the treatment. Pearson correlation test was used to examine the correlation between H-FABP and CIMT values of the patients. $p<0.05$ values were accepted statistically significant in comparison of the data.

RESULTS

Demographic and Laboratory Results

Total cholesterol and LDL were found significantly higher in OH groups in comparison with other groups ($p<0.01$). Serum fT4 and fT3 levels were also significantly lower in OH groups ($p<0.01$). Serum TSH level was also signficicantly higher in OH group ($p<0.01$). Age, gender, smoking, body mass index(BMI), systolic and diastolic blood pressure, serum fasting plasma glucose(FPG), triglyceride, and HDL levels were found similar in groups. Demographic and laboratory results and statistical values of the patients are given in Table 1.

Table 1: Demographic and laboratory results of the groups.

	Group 1	Group 2	Group 3	p value
Age (year ±SD)	44.18±11.4	40.48±10.2	40.7±8.7	0.288
Gender (M/F)	30% / 70%	15% / 85%	33 %/ 67%	0.156
Body Mass Index ±SD	28.78±6.5	28.96±4.4	26.91±6.01	0.291
Waist/Hip Ratio	0.878	0.873	0.894	0.822
Systolic Blood Pressure (mm Hg ±SD)	113.54±9.1	117.07±6.4	117.08±7.3	0.180
Diastolic blood pressure (mm Hg ±SD)	74.79±7.1	76.38±5.3	76.88±5.4	0.453
Fasting plasma glucose (mg/dL±SD)	97.36±12.5	95.04±11.3	94.84±9.5	0.674
Total Cholesterol(mg/dL±SD)	204±44.6	175.5±35.6	169.95±32.9	**0.005***
Triglyceride (mg/dL±SD)	135.24±59.6	120.46±54.4	108.54±33.9	0.209
LDL cholesterol (mg/dL±SD)	129.68±36.3	99.57±23.4	93.95±22.6	**<0.001***
HDL cholesterol (mg/dL±SD)	42.4±8.8	45.15±13.7	43.09±7.6	0.627
TSH (μIU/mL±SD)	34.37±6.7	7.15±1.6	1.72±0.6	**<0.001***
fT3 (pg/mL±SD)	2.42±0.6	3.02±0.3	2.96±0.4	**<0.001***
fT4 (ng/dL±SD)	0.45±0.2	0.74±0.1	0.82±0.1	**<0.001***

$p<0.05$ values are statistically significant

When the groups were evaluated in terms of thyroid antibody levels, antiTPO was found to be positive in 26(65%) patients in Group OH, positive in 23(57.5%) patients in Group SH and negative in all patients in control group. These distributions were statistically significant between the groups (p<0.01). Similarly, when groups were evaluated in terms of AntiTg, it was positive in 10(25%) patients in group OH, positive in 13(32.5%) patients in group SH and negative in all patients in control group. This distribution was also statistically significant among the groups (p<0.01).

None of the patients with diabetes mellitus, hypertension and a history of coronary artery diseases were included in the groups. According to terms of smoking, 5 patients (12.5%) in Group OH, 3 patients (7.5%) in Group SH, 2 patients(6.7%) in control groups were tobacco users and this distribution was not statistically significant (p=0.63).

Levels of Serum H-FABP

Serum H-FABP levels of all patients in all three groups and serum H-FABP levels of the patients in Group OH were measured after levothyroxine treatment. The mean levels of serum H-FABP in the groups of group OH, group SH and the control group were found as 5.87±4.5 ng/dl, 3.47±2.5 ng/dl and 2.7±1.8 ng/dl respectively (p<0.01) (Figure 1A). Besides, the mean levels of serum H-FABP at pre-treatment and post-treatment period in group OH were found as 5.87±4.5 and 4.54±3.2 respectively (p<0.01) (Figure 1B).

In the light of the data given in the figures, the mean level of serum H-FABP in Group OH 5,87 ng/dl, and this value was found to be significantly higher in comparison with Group SH and control groups (p<0.01). Although the mean level of serum H-FABP of the patients in Group SH was found to be higher in comparison with the control group, there was no statistical significance (p>0.05).

According to the mean levels of serum H-FABP of the patients in Group OH at pre-treatment and posttreatment period, it was observed that the mean post-treatment serum H-FABP level was lower in these patients and it was statistically significant (p<0.01).

