ORIGINAL RESEARCH / ÖZGÜN ARAŞTIRMA

Lipid profile and levels of homocysteine, leptin, fibrinogen and C-reactive protein in hyperthyroid patients before and after treatment

Hipertiroid hastalarda tedavi öncesi ve sonrası lipid profili ile homosistein, leptin, fibrinojen ve C-reaktif protein düzeyleri

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ABSTRACT

Objectives: The present study was carried out to determine whether thyroid hormones affect lipid profile and levels of erithrocyte sedimentation rate (ESR), serum total homocysteine (t-hcy), leptin, fibrinogen, C-reactive protein (CRP in patients with hyperthyroidism.

Materials and methods: This study was carried out on 23 hyperthroid subjects (3 men / 20 women, mean age 41.8 ± 2.4 years). Serum levels of homocysteine, leptin, fibrinogen, CRP, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and ESR were measured and body mass index (BMI) were calculated before and after treatment of hyperthyroidism.

Results: Pretreatment t-hcy, TC, LDL-C, HDL-C levels and BMI of patients were significantly lower than those of the post-treatment ($p<0.001$, for each variable). However, fibrinogen and ESR decreased after the treatment ($p<0.001$ and $p<0.05$, respectively). There were no differences in leptin and CRP levels between pre- and post-treatment periods. Pre and post treatment TC and LDL-C levels were negatively correlated with free triiodothyronine (fT3) levels ($r=-0.588$, $p<0.01$; $r=-0.534$, $p<0.01$; $r=-0.543$, $p<0.01$ and $r=-0.653$, $p<0.01$, respectively). Pre-treatment HDL-C was inversely correlated with TSH ($r=-0.423$, $p<0.05$). Pre-post- treatment LDL-C was negatively correlated with free thyroxine (fT4) levels ($r=-0.536$, $p<0.001$ and $r=-0.422$, $p<0.05$ respectively). Pre-treatment TC was inversely correlated with fT4 ($r=-0.590$, $p<0.01$).

Conclusion: Hyperthyroidism is associated with high plasma fibrinogen and ESR levels. Elevated plasma fibrinogen and ESR levels may be a possible explanation for the high cardiovascular morbidity among hyperthyroidic subjects. These changes may reflect low-grade inflammation or disturbances in coagulation in hyperthyroidism.

Keywords: Hyperthyroidism, homocysteine, leptin, lipid profile, treatment

ÖZET

Amaç: Bu çalışma hipertiroidizmli hastalarda tiroid hormonlarının lipid profilini, eritrosit sedimentasyon hızını (ESR), serum total homosistein (t-hcy), leptin, fibrinojen ve C-reaktif protein (CRP) düzeylerini etkileyip etkilemediğini tespit etmek için tasarlanmıştır.

Gereç ve yöntem: Bu çalışma yaş ortalaması 41.8±2.4 yıl arasında olan 23 hipertiroid (3 erkek/ 20 kadın) ile gerçekleştirildi. Homosistein, leptin, fibrinojen, CRP, total kolesterol (TK), yüksek dansiteli lipoprotein kolesterol (HDL-K), düşük dansiteli lipoprotein kolestrol (LDL-K)'ün serum düzeyleri ve ESR ölçüldü ve vücut kütle indeksi (BMI) tedaviden önce ve sonra hesaplandı.

Bulgular: Hipertiroid hastalarının tedavi öncesi t-hcy, TC, LDL-Kolesterol, HDL-Kolesterol düzeyleri ve BMI tedavi sonrası düzeylerden daha düşüktü (tüm değişkenler için, $p<0.001$). Bununla birlikte, fibrinojen ve ESR tedaviden sonra azaldı (sırasıyla, $p<0.001$; $p<0.05$). Tedavi öncesi ve sonrası leptin ve CRP seviyeleri arasında fark yoktu ($p>0.05$). Tedavi öncesi ve sonrası TC ve LDL-K serbest triiodotironin (fT3) düzeyleri ile negatif olarak korele idi (sırasıyla, $r=-0.588$, $p<0.01$; $r=-0.534$, $p<0.01$; $r=-0.543$, $p<0.01$ ve $r=-0.653$, $p<0.01$). Tedavi öncesi HDL-K TSH ile tersine uyumluydu ($r=-0.423$, $p<0.05$). Tedavi öncesi ve sonrası LDL-K serbest tiroksin (fT4) düzeyleri ile negatif uyumluydu (sırasıyla, $r=-0.536$, $p<0.001$ ve $r=-0.422$, $p<0.05$). Tedavi öncesi TC seviyeleri ile fT4 arasında tersine bir uyum vardı ($r=-0.590$, $p<0.01$).

