Subclinical Hypothyroidism is not Associated with Hyperhomocysteinyemia

Subklinik Hipotiroidi Hiperhomosisteinemi ile İlişkili Değildir

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Abstract

Objective: There are controversial reports regarding subclinical hypothyroidism and its association with hyperhomocysteinyemia. We aimed to evaluate whether subclinical hypothyroidism is associated with hyperhomocysteinyemia and sought to explain the observed increased risk of coronary artery disease in patients with subclinical hypothyroidism.

Materials and Methods: Seventy patients (56 women, 14 men; mean age, 57.0±12.4 years) with subclinical hypothyroidism and 124 euthyroid control subjects (98 women, 26 men; mean age, 55.7±13.7 years) were enrolled in this study. Demographics and laboratory tests were assessed.

Results: There were no significant differences between study patients and controls in weight, height, smoking habits, history of alcohol use, and serum levels of vitamin B12, folic acid, insulin, or C-reactive protein. None of the individuals were taking a drug that could affect serum homocysteine levels. The mean values (±SD) for total homocysteine in the study patients and controls were 11.6±5.7 μmol/L and 12.4±5.2 mmol/L, respectively (P=0.307).

Conclusions: Although the association of overt hypothyroidism with hyperhomocysteinyemia has been well established, we found no association between subclinical hypothyroidism and hyperhomocysteinyemia in this study. We also conclude that the atherogenicity of subclinical hypothyroidism may be mediated by hyperlipidemia rather than by hyperhomocysteinyemia. *Turk Jem 2008; 12: 42-5*

Key words: Subclinical hypothyroidism, hyperhomocysteinyemia

Özet

Amaç: Subklinik hipotiroidi ve hiperhomosistinemi ile ilişkisi ile ilgili çelişkili yayınlar mevcuttur. Bu çalışmada biz subklinik hipotiroide hiperhomositinemi olup olmadığını ve bu hastalarda artmış koroner arter hastalığı riski ile ilişkili olup olmadığını inceledik.

Gereç ve Yöntemler: 77 subklinik hipotiroidisi olan hasta (56 kadın, 14 erkek; ortalama yaş 57.0±12.4 yıl) ve 124 ötiroid kontrol grubu (98 kadın, 26 erkek; ortalama yaş, 55.7±13.7 yıl) çalışmaya alındı.

Bulgular: Hasta ve kontrol grubu arasında kilo, boy, sigara kullanım öyküsü, alkol kullanım öyküsü, serum vitamin B12, folik asid, insulin ve C-reactive protein açısından anlamlı fark saptanmadı. Çalışmaya alınan bireylerden hiçbiri serum homositein seviyesini etkileyecek herhangi bir ilaç kullanmıyordu. Çalışma ve kontrol grubunda ortalama (±SD) homosistein değerleri μmol/L cinsinden sırasıyla 12.4±5.2 ve 11.6±5.7 olarak saptandı (P=0.307).

Sonuç: Belirgin hipotiroidi ve hiperhomosisteinemi arasındaki ilişki iyi tanımlanmamış olsada, bu çalışmada subklinik hipotiroidi ve hiperhomosisteinemi arasında ilişki saptanmadı. Subklinik hipotiroidiye bağlı aterojenitenin hiperhomosisteinemiden çok hiperlipidemiye bağlı olduğunu düşünmekteyiz. *Turk Jem 2008; 12: 42-5*

Anahtar kelimeler: Subklinik hipotiroidi, hiperhomosisteinemi

Introduction

Elevated levels of homocysteine (Hcy) are associated with an increased risk of atherosclerosis (1,2). Hyperhomocysteinyemia is also a risk factor for peripheral vascular disease and stroke (3,4).

Many predicting factors have been found for plasma Hcy concentrations (5). These include plasma levels and intake of pyridoxine (which regulates post-meal or post-methionine plasma Hcy) and of folic acid and vitamin B12 (which regulate fasting Hcy) (5). As a result, low serum folate and vitamin B12 levels are thus strongly associated

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with increased serum Hcy (6). Furthermore, various drugs and hormones also play a role in plasma Hcy levels (7).

Overt hypothyroidism is also an independent risk factor for coronary artery disease. Low-density lipoprotein levels and hypertension, in part, are responsible for this risk factor (8). It is also known that overt hypothyroidism causes slight increases in Hcy levels (9,10).

Subclinical hypothyroidism (SCH) is defined as high levels of thyrotropin (also known as thyroid stimulating hormone [TSH]), and normal levels of free thyroxine (T4) and triiodothyronine (T3) (11). Subclinical hypothyroidism has been found to increase the risk of atherosclerosis and coronary heart disease (12-15). The increased risk of atherosclerosis in SCH has been shown to be associated with hypertension and increased serum cholesterol and triglyceride levels (12,15), but not with serum C-reactive protein, lipoprotein(a) (Lp(a)), apolipoprotein A1 or Hcy levels (16,17).

