Association Between Dyslipidemia, Homocysteine Levels and Subclinical Hypothyroidism

Subklinik Hipotiroidizm, Dislipidemi ve Homosistein Düzeyleri Arasındaki İlişki

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Geliş Tarihi/*Received:* 10.10.2008
Kabul Tarihi/*Accepted:* 26.04.2009

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ABSTRACT Objective: Subclinical hypothyroidism is seen more frequently than overt hypothyroidism, but the etiologies of the two are the same. While a relation to dyslipidemia and cardiovascular disease is apparent for overt hypothyroidism, this relation remains controversial for subclinical hypothyroidism. The purpose of this study was to evaluate lipid profiles and homocysteine levels in patients with subclinical hypothyroidism. **Material and Methods:** A total of 110 participants were enrolled in this study (55 patients diagnosed with subclinical hypothyroidism, 55 healthy controls). For the definition of subclinical hypothyroidism, the lower limit for serum TSH was set at 4.94 mIU/ml. Other measured parameters included serum levels of total cholesterol (TC), triglycerides (TG), high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), very low density lipoprotein-cholesterol (VLDL-C), TSH, free T3 and T4, thyroid autoantibodies and homocysteine. **Results:** Between the group with subclinical hypothyroidism and the control group, statistically significant differences were found in terms of TC, TG, LDL-C, and LDL-C/HDL-C (p= 0.03, 0.02, 0.01, 0.04 respectively). There was positive correlation between serum TSH and tHcy levels (r= 0.34, p= 0.04). However, no significant differences were found between the groups in terms of homocysteine, VLDL-C, HDL-C and TC/HDL-C. In the subclinical hypothyroidism group, no significant correlation was found between serum TSH levels and TC, TG, LDL-C and LDL-C/HDL-C. **Conclusion:** Our study reveals that SCH is not associated with hyperhomocysteinemia whereas it is associated with some atherogenic lipoprotein abnormalities, particularly elevated TC, LDL-C, TG and LDL-C/HDL-C levels. Therefore, patients with SCH should be carefully evaluated with respect to the dyslipidemia.

Key Words: Hypothyroidism, dyslipidemias, homocysteine

ÖZET Amaç: Her ikisinin etiyolojisi benzer olmasına rağmen subklinik hipotiroidi aşikar hipotiroididen daha sık görülmektedir. Dislipidemi ve kardiyovasküler hastalık ilişkisi aşikar hipotiroidide açık iken, subklinik hipotiroidide bu ilişki halen tartışmalıdır. Bu çalışmanın amacı, subklinik hipotiroidili hastalarda lipid profili ve homosistein düzeylerinin değerlendirilmesidir. **Gereç ve Yöntemler:** Çalışmaya toplam 110 katılımcı alındı (55 subklinik hipotiroidi tanısı alan hasta, 55 sağlıklı kontrol grubu). Subklinik hipotiroidizm tanısında serum TSH alt sınırı 4.94 mIU/mL olarak kabul edildi. Ölçülen diğer parametreler serum total kolesterol (TK), trigliserid (TG), yüksek yoğunluklu lipoprotein-kolesterol (HDL-K), düşük yoğunluklu lipoprotein-kolesterol (LDL-K), çok düşük yoğunluklu lipoprotein-kolesterol (VLDL-K), TSH, sT4, sT3, tiroid otoantikorları ve homosistein düzeylerini içermekteydi. **Bulgular:** Subklinik hipotiroidi ve kontrol grubu arasında TK, TG, LDL-K, LDL-K/HDL-K düzeyleri açısından istatistiksel olarak anlamlı farklılık bulundu (p= 0.03, 0.02, 0.01, 0.04 sırasıyla). Serum TSH düzeyi ile homosistein arasında pozitif korelasyon vardı (r= 0.34, p= 0.04). Bununla birlikte homosistein, VLDL-K, HDL-K, TK/HDL-K düzeyleri açısından gruplar arasında anlamlı farklılık bulunmadı. Subklinik hipotiroidi grubunda, serum TSH düzeyi ile TK, TG, LDL-K ve LDL-K/HDL-K düzeyleri arasında anlamlı korelasyon yoktu. **Sonuç:** Çalışmamız subklinik hipotiroidi ile bazı aterojenik lipoprotein anormallikleri, özellikle artmış TK, LDL-K, TG ve LDL-K/HDL-K düzeyleri arasında ilişki varken hiperhomosisteinemi arasında ilişki olmadığını göstermektedir. Bu nedenle subklinik hipotiroidili hastalar dislipidemi açısından dikkatli değerlendirilmelidir.