Sonuç: Hipertiroid durumu, yüksek plazma fibrinojen ve ESR düzeyleri ile ilişkilidir. Yükselmiş plazma fibrinojen ve ESR düzeyleri bu durumdan etkilenmiş kişiler arasında yüksek kardiovasküler morbidite için açıklanabilen muhtemel bir durum olabilir. Bu değişimler düşük seviye inflamasyonu ya da hipertitoidizmdeki dağılımı yansıtabilir.

Anahtar kelimeler: Hipertiroidi, homosistein, leptin, lipid profii, tedavi

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INTRODUCTION

Hyperthyroidism has profound effects on cardiovascular system, including reduced systemic vascular resistance due to relaxation of vascular smooth muscle cells, enhanced heart rate and cardiac output due to increase in cardiac diastolic relaxation, contractility and heart rate[1]. Hyperthyroidism is characterised by reduced serum TSH levels despite increased free thyroxine (fT4) and free triiodothyronine (fT3) levels.

Altered lipid profile is a well-known manifestation of thyroid dysfunction. Both plasma LDL-C and HDL-C increase in hypothyroidism and decrease in hyperthyroidism[2]. Recently serum homocysteine, C-reactive protein (CRP), fibrinogen, leptin have emerged as new cardiovascular risk factors, but studies on changes of these markers with respect to thyroid function status have produced variable results[3,4,5,6].

Thyroid hormones exert effects on different levels of the hemostatic system, such as modulation of fibrinolytic activity and coagulation proteins[7]. In this context, particularly alteration of fibrinogen levels may play a key role. High fibrinogen is an independent risk factor for atherosclerotic and cardiovascular diseases[8]. Genetic determination and numerous environmental factors influence plasma fibrinogen levels, including inflammatory diseases, gender and cigarette smoking[9,10]. Although, several reports demonstrated an association between thyroid function and plasma fibrinogen levels the direction of this relation is still debatable. High plasma fibrinogen levels were demonstrated in hyperthyroid as well as in hypothyroid states[4,10].

CRP is composed of 187 amino acids and is an acute phase protein synthesized by the stimulation of leukocyte endogenous mediator[11]. Researchers have recently focused on the role of inflammatory reactions as a pathogenetic mechanism for atherosclerosis. Some studies have reported that CRP is increased in patients with atherosclerosis and this is related to prognosis. Furthermore, CRP is related to the development of cardiovascular disease and is an important factor for prognosis along with fibrinogen[12]. Anderson et al[13] reported that the level of serum CRP is increased by more than two fold in patients with coronary artery disease. Despite the fact, no clear mechanism has been established in relationship between CRP and atherosclerosis[14].

Homocysteine is a sulphur-containing amino acid which in humans can only be derived from the metabolism of essential amino acid methionine. Vitamin B12 is an essential cofactor for methionine synthase. Homocysteine is metabolized by one of the two pathways; remethylation and trans-sulphuration[2,15]. Hyperhomocysteinemia is an independent risk factor for atherosclerosis and atherothrombosis[16,17]. Plasma homocysteine levels increase in states of congenital deficiency of enzymes involved in homocysteine metabolic pathway or due to deficiency of substances required for the metabolism of homocysteine such as folic acid, vitamin B12 or vitamin B6. Hyperhomocysteinemia has many detrimental effects in the body: Some of these are its free radical behaviour that leads to endothelial damage and thereafter platelet activation, modification of coagulation factors, procoagulant effects such as thrombosis, oxidative damage in biological membranes and proatherogenic effects through LDL oxidation[18,19].

Leptin, the protein product of the ob gene, is an important circulating signal for the regulation of body weight[20]. Furthermore, it has been found to increase energy expenditure in rodents[21]. Although its plasma levels have some relationship with other hormones such as glucocorticoids and insulin[22,23] its precise role in the endocrine system remains to be determined. Abnormal thyroid function is associated with changes in body weight and energy expenditure, but it remains to be established whether thyroid hormones independently affect plasma leptin in humans. Several studies with diverse methodologies have addressed the field of leptin and thyroid function in humans[24].

Hypothyroid patients gain weight despite a decrease in appetite, whereas hyperthyroid patients lose weight despite an increase in appetite, consistent with the fact that thyroid hormones play a role in energy expenditure. However, it remains controversial whether leptin and the pituitary axis interact with, or whether dysregulation of leptin contributes to energy imbalance in thyroid states. The existing data on the relationship between the thyroid hormones and leptin are conflicting[25].