The Correlation between H-FABP and CIMT in Patients with Overt Hypothyroidism

The correlation between serum H-FABP levels and CIMT measurements in the patients with overt hypothyroidism was evaluated with Pearson correlation test. It was indicated that there was a slight positive correlation between H-FABP levels and CIMT (r=0.27). However, this correlation was not statistically significant (p>0.05). It has been found that no correlation has been found between H-FABP levels and CIMT in these patients after the 6-month levothyroxine treatment period.

DISCUSSION

Overt hypothyroidism which is characterized with high fT3 and fT4 levels, is a condition of thyroid hormone deficiency commonly encountered in population (1,14). Apart from overt hypothyroidism, subclinical hypothyroidism which occurs with high TSH and normal fT4 ratios has also been reported (14). The risk of atherosclerosis and ischemic heart disease increases in patients with hypothyroidism (8). CIMT is recently used as a non-invasive indicator in atherosclerosis development and many researchers have reported that increased CIMT is a strong indicator of stroke, myocardial infarction and cardiovascular death risk (9). Many researchers report that H-FABP is one of the indicators of myocardial damage (12). In our study, we aimed to investigate the relationship between H-FABP levels and CIMT and hypothyroidism.

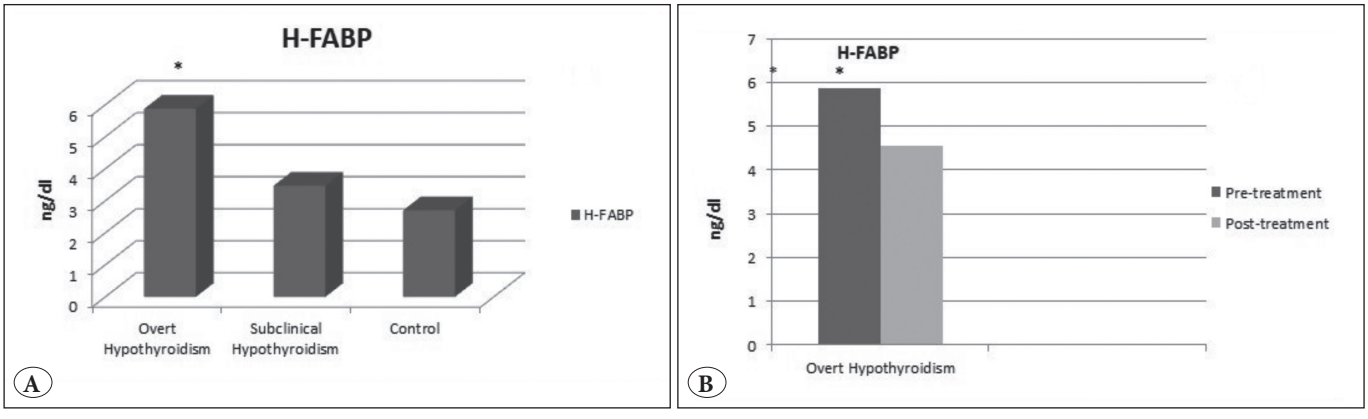

Figure 1: A) The means of serum H-FABP levels of groups. **B)** The means of serum H-FABP levels in OH group pretreatment and postreatment period.
** There was a statistically significance between groups (p<0.05)*

Both overt hypothyroidism and subclinical hypothyroidism is often observed in the females (14). Similar to the literature, the percentage of the females was more than the percentage of the males in all three groups in our study. The mean fasting blood glucose of the patients in groups OH, SH and control were found as 97.36±12.5, 95.04±11.3 and 94.84±9.6 respectively and there were no statistically significance among them. The presence of smoking behaviour was in ranges between 6.7% and 12.5% among the groups and there were no statistically significance. We believe that the reason of low presence of atherosclerotic risk factors can be attributed to our groups including young patients. The absence of these risk factors decreases the atherosclerosis in these patients and makes a chance for higher valuable investigation on the atherosclerotic process in hypothyroidism.