Anahtar Kelimeler: Hipotiroidizm, dislipidemi, homosistein

Turkiye Klinikleri J Cardiovasc Sci 2009;21(2):178-83

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Subclinical hypothyroidism (SCH) is defined as a condition in which a patient has normal serum levels of free thyroxine (fT4) and free triiodothyronine (fT3) in the presence of high levels of TSH.[1] Most patients are asymptomatic, although a small proportion of patients may experience symptoms. For this reason, SCH is primarily a laboratory-based diagnosis.[1] Although the prevalence of SCH is not known with certainty, it appears to be between 1.3% and 17.4%, and is related to age, gender and iodine intake.[2] With the increasing use of sensitive TSH assays for screening, SCH is becoming more frequently encountered. Although subclinical hypothyroidism is seen more frequently than overt hypothyroidism, the two have similar etiologies. Autoimmune thyroiditis, antithyroid drug therapy, severe iodine deficiency, thyroidectomy and neck irradiation are among the most common causes of SCH.[3]

SCH is associated with increased risk for cardiovascular disease.[4] This increased risk has been attributed to elevated LDL-C.[5] However, some patients with SCH do not have elevated LDL-C.[6] Positive correlation between SCH and high coronary artery disease risk is not shown clearly; however slight changes in lipid metabolism is shown in SCH.[7] Other mechanisms therefore appear to be involved in this increase in cardiovascular risk.

Hyperhomocysteinemia represents an independent risk factor for coronary artery disease.[8] However, the role of homocysteine as a causal risk factor for coronary artery disease remains controversial. For mild to moderate hyperhomocysteinemia a positive relation with atherosclerosis has been found, and in patients with serum homocysteine levels above 15 mmol/L an increase in relative risk by a factor of 1-1.5 has been reported.[9] There are not enough evidences that treatment of hyperhomocysteinemia decreases atherosclerosis. Plasma values of total homocysteine (tHcy) have been linked to several lifestyle factors, physiological factors like age and gender, folic acid and cobalamin status, and renal function.[10-13] In addition to these, hypothyroidism, renal insufficiency, and the use of folate antagonists such as carbamazepine are common causes of hyperhomocysteinemia. In overt hypothyroidism, tHcy values are elevated and they decrease during T4 therapy.[14] Studies of SCH have generally reported that it has no positive relation to hyperhomocysteinemia and that homocysteine levels are unaffected by LT4 therapy, but the lowering of homocysteine levels in patients with SCH who receive LT4 therapy has also been reported.[15] In patients with SCH, if we make clear the relationship between atherosclerosis and lipid parameters which are traditional risk factors and homocyteine which is emerging risk factor, we can give direction to LT4 treatment in SCH. May be we can give LT4 treatment or not according to results of this study. The purpose of this study was to evaluate homocysteine levels in addition to lipid parameters which are accepted as traditional risk factors in arteriosclerosis in patients with SCH.

MATERIAL AND METHODS

STUDY DESIGN AND PARTICIPANTS

The study was designed prospectively. The participants were 55 healthy controls and 55 patients newly diagnosed with SCH at the internal medicine outpatient clinics of Ankara Numune Training and Research Hospital. All participants signed an informed consent form in accordance with the Declaration of Helsinki.

For the study, SCH was defined as a TSH level higher than 4.94 mIU/mL in the presence of normal serum levels of fT3 and fT4. Criteria for exclusion from the study were as follows: cardiovascular risk factors such as hypertension, diabetes mellitus, hyperlipidemia, or coronary artery disease; use of drugs that affect thyroid hormones (such as propylthiouracil, methimazol, glucocorticoids, lithium, amiodarone, propranolol, radioiodine therapy), previous history of hypothyroidism, current hyperthyroidism, history of thyroid surgery, current pregnancy, pituitary or hypothalamic disorders, presence of factors that could affect serum lipids (use of antihyperlipidemia drugs, oral contraceptive use, tobacco use, liver or kidney dysfunction). The control group was composed of 55 healthy volunteers (46 women, 9 men) with an overall mean age of 37.7 ± 12.5 ye-

ars (range 19-66 years). The SCH group was composed of 55 patients (49 women, 6 men) with an overall mean age of 36.9 ± 12.2 years (range 16-65 years). All patients had normal findings on 12-lead electrocardiography.

LABORATORY STUDIES

For all parameters except tHcy, blood samples were drawn between 8:00 and 8:30 a.m. after an overnight fast and were immediately placed in ice until separation, and sera was used promptly. For measurements of tHcy, the patient refrained from eating meat during the previous day. Blood samples were drawn in the morning after an overnight fast, as for the other parameters, and samples were collected in ice-cooled tubes containing EDTA. They were then immediately centrifuged at 5000 G for 10 minutes. Samples of the plasma fraction were kept frozen at –20^{O} until analyzed. Levels of tHcy were measured via high-pressure liquid chromatography. A reference range of 0-15 μmol/L was accepted for homocysteine levels.