The aim of this study was to investigate lipid profiles, homocystein, fibrinogen, C-reactive protein, leptin concentrations in hyperthyroid patients before and after treatment.

MATERIALS AND METHODS

This study was carried out on 23 hyperthyroid subjects (3 men / 20 women) (mean age 41.8±2.6 years) who attended the Internal Medicine Clinic of our hospital between 2004-2005. The study protocol was approved by the Local Ethical Committee and all subjects gave informed consent.

The diagnosis of hyperthyroidism was made on the basis of clinical examination, elevated circulating levels of free T4 (fT4) or free T3 (fT3) and suppressed TSH levels The cause of hyperthyroidism were Graves disease in all of the patients.

Fasting blood samples to determine the thyroid function TSH, fT4, fT3, leptin, t-hcy, fibrinogen, CRP, TC, LDL-C and HDL-C were drawn at beginning of the study. Following baseline blood sampling, subjects with hyperthyroidism were treated with anti-thyroid drugs (propylthiouracil). Serum creatinine levels were measured and only the patients with creatinine levels below 1.5 mg/dl were included in the study. Also vitamin B12 and folate deficiency were excluded from the study. None of the patients had any systemic disease other than hyperthyroidism and they were not taking any medication that could affect levels of inflammation markers, homocysteine, leptin or lipid levels. Final blood samples were drawn when the patients eventually became euthyroid. All patients reached euthyroid state after approximately 4 months.

Levels of total cholesterol, LDL-C and HDL-C were measured by means of B.M. Hitachi 742 autoanalyzer, using Boehringer Mannheim diagnostic kits and enzymatic methods. Levels of serum TSH, fT3 and fT4 were measured by electrochemiluminescent method (Roche-Modular analytic E-170). Plasma t-hcy levels were determined by ELISA (Ceres 900 HDI, Bio-tec. Instrument Inc) with Axis-Shiels AS original kits. Serum leptin levels were determined by ELISA (R&Systems, Inc.614 McKinley Place N.E Minneapolis. MN554 13 USA) method. CRP levels were measured nephelometrically (Beckman Image). Fibrinogen levels were measured coagulometrically with Stago-Compact analyzer.

The body mass index (BMI) [wt (kg) / ht (m2)] was calculated using by measured height and weight before and after the therapy.

Statistical Analysis

The data are presented as means ± standard error (S.E). The results were analyzed with regard to statistical significance using Paired t-test and Pearson correlation analysis was used to determine the correlation between the levels of serum thyroid hormones, serum lipid profiles, leptin, t-hcy, ESR and BMI. The level of significance was accepted as $p<0.05$.

RESULTS

Pre-treatment and post-treatment TSH, fT3, fT4, t-hcy, leptin, fibrinogen, CRP, TC, LDL-C and HDL-C, BMI and ESR values in 23 hyperthyroid subjects are shown in Table 1. Post-treatment TSH, t-hcy, TC, LDL-C, HDL-C levels and BMI were higher than pre-treatment levels ($p<0.001$, for each pair comparisons). However fT3, fT4, fibrinogen levels and ESR decreased after the treatment ($p<0.001$, $p<0.001$, $p<0.001$ and $p<0.05$, respectively). No significant differences were found in the levels of CRP and leptin ($p>0.05$).

Table 1. BMI, fibrinogen, serum T.C, LDL-Cholesterol, HDL-Cholesterol, T-Hcy, Leptin, fibrinogen, CRP levels and thyroid hormones of subjects before and after therapy.

Laboratory Characteristics	Pre-therapy (n= 23)	Post-therapy (n= 23)	P
BMI (kg/m^2)	25.1±1.0	27.6±1.1	0.001
TSH (mUL/ml)	0.032±0.016	1.58±0.29	<0.001
fT3 (pg/ml)	12.9±2.1	3.2±0.2	<0.001
fT4 (ng/dl)	3.4±0.4	1.0±0.1	<0.001
T-Hcy (µmol/l)	10.4±0.3	14.50±0.3	<0.001
Leptin (ng/ml)	68.6±23.2	70.1±2.8	n.s
Fibrinogen (mg/dl)	389.4±17.8	311.3±18.0	<0.001
CRP (mg/dl)	0.34±0.53	0.33±0.69	n.s
TC (mg/dl)	161.4±7.3	203.31±10.3	<0.001
LDL-C (mg/dl)	90.8±7.2	119.3±9.0	<0.001
HDL-C (mg/dl)	50.2±2.9	59.4±3.3	0.031
ESR (ml/h)	22.8±4.2	15.2±3.6	0.025