Hypothyroidism causes susceptibility to hypertension that is one of the risk factors of atherosclerosis. It is reported that diastolic hypertension develops in patients who have hypothyroidism after thyroidectomy and hypertension incidence in patients with overt hypothyroidism increases three times (15). Diastolic blood pressure also increases in patients with subclinical hypothyroidism (16). The development of systolic and diastolic hypertension in overt hypothyroidism occurs depending on the increase in peripheral vein resistance and myxoedema of the arterial wall (4,17). Dyslipidaemia is another atherosclerotic risk factor in hypothyroidism. Hypercholesterolemia could be seen in overt hypothyroidism, and hypothyroidism is detected in 4-14% of patients diagnosed with hypercholesterolemia (18). It is reported that there was an increase in serum total cholesterol, LDL and apolipoprotein B levels of patients with overt hypothyroidism (19). However, the increased cholesterol levels depend on the increase in large-LDL and large-HDL levels, which are less atherogenic (20). Staels et al. showed a decreased LDL receptor levels and a prolonged half-life of HDL in rats (21). In addition, serum HDL level decreases in overt hypothyroidism (22). According to blood pressures of the patients in our study, there was no significant difference in systolic and diastolic blood pressures among the groups. The reason of this might be related to the younger age of the patients and including patients who were recently diagnosed with hypothyroidism. On the other hand, the mean total cholesterol and LDL cholesterol values of the patients with overt hypothyroidism were significantly higher. Although HDL cholesterol levels were lower in the OH group, it was not statistically significant. In our study, it is seen that this lipid profile detected in the patients with overt hypothyroidism creates a risk factor for the development of atherosclerosis.

The increasing in CIMT is associated with gender, age, smoking, diabetes, HDL, LDL, triglyceride, hypertension, systolic blood pressure and body mass index (23,24). Several studies reported that CIMT values were higher in diabetes mellitus and impaired glucose metabolism and it might be used to detect potential cardiovascular risk (25,26). Nagasaki et al. detected increased CIMT in patients with hypothyroidism and they determined a decrease in CIMT following one year levothyroxine treatment (27). It is also reported that CIMT increasing during subclinical hypothyroidism did not decrease sufficiently after levothyroxine treatment (28). On the other hand, Kim et al. reported a decreased CIMT in patients with subclinical hypothyroidism who received a 1-year levothyroxine treatment (29). In our study, CIMT in patients with overt hypothyroidism was found significantly higher. Although CIMT in the patients with subclinical hypothyroidism was found to be higher in comparison with the control group, there was no statistical significance. We suppose that increased CIMT in overt hypothyroidism indicates increased atherosclerosis and cardiovascular disease risk. Besides, CIMT following a 6-month levothyroxine treatment in patients with overt hypothyroidism was significantly lower in comparison with pre-treatment CIMT values. This result shows that levothyroxine treatment in patients with overt hypothyroidism is protective for cardiovascular disease and atherosclerosis.

Elevated plasma H-FABP levels show progressive disruption in ventricular function in patients with congestive heart failure and it shows a poor prognosis (30). It has been also reported that H-FABP level in serum might be used as an additional cardiac indicator in diagnosis of acute myocardial infarction (31). Karbek et al. have detected that serum H-FABP levels increase and CIMT is higher in prediabetic patients in comparison with the control group, and there is a positive correlation between them (32). In our study, we found that H-FABP levels in patients with overt hypothyroidism were significantly higher than both patients with subclinical hypothyroidism and the control group. Although serum H-FABP levels in the patients with subclinical hypothyroidism were found to be higher than the control group, there was no statistically significance. Besides, serum H-FABP levels in the patients with overt hypothyroidism reduced significantly following a 6-month treatment in our study. Accordingly, the increased H-FABP levels, especially in patients with overt hypothyroidism, may show that it is an indicator of subclinical atherosclerosis and disruption in fatty acid metabolism. We thought that H-FABP could not explain the whole atherosclerotic process

alone because of the insignificant slightly positive correlation between CIMT and serum H-FABP levels in our study.

There are some limitations in our study. The most significant of them is the limited sampling in our study. Moreover, lower mean age of patients with hypothyroidism and unknown duration of hypothyroidism made the evaluation of lipid profile and atherosclerotic indicators difficult. Another limitation of the study is the absence of lipid profiles of the patients after the 6-month levothyroxine treatment. Therefore, we could not evaluate the correlation between lipid profile and CIMT and serum H-FABP values according to the treatment in patients with overt hypothyroidism.

Overt hypothyroidism has a predisposition for atherosclerosis and impaired lipid profile in comparison with subclinical hypothyroidism and control groups. Increased CIMT and H-FABP might be used as effective predictors for impaired lipid metabolism and subclinical atherosclerosis in patients with overt hypothyroidism. The decreased CIMT and H-FABP levels in post-treatment period showed that the atherosclerosis in patients with overt hypothyroidism might be treated with levothyroxine.

Acknowledgement

None.