Serum TC was measured via the cholesterol oxidase method with Randox kits in an Olympus AU 2700 analyzer (Olympus, Japan). Normal values were defined as 112-200 mg/dL. Serum TG levels were measured via the GPO-PAP method with Randox kits in an Olympus AU 2700 analyzer (Olympus, Japan). Normal values were defined as 50-179 mg/dL. Serum HDL levels were measured after phosphotungstic acid precipitation of sera, via the supernatant cholesterol oxidase method with Randox kits in an Olympus AU 2700 analyzer (Olympus, Japan). Normal values were defined as 28-75 mg/dL. Serum LDL and VLDL levels were calculated with the Friedewald formula.[16] TSH, free T3 and free T4 were measured via chemiluminescence in an Architect analyzer (Abbott, USA). For the kits used, normal values for TSH were defined as 0.35-4.94 μIU/mL, for fT3 as 1.71-3.71 pg/mL, and for fT4 as 0.70-1.48 pg/mL. Antimicrosomal antibody and antithyroglobulin were measured via radioimmunoassay. Normal values for antimicrosomal antibody were defined as 0-34 IU/mL, and for antithyroglobulin as 0-115 IU/mL.

STATISTICAL ANALYSIS

Statistical analyses were performed with SPSS version 10.0 (SPSS Inc., USA). Numerical variables of the two groups (SCH and control) were expressed as mean ± standard deviation and were compared via Student's t-test. Correlation between numerical variables was evaluated in terms of Pearson's correlation coefficient. Proportional variables of the two groups were compared via Pearson's chi-square test and Fisher's exact test. Statistical significance was defined as $p < 0.05$.

RESULTS

Between the group of patients with SCH and the control group, no significant differences were found in terms of age, gender, body mass index and blood pressure. However, antimicrosomal antibody and antithyroglobulin levels were significantly higher among patients with SCH ($p< 0.05$, Table 1).

Between the control group and the patients with SCH, statistically significant differences were found in TC, TG, LDL-C, and LDL-C/HDL-C ($p= 0.03, 0.02, 0.01, 0.04$ respectively) (Table 1). However, no significant differences were found in homocysteine, VLDLC, HDL-C and TC/HDL-C.

In the patients with SCH, no correlation was found between serum TSH level and age, body mass index, TC, TG, LDL-C, VLDL-C, or HDL-C. Similarly, in these patients no correlation was found between serum tHcy level and age, body mass index, TC, TG, LDLC, VLDL-C and HDL-C. There was found positive correlation between serum TSH and tHcy levels ($r=0.34$, $p=0.04$, Table 2).

DISCUSSION

A relation between overt hypothyroidism, dyslipidemia and cardiovascular disease has been known for many years.[17-18] However, whether the same relation holds for subclinical hypothyroidism is still controversial.[19-23] In our study, we found relation between SCH and dyslipidemia. SCH-related mechanisms, including lipid alterations, have not been exactly understood. The cause of these variations may be increased cholesterol synthesis and decreased activity of lipoprotein lipases in hypothyroi-

TABLE 1: Demographic and biochemical characteristics of patients with SCH versus those of healthy controls.

Parameters	Control Group (n= 55) Mean ± SD	Patients With SCH (n= 55) Mean ± SD	P
Age	37.7 ± 12.5	36.9 ± 12.2	0.13
Gender	46F + 9M	49F + 6M	0.08**
BMI (kg/m²)	27.9 ± 4.6	28.1 ± 4.9	0.07
Anti-M (IU/mL)	35.3 ± 77	249.3 ± 261	0.00*
Anti-TG (IU/mL)	63.7 ± 83.6	321.3 ± 605.8	0.09*
VitamınB12 (pg/mL)	194.8 ± 86	184 ± 76.3	0.54
Folic acid (ng/mL)	5.6 ± 1.77	5.39 ± 1.77	0.58
fT3 (pg/mL)	2.51 ± 0.44	2.77 ± 0.52	0.17
fT4 (ng/dL)	0.99 ± 0.13	0.95 ± 0.37	0.55
TSH (mIU/L)	1.5 ± 0.92	9.28 ± 4.30	0.01*
Total cholesterol (mg/dL)	174 ± 31	193 ± 43	0.03*
Triglycerides (mg/dL)	98 ± 49	140 ± 71	0.02*
VLDL-C (mg/dL)	22 ± 16	26 ± 13	0.22
LDL-C (mg/dL)	108 ± 28	125 ± 33	0.01*
HDL-C (mg/dL)	42 ± 7	42 ± 9	0.91
Total cholesterol/HDL-C	4.18 ± 1.04	4.63 ± 1.1	0.06
LDL-C/HDL-C	2.60 ± 0.89	2.99 ± 0.84	0.04*
tHcy (µmol/L)	11.6 ± 2.9	11.2 ± 2.7	0.06