BMI: Body mass index, TSH: Thyroid-stimulating hormone, fT3: free triiodothyronine, fT4: free thyroxine, T-Hcy: Total homocysteine, CRP: C- reactive protein, TC: Total Cholestero, LDL-C: Low density lipoprotein cholesterol, HDL-C: High density lipoprotein cholesterol, ESR: Erythrocyte sedimentation rate, n.s. not significant

Pre-treatment, serum fT3 levels were negatively correlated with TC (r=-0.588, p<0.01), LDL-C (r=- 0.534, p<0.01). We observed negative correlation between pre-treatment serum TSH and HDL-C levels (r=- 0.423, p<0.05). Pre-treatment serum fT4 levels were negatively correlated with T.C (r=- 0.590, p<0.01) and also, post-treatment, serum fT4 levels were negatively correlated with LDL-C (r=- 0.422, p<0.05). Post-treatment, serum fT3 levels were negatively correlated with TC (r=- 0.543, p<0.01), LDL-C (r=- 0.653, p<0.01). TSH, fT3 and fT4 did not correlate with BMI, fibrinogen, Leptin, t-hcy or ESR. (Table 2).

Table 2. The correlation coefficiants between mean BMI, T-Hcy, Leptin, fibrinogen, CRP, ESR, lipid profiles according to thyroid function status before and after therapy.

	Before Therapy (n= 23)			After Therapy (n= 23)		
Laboratory values	TSH (mUL/ml)	fT3 (pg/ml)	fT4 (ng/dl)	TSH (mUL/ml)	fT3 (pg/ml)	fT4 (ng/dl)
BMI (kg/m^2)	0.206	-0.272	-0.301	0.132	-0.376	-0.330
T-Hcy (µmol/l)	0.090	0.182	-0.009	-0.091	0.221	0.260
Leptin(ng/ml)	-0.270	0.200	-0.148	0.221	0.007	-0.128
Fibrinogen(mg/dl)	-0.018	-0.210	-0.263	-0.155	-0.205	-0.016
CRP (mg/dl)	-0.124	-0.124	-0.227	-0.072	-0.082	-0.087
TC (mg/dl)	0.042	-0.588*	-0.590**	0.298	-0.543*	-0.353
LDL-C (mg/dl)	-0.108*	-0.534*	-0.536**	0.306*	-0.653*	-0.422*
HDL-C (mg/dl)	-0.423**	-0.080	0.014	-0.004*	0.243	0.048
ESR (ml/h)	-0.115	-0.148	-0.100	0.124	-0.225	-0.186

Numbers represent r values (correlation coefficient) between the parameters, *p<0.05, ** p< 0.01
BMI: Body mass index, TSH: Thyroid-stimulating hormone, fT3: free triiodothyronine, fT4: free thyroxine, T-Hcy: Total homocysteine, CRP: C- reactive protein, TC: Total Cholestero, LDL-C: Low density lipoprotein cholesterol, HDL-C: High density lipoprotein cholesterol, ESR: Erythrocyte sedimentation rate.

DISCUSSION

There are consistent reports demonstrating that thyroid status is an important determinant of the plasma/serum concentration of homocysteine[5,26], which has been established as an independent risk factor of vascular occlusive disease[27]. In recent years, several studies have been performed in order to investigate plasma homocysteine levels in hypo- and hyperthyroid patients. While in some studies plasma homocysteine levels were reported to be increased in hypothyroidism, there are also studies that report plasma homocysteine levels to be unchanged in hypo or hyperthyroidism[5,28]. Nedrebo et al.[26] reported that plasma homocysteine levels were not significantly different between hyperthyroid patients and euthyroid controls. Dickman et al.[5] reported hyperhomocysteinemia in hypothyroid and hypohomocysteinemia in hyperthyroid patient and explained these findings by decreased folate and creatinine clearance levels in hypothyroid patients and increased creatinine clearence levels in hyperthyroid patients. Demirbas et al.[28] have found decreased homocysteine levels in hyperthyroid patients after achievement of euthyrodism and explained this fact by the increased creatinine clearance levels. In our study, serum homocysteine levels were found to be increased after the treatment of hyperthyroid patients.