Authorship Contributions

Study concept/Design: **Gülsüm Gönülalan, Mustafa Kulaksızoğlu,** Data Collection: **Gülsüm Gönülalan, Erkan Taşyürek**, Data Analysis and Interpretation: **Gülsüm Gönülalan, Mustafa Kulaksızoğlu**, **Erkan Taşyürek,** Post draft: **Güslüm Gönülalan**, **Mustafa Kulaksızoğlu**, Critical review of the content: **Mustafa Kulaksızoğlu, Mustafa Sait Gönen**, Final approval and responsibility: **Gülsüm Gönülalan**, Supervision: **Gülsüm Gönülalan, Mustafa Kulaksızğlu.**

Conflicts of Interest

The authors declare no conflicts of interest.

Financial Disclosure

This study has no sponsoring foundation and institution.

Ethical Approval

This study has been approved by The Clinical Researches Ethical Committee of Necmettin Erbakan University (Number: 2012/43). Declaration of Helsinki was followed in this study design and report.

Peer-Review Process

Extremely peer-reviewed.

REFERENCES

1. Vanderpump MP. The epidemiology of thyroid disease. Br Med Bull 2011;99: 39-51.
2. Zulewski H, Muller B, Exer P, Miserez AR, Staub JJ. Estimation of tissue hypothyroidism by a new clinical score: evaluation of patients with various grades of hypothyroidism and controls. J Clin Endocrinol Metab 1997;82(3): 771-776.
3. McAllister RM, Delp MD, Loughlin MH. Thyroid status and exercise tolerance. Cardiovascular and Metabolic Consideration. Sport Med 1995;20 (3): 189-198.
4. Klein I, Ojamaa K. The cardiovascular system in hypothyroidism. In: Braverman LE, Utiger RD (Eds.) Warner & Ingbar's The Thyroid: A Fundamental and Clinical Text, edit. 8. Philadelphia: Lippincott Williams & Wilkins, 2000, 777-782.
5. Kahaly GJ. Cardiovascular and atherogenic aspects of subclinical hypothyroidism. Thyroid 2000;10 (8): 665-679.
6. Di Bello V, Monzani F, Giorgi D, Bertini A, Caraccio N, Valenti G, Talini E, Paterni M, Ferrannini E, Giusti C. Ultrasonic myocardial textural analysis in subclinical hypothyroidism. J Am Soc Echocardiogr 2000;13 (9): 832-840.
7. Cappola AR, Ladenson PW. Hypothyroidism and atherosclerosis. J Clin Endocrinol Metab 2003;88 (6) : 2438-2444.
8. Ichiki T. Thyroid hormone and atherosclerosis. Vascular Pharmacology 2010;52 (3-4): 151-156.
9. Peters SAE, Grobbee DE, Bots ML. Carotid intima-media thickness: a suitable alternative for cardiovascular risk as outcome? Eur J Cardio Prevention and Rehab 2011;18(2): 167-174.
10. Lorenz MW, Markus HS, Bots ML, Rosval M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. Circulation 2007;115 (4): 459-467.
11. Zschiesche W, Kleine AH, Spitzer E, Veerkamp JH, Glatz JF. Histochemichal localization of heart-type fatty acid binding protein in human and murine tissues. Histochem Cell Biol 1995;103 (2): 147-156.
12. Pelsers MM, Hermens WT, Glatz JF. Fatty acid-binding proteins as plasma markers of tissue injury. Clin Chim Acta 2005;352 (1-2): 15-35.
13. Ishii J, Ozaki Y, Lu J, Kitagawa F, Kuno T, Nakona T, Nakamura Y, Naruse H, Mori Y, Matsui S, Oshima H, Nomura M, Ezaki K, Hishida H. Prognostic value of serum concentration of heart-type fatty acid-binding protein relative to cardiac troponin T on admission in the early hours of acute coronary syndrome. Clin Chem 2005;51(8):1397-1404.
14. Almandoz JP, Gharib H. Hypothyroidism: Etiology, Diagnosis and Management. Med Clin North Am 2012;96(2) : 203-221.
15. Saito I, Saruta T. Hypertension in thyroid disorders. Endocrinol Metab Clin North Am 1994;23(2): 379-386.