There are controversial reports regarding SCH and its association with hyperhomocysteinyemia (18-23). Sengul et al. found higher Hcy levels in patients with SCH than in euthyroid individuals (19). However, in population-based and randomized, placebo-controlled studies, Hcy levels were similar in patients with SCH and euthyroid controls (22,23).

Based on these conflicting reports, we aimed to evaluate whether SCH is associated with hyperhomocysteinyemia in patients with SCH compared with patients without SCH. Additionally, we also sought to examine the observed increased risk of coronary artery disease in patients with SCH.

Materials and Methods

Study subjects

Seventy patients (56 women, 14 men; mean age, 57.0±12.4 years) with newly diagnosed SCH and 124 euthyroid control subjects (98 women, 26 men; mean age, 55.7±13.7 years) were enrolled into this study. All patients were followed at Baskent University Endocrinology and Metabolism Clinic in Ankara, Turkey. None of the patients had a history of thyroid surgery or radioiodine therapy. Patients with overt atherosclerosis were excluded from the study. All patients had Hashimoto's disease. Control subjects were euthyroid patients from Baskent University Endocrinology and Metabolism Clinic.

None of the patients were taking a drug that might interfere with Hcy metabolism, and none of the patients had a history of chronic disease, smoking, or chronic alcoholism. The study was approved by the local ethics committee.

Basic relevant demographic and clinical data, including age, sex, weight, body mass index, and associated medical problems were recorded. Blood samples were obtained after a 12-to 14-hour fasting period.

Laboratory studies

Blood samples were obtained from all subjects to test the fasting glucose, fasting plasma total Hcy, vitamin B12, folic acid levels, insulin, CRP (0-10 μg/L), thyrotropin (0.3-5 mIU/L), free T3 (1.8-4.2 pg/mL), free T4 (0.7-1.85 ng/dL), anti-thyroglobulin (0-40 IU/mL), anti-thyroid peroxidase antibody (0-50 IU/mL), total cholesterol, HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), very-low-density lipoprotein-cholesterol (VLDL-C), triglycerides, and Hcy.

Serum glucose was measured by the glucose oxidase technique (Roche Diagnostics GmbH, Mannheim, Germany). Insulin levels were measured by microparticle enzyme immunoassay (Abbott, Weisbaden-Delkenheim, Germany). Total cholesterol, HDL-C, and triglyceride concentrations were measured by enzymatic assay (Boehringer-Mannheim, Mannheim, Germany). LDL-C was calculated with the Friedewald formula (LDL-C = total cholesterol - (HDL-C + triglyceride/5). CRP and was analyzed by the immunoturbidimetric method (Boehringer-Mannheim, Mannheim, Germany). Free T3, free T4, TSH, anti-thyroglobulin, and anti-thyroid peroxidase antibody levels tests were determined by immunometric assays (Diagnostic Products Corporation, Los Angeles, CA, USA). Persistent SCH was confirmed at least once. Plasma Hcy, folic acid, and vitamin B12 levels were measured with a chemiluminescent method using an Immulite 2000 immunoassay analyser (Diagnostic Products Corporation, Los Angeles, Calif, USA). The reference range for the total Hcy assay in our laboratory was 3.9 to 10.8 μmol/L.

For comparing groups, the Student t and Mann-Whitney U tests were used. To study potential determinants of plasma Hcy levels, a nonlinear correlation analysis with different factors was used. Significant determinants were entered into a multiple regression model. Statistical analyses were performed using SPSS software (Statistical Package for the Social Sciences, version 10.0, SSPS Inc, Chicago, IL, USA). The statistical significance level was defined as $P<0.05$. Data are presented as mean±standard deviation, as appropriate.

Results

The clinical and biochemical characteristics of all study participants are summarized in Table 1. There was no significant difference between patients and controls with regard to age, weight, height, body mass index, smoking habits, alcohol drinking, or serum levels of vitamin B12, folic acid, insulin, or CRP. The mean values (±SD) for total Hcy were 11.6±5.7 μmol/L in SCH patients and 12.4±5.2 mmol/L in control subjects (P=0.307). There was a borderline significant difference in LDL-C concentration (P=0.05), and a significant difference in thyroid auto antibodies ($P<0.001$) between euthyroid controls and patients with SCH.

Multiple regression analyses showed that vitamin Bl2, age, and sex were significant determinants of the variance of Hcy.

Discussion

The prevalence of SCH has been reported to be between 4% and 10% of the adult population samples from large studies (24-26). In one study, 75% of individuals with SCH had serum TSH levels between 5 and 10 mIU/L (26). However, the management and treatment of mild hypothyroidism are controversial (13,27-29).

Given the high prevalence of SCH in the general population, it is important to establish whether these alterations in thyroid function entail a cardiovascular risk. Some potential cardiovascular risk factors were reported in patients with SCH (30-33). Specifically, in patients with mild and subclinical hypothyroidism, the identified cardiovascular risk factors include the following: diastolic dysfunction, increased arterial stiffness, endothelial dysfunction, and increased systemic vascular resistance (34-38). Moreover, all of these abnormalities in cardiovascular parameters may regress or improve with levothyroxine (L-T4) replacement therapy.