* Statistically significant, Data are means ± SD.
By two-group Student's t test for means, **Chi-square test
BMI: Body mass index, Anti-M: Antimicrosomal antibody, Anti-TG: Antithyroglobulin antibody, fT3: Free triiodothyronine, fT4: Free thyroxine, TSH: Thyroid-stimulating hormone, VLDL-C: Very-low-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, tHcy: Total homocysteine.

TABLE 2: Spearman correlation analysis of TSH and homocysteine in patients with subclinical hypothyroidism.

	Relation to TSH		Relation to homocysteine	
	*r	p	*r	p
TSH (mIU/L)	-	-	0.32	0.04
tHcy (µmol/L)	0.32	0.04	-	-

* r represents the coefficient of correlation, p the level of significance. TSH: Thyroid-stimulating hormone, tHcy: Total homocysteine.

dism.[24] In addition, decreased cholesterol excretion, reduced number of LDL receptors on the liver cell surface and plasma are the possible mechanisms leading to dyslipidemia in hypothyroidism.[25]

Our results are consistent with the findings from several prior studies.[4,26,27] Some of these studies have reported increased levels of LDL and TG, while others mention only an increase in LDL levels.[27] In the Colorado study, a large series of 25862 participants, even minimal reductions in thyroid function were associated with increases in TC and LDL levels, and these increases were paralleled by increases in TSH.[5] Conversely, lipid profiles in patients with SCH have been reported to improve significantly when thyroid hormone therapy is initiated.[28]

A few studies have reported the lack of an association between SCH and abnormal lipid profiles.[20] Other studies have found SCH and cardiovascular problems to be unrelated.[29] Treatment of SCH with thyroxine has been found to normalize TSH levels without significantly affecting serum TG and cholesterol.[30] Vierhapper et al, did not find any relationship between serum concentration of TSH ranging from 4.0 to 49 mU/L and concentrations of LDL cholesterol.[6] One other study found no association between these.[29] Lindeman et al, proposed that in their group of elderly patients, subclinical hypothyroidism was not associated with coronary heart disease.[31]

It is already known that overt hypothyroidism gives rise to a slight hyperhomocysteinemia. However, the effects of subclinical hypothyroidism on the levels of homocysteine are not known. If an elevation in serum tHcy concentrations with associated atherosclerotic cardiovascular disease could be demonstrated in patients with SCH, this would be a reason to identify and treat this disorder with thyroid replacement therapy.

In our study, we did not find significant differences in tHcy levels between subclinic hypothyroid patients and control subjects whereas we established a positive correlation between serum TSH and tHcy levels.

Very few studies have reported a significant relation between SCH and tHcy.[26] Confirming our results, most investigators have indicated that total homocysteine levels do not change in patients with SCH.[15,31,34] Deicher et al, determined plasma total homocysteine levels in patients with SCH before and after 4 months of thyroid hormone replacement therapy.[15] They reported that there was no change in total homocysteine levels in patients with SCH. Lindeman et al measured serum homo-

cysteine concentration in elderly patients (mean age 74.1 years) with SCH.[31] When the participants with elevated TSH levels were compared to those with normal values, no differences or even trends could be appreciated in serum tHcy concentrations after adjusting for differences in age, gender, ethnicity, folate, vitamin B12, and creatinine concentrations. However, the authors indicated that since the age of their study population was 65 years and older, these finding might not be applicable to younger individuals with SCH. Luboshitzky et al, comparing 57 women with SCH to 34 healthy controls, reported a nonsignificant increase in the prevalence of hyperhomocysteinemia (tHcy 10.98 *m*mol/L).[35] Thus, based on this data, tHcy does not determine the onset of L-T4 replacement in mild thyroid failure.

In conclusion, our study shows that SCH is not associated with hyperhomocysteinemia wheras it is associated with some atherogenic lipoprotein abnormalities, particularly elevated TC, LDL-C, TG and LDL-C/HDL-C levels. Therefore, patients with SCH should be carefully evaluated with respect to dyslipidemia.

Prospective studies of large populations are needed to clarify the relationship between subclinical hypothyroidism, dyslipidemia and emerging cardiovascular risk factors including serum total homocysteine concentrations.

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