16. Nagasaki T, Inaba M, Kumeda Y, Hiura Y, Shirakawa K, Yamada S, Henmi Y, Ishimura E, Nishizawa Y. Increased pulse wave velocity in subclinical hypothyroidism. J Clin Endocrinol Metab 2006;91(1): 154-158.
17. Dernellis J, Panaretou M. Effects of thyroid replacement therapy on arterial blood pressure in patients with hypertension and hypothyroidism. Am Heart J 2002;143(4): 718-724.
18. Morris MS, Bostom AG, Jacques PF, Selhub J, Rosenberg IH. Hyperhomocysteinemia and hypercholesterolemia associated with hypothyroidism in the third US National Health and Nutrition Examination Survey. Atherosclerosis 2001;155(1): 195-200.
19. Staub JJ, Althaus BU, Engler H, Ryff AS, Trabucco P, Marquardt K, Burckhardt D, Girard J, Weintraub BD. Spectrum of subclinical and overt hypothyroidism: effect on thyrothropin prolactin and thyroid reserve and metabolic impact on peripheral target tissues. Am J Med 1992;92(6): 631-642.
20. Pearce EN, Wilson PW, Yang Q, Vasan RS, Braverman LE. Thyroid function and lipid subparticle sizes in patients with short-term hypothyroidism and a population-based cohort. J Clin Endocrinol Metab 2008;93(3): 888-894.
21. Staels B, van Tol A, Chan L, Will H, Verhoeven G, Auwerx J. Alterations in thyroid status modulate apolipoprotein, hepatic triglyceride lypase, and low density lipoprotein receptor in rats. Endocrinology 1990;127(3): 1144-1152.
22. Kung AW, Pang RW, Janus ED. Elevated serum lipoprotein(a) in subclinical hypothyroidism. Clin Endocrinol (Oxf) 1995;43(4): 445-449.
23. Chambless LE, Folsom AR, Davis V, Sharrett R, Heiss G, Sorlie P, Szklo M, Howard G, Evans GW. Risk factors for progression of common carotid atherosclerosis: The Atherosclerosis Risk in Communities Study, 1987-1998. Am J Epidemiol 2002;155(1): 38-47.
24. Van der Meer I, Iglesias del SA, Hak AE, Bots ML, Hofman A, Witteman JC. Risk factors for progression of atherosclerosis measured at multiple sites in the arterial tree: the Rotterdam Study. Stroke 2003;34(10): 2374-2379.
25. Escobedo J, Schargrodsky H, Champagne B, Silva H, Boissonnet CP, Vinueza R, Torres M, Hernandez R, Wilson E. Prevalence of metabolic syndrome in Latin America and its association with subclinical carotid atherosclerosis: the CARMELA cross-sectional study. Cardiovasc Diabetol 2009;26(8): 52.
26. Ito H, Komatsu Y, Mifune M,Antoku S, Ishida H, Takeuchi Y, Togane M. The estimated GFR, but not the stage of diabetic nephropathy graded by the urinary albumin excretion, is associated with the carotid intima-media thickness in patients with type 2 diabetes mellitus: a cross-sectional study. Cardiovasc Diabetol 2010;15(9): 18.
27. Nagasaki T, Inaba M, Henmi Y. Decrease in carotid intima-media thickness in hypothyroid patints after normalization of thyroid function. Clin Endocrinol 2003;59(5): 607-612.
28. Monzani F, Caraccio N, Kozàkowà M, Dardano A, Vittone F, Virdis A, Taddei S, Palombo C, Ferrannini E. Effect of levothyroxine replacement on lipid profile and intima-media thickness in subclinical hypothyroidism: A Double-Blind, Placebo-Controlled Study. J Clin Endocrinol Metab 2004;89(5): 2099-2106.
29. Kim SK, Kim SH, Park KS, Park SW, Cho YW. Regression of the increased common carotid artery-intima media thickness in subclinical hypothyroidism after thyroid hormone replacement. Endocr J 2009;56(6): 753-758.
30. Setsuta K, Seino Y, Ogawa T, Arao M, Miyatake Y, Takano T. Use of cytosolic and myofibril markers in detection of ongoing myocardial damage in patients with chronic heart failure. Am J Med 2002;113(9): 717-722.
31. Anvari MS, Karimi M, Shafiee A, Boroumand M, Bozorgi A, Sedaghat R, Jalali A. Complementary Diagnostic Value of Heart Type Fatty Acid-binding Protein in Early Detection of Acute Myocardial Infarction. Crit Pathw Cardiol 2018;17(1): 43-46.
32. Karbek B, Özbek M, Bozkurt NC, Ginis Z, Güngünes A, Ünsal IÖ, Cakal E, Delibası T. Heart-type fatty acid-binding protein (H-FABP): Relationship with arterial intima-media thickness and role as diagnostic marker for atherosclerosis in patients with impaired glucose metabolism. Cardiovasc Diabetol 2011;10: 37.