Regardless of these risk factors, epidemiological studies in which cardiovascular morbidity and mortality have been evaluated in patients with mild thyroid hormone deficiencies have yielded conflicting data (14,39-45). These results may be due to differences in the populations studied in terms of age, sex, race, definition of mild hypothyroidism, and differences in the duration of follow-up. Further larger randomized trials are necessary to evaluate the potential benefit of L-T4 therapy. However, based on the data available, it appears that L-T4 replacement should be considered in patients with mild hypothyroidism that have associated cardiovascular risk factors in the attempt to reverse these negative prognostic factors and improve the cardiovascular risk.

Although overt hypothyroidism is associated with hyperhomocysteinyemia (9,10), there are contradictory reports in the literature about the association of SCH and hyperhomocysteinyemia (18-23). In our study, Hcy values in patients with SCH were similar to the levels found in euthyroid subjects, indicating a lack of association. Hcy levels are controlled by genetic, nutritional, and acquired factors (5). In overt hypothyroidism, decreases in the glomerular filtration rate may be partly responsible for elevated Hcy levels (46). Smoking, as well as vitamin B12 and folic acid levels has been shown to affect Hcy levels. Since vitamin B12 deficiency is frequently seen in autoimmune thyroid disease (47), this may affect the Hcy results in SCH and overt hypothyroidism.

Patient selection criteria also may affect the different results in studies. In this study, patients with overt atherosclerosis and presumably higher Hcy levels were not. The mean age in our study was higher than that in studies which showed that SCH is related with hyperhomocystinemia (22,23). However, in one study with results similar to ours, the mean age was even younger than it was in studies with positive results (19).

Based on data from this study, we conclude that substantial reductions of thyroid hormone levels are needed to produce significant effects on Hcy metabolism. However, the LDL-C concentration was increased in patients with SCH in our study, which shows that the increased cardiovascular risk of SCH may be mediated by hyperlipidemia rather than by hyperhomocysteinyemia. Some cross-sectional studies suggested that serum cholesterol levels are significantly higher in individuals with mild thyroid failure, while other studies did not (28,48-50). The findings in our study are consistent with the findings of previous studies showing that increased risk of atherosclerosis in SCH is associated with increased serum cholesterol and triglyceride levels (12,15,16,51).

Conclusions

Although an association of overt hypothyroidism with hyperhomocysteinyemia is well established, we found no association between SCH and hyperhomocysteinyemia in the current study. Moreover, we conclude that the atherogenicity of SCH may be mediated by hyperlipidemia rather than by hyperhomocysteinyemia.

Table 1. Characteristics of subjects with SCH versus controls*

Parameter	Euthyroid Patients (n=124)	SCH Patients (n=70)	P value
Sex (male/female)	26/98	14/56	NS
Basal homocysteine (μmol/L)	12.4±5.2	11.6±5.7	NS
Age (years)	55.7±13.7	57.0±12.4	NS
Weight (kg)	74.9±13.6	72.0±13.4	NS
Body mass index (kg/m^2)	28.3±4.9	27.9±6.0	NS
Creatinine (mg/dL)	1.0±1.4	0.8±0.2	NS
Urea (mg/dL)	14.2±9.8	13.4±4.3	NS
TSH (mIU/L)	1.3±0.9	6.6±2.4	<0.001
Free T3 (pg/mL)	3.6±2.2	3.1±1.1	NS
Free T4 (ng/dL)	1.4±1.0	1.0±0.3	NS
Cholesterol (mg/dL)	206.4±39.2	216.4±37.4	NS
LDL-C (mg/dL)	123.9±35.6	133.5±32.1	0.05
HDL-C (mg/dL)	51.9±12.1	55.2±14.8	NS
Triglyceride (mg/dL)	131.3±58.5	146.0±67.6	NS
Fasting glucose (mg/dL)	99.8±23.4	95.6±21.0	NS
Basal insulin (mIU/mL)	8.9±6.8	9.4±9.0	NS
Anti-TPO (IU/mL)	169.1±373.4	443.4±563.1	<0.001
Anti-tg (IU/mL)	68..0±147.5	374.4±793.5	<0.001
CRP (μg/L)	3.6±4.7	3.8±5.0	NS
Folic acid (ng/mL)	13.1±44.2	9.6±5.5	NS
Vitamin B12 (pg/mL)	288.9±114.8	301.9±134.7	NS

*Data were given as mean±SD, except for sex.
SCH: Subclinical hypothyroidism, NS: Not significant, TSH: Thyroid stimulating hormone, T3: Triiodothyronine, T4: Thyroxine, LDL-C: Low-density lipoprotein-cholesterol, HDL-C: High-density lipoprotein-cholesterol, TPO: Thyroid peroxidase, tg: Thyroglobulin, CRP: C-reactive protein.

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