CRP is an important risk factor for atherosclerosis and coronary artery disease[29]. Vincenzo et al[30]. proposed that CRP directly stimulates the inflammatory reaction of arteriosclerosis by inducing the expression of adhesion molecule in vascular endothelial cells and further hypothesized that CRP could be a treatment target for arteriosclerosis. Despite the expected differences in serum CRP levels according to the level of thyroid dysfunction, in view

of the close relationship between hypothyroidism and atherosclerosis, studies on this topic are scarce. CRP levels have not been routinely used to diagnose thyroid disease, although many thyroid conditions involve inflammation. For this reason we measured CRP levels in hyperthyroid patients. There was no difference in CRP levels before and after treatment. Our results are in agreement with those Burggoaf[31] and Won-Young[3].

Several papers concerning abnormalities of blood coagulation and fibrinolysis during hyperthyroidism have been published. Increased fibrinogen levels have been reported. However, there is controversy concerning the presence of a hypercoagulable state in hyperthyroidisim[32].

Various mechanisms regarding the interaction of thyroid hormones and blood coagulation may explain our findings. First, enhanced fibrigonen synthesis by activation of liver function may have contributed to the elevated plasma fibrinogen levels[31,33,34]. Secondly, a direct effect of thyroid hormones on plasma protein regulation was assumed[33]. Recent in vitro studies and in vivo rat models demonstrated important role of T3 in the direct up-regulation of coagulation proteins such as fibrinogen[35]. Finally, elevated plasma fibrinogen levels might be due to a chronic inflammatory state induced by inflammatory diseases of the thyroid disorders as well as an increase in inflammatory plasma proteins.

Our results suggest that high plasma fibrinogen levels might be a supplementary factor, contributing to the increased cardiovascular mortality in subjects with decreased serum TSH levels[36] taking into account that fibrinogen is a major risk factor for cardiovascular morbidity and mortality[8,9]. In our study, propylthiourasil treatment lowered fibrinogen levels.

It is well-known that thyroid dysfunctions have profound effects on lipoprotein metabolism[37,38]. The main cause of the differences in total cholesterol concentrations is the alterations of LDL-C levels. In hyperthyroidism, the increase in LDL receptor mRNA leads to an increase in activity and number of LDL receptors[37,39]. This in turn, leads to a decrease in concentrations of LDL-C and TC levels. In hyperthyroid cases a decrease in HDL-C levels are also observed[40]. This decrease suggested to be due to increased hepatic triglyceride lipase activity. Through the effects of thyroid hormones, hepatic lipase, a decrease, in HDL2/ HDL3 is reported. The most prominent alteration in HDL-C is due to the changes in HDL2 subfraction[38]. In our study, we found increased levels TC, LDL-C and HDL-C after the treatment compared to pretreatment levels. These findings are consistent with the literature[41].

Many studies on serum leptin levels during thyroid dysfunction revealed conflicting results. Some studies related to hyperthyroid state before and after treatment have shown similar leptin levels to those of controls[20,42]. However other studies showed that the serum leptin concentration increased during antithyroid drug therapy[43,44]. Some authors found relative hypoleptinemia in hyperthyroid patients[6,43,45]. It has been suggested that this hypoleptinemia might be related to the degree of adiposity than to the levels of thyroid hormones[6]. We have observed leptin levels increased with therapy but not to a statistically significant level[25,46]. In conclusion, adiposity was the major determinant of leptin concentration, but thyroid hormones did not appear to play any relevant role in leptin synthesis and secretion in human.

In conclusion, thyroid hyperfunction is associated with increased plasma fibrinogen and ESR levels which both reflects increased inflammatory activity. However, CRP level which also is a marker of inflammatory is not significantly elevated in untreated hyperthroid patients. Indeed, CRP levels are higher in untreated hyperthyroid patients compared to the post-treatment period. But this significance is not statistically significant. Since a low-grade inflammation is expected in hyperthyroid state it could be better if we studied high sensitive CRP levels. Hyperthyroid state is an independent risk factor for elevated plasma fibrinogen levels and this may be a possible explanation fort he high cardiovascular morbidity among affected subjects. Fibrinogen levels and ESR levels significantly decrease when euthyroid state is achieved. The suggests that thyroid hyperfunction predisposes to a hypercoagulable medium and also by inducing inflammation may contribute to the process of atherosclerotic vascular disease.

It is important to achieve an euthyroid state as soon as possible in hyperthyroid patients. However, normalization of hyperthyroid hormones are frequently associated with the elevation of proatherogenic lipids. Moreover, during this period homo-

cysteine levels may also increase and the patient may gain some weight. Patients should be advised about caloric restriction and exercise while on treatment. Also, we suggest folic acid and vitamin B12 supplementation in order to prevent the elevation of serum homocysteine levels after treatment with antithyroid drugs.

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