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Subclinical Hypothyroidism may be Associated with Elevated High-sensitive C-Reactive Protein (Low Grade Inflammation) and Fasting Hyperinsulinemia

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Abstract. The ssociation between coronary heart disease and subclinical hypothyroidism (SCH) is unclear. We aimed to determine hs-CRP concentrations in patients with SCH. Seventy-seven patients (age 34.6 ± 13.7 yr) with SCH (TSH >4.2 μIU/ml and serum free thyroxine level between 0.932–1.71 ng/dL), and 80 control subjects (age 33.9 ± 13.3 yr) were studied. Thyroid hormones, C-reactive protein, insulin, glucose, total, HDL, LDL and VLDL-cholesterol levels and HOMA-IR index were also determined. TSH levels of SCH group were higher than control (7.4 ± 2.9 and 1.55 ± 0.78 μIU/ml, respectively, p = 0.0001). However, FT4 levels were lower than control subjects (1.18 ± 0.22 ng/dL and 1.38 ± 0.26, respectively, p = 0.001). Serum hs-CRP levels of subjects with SCH were higher than control subjects (4.2 ± 0.8 mg/l and 1.05 ± 0.3 mg/l respectively, p = 0.0001). Insulin levels of SCH group were higher than control (8.5 ± 4.3 μU/ml and 7.1 ± 3.1 μU/ml respectively, p<0.02) but, Homa-IR levels of the two groups were not different. Mean total and LDL-cholesterol levels of SCH group were higher than control (p = 0.01 and p<0.02). We also found a positive correlation between hs-CRP levels and insulin (r = 0.362, p = 0.002 in men, r = 0.358, p = 0.0001 in women), TSH (r = 0.611, p = 0.0001 in men, r = 0.411 p = 0.0001 in women), and prolactin (r = 0.340, p = 0.01 in men r = 0.553, p = 0.0001 in women). Conclusions: Patients with SCH, irrespective of gender, have higher serum hs-CRP, insulin, total and LDL-cholesterol levels than healthy subjects. 2- High hs-CRP level, and thereby low grade inflammation may be associated with fasting hyperinsulinemia before insulin resistance becomes evident in patients with SCH.

Key words: Subclinical hypothyroidism, C-reactive protein, Prolactin, Fasting insulin and insulin resistance
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THE term subclinical hypothyroidism applies to mildly elevated serum TSH and normal levels of serum T4. In the absence of other causes of elevated serum TSH, a combination of abnormally high serum TSH and normal or low-normal serum thyroid hormone levels is diagnostic of SCH [1]. SCH is usually asymptomatic and is detected either on routine sensitive TSH screening or when non-specific symptoms are evaluated. Several studies on the association between coronary heart disease and SCH have been carried out, but the results are not clear yet. It was argued that both SCH and overt hypothyroidism were associated with cardiovascular disease, but there are some studies reporting that there was no association between SCH and cardiovascular disease [2–5].

Inflammation is thought to play an important role in the progression and complications of atherosclerosis. Circulating concentrations of C reactive protein (CRP) fluctuate widely during acute responses to tissue damage or infection. In recent years, this "acute phase reactant" has been studied as potential markers of more subtle and persistent systemic alterations that may be loosely called low grade inflammation [6]. Recent studies reporting that moderate elevations of CRP (below those of most routine CRP assays) correlate with future cardiovascular events validate the use of this test

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to assess cardiovascular risk [6]. To identify these moderate elevations, performance of high-sensitivity assays for CRP (hs-CRP) is recommended to better identify CRP variations. Kushner and Sehgal [2] recommended that hs-CRP is an effective screening test for cardiovascular risk. Although Christ–Crain *et al.* [8] showed that CRP values increased with progressive thyroid failure and might be considered as an additional risk factor for the development of coronary heart disease in hypothyroid patients, hs-CRP levels in SCH is not a well studied subject. We aimed to evaluate hs-CRP values in patients with SCH and compare them with those for control groups.

Subjects and Methods

A-Subjects

Seventy-seven subjects with SCH (mean age 34.6 ± 13.7 yr, 36 male, 41 female) were included to the study. Eighty age, and BMI, matched, euthyroid healthy hospital staff were selected as control group (mean age 33.9 ± 13.3 yr, 38 male, 42 female). There were 3 post-menopausal women in SCH, 4 post-menopausal women in healthy group, but none of them were taking hormone replacement therapy. Histories, physical examination, ECG, chest radiography, and routine chemical analysis showed that the control subjects had no evidence for any disease. Diabetic subjects, smokers, alcohol users, those with pituitary/hypothalamic disorders, those taking thyroid hormone medication up to 3 months before enrollment and drugs known to affect TSH, CRP and lipid levels were excluded from the study. Patients with a history of acute myocardial infarction or angioplasty within the preceding 6 months and patients diagnosed with concomitant diseases (arthritis) or conditions that could possibly be associated with an acute-phase reaction (such as estrogen use) were also excluded. SCH was defined as an elevated thyroid stimulating hormone (TSH) level (>4.2 μIU/ml) and a normal serum free thyroxine (FT4) level (0.932–1.71 ng/dL). Euthyroidism was defined as a normal TSH level (0.4 to 4.0 mU/L) and a normal serum FT4 levels (0.932–1.71 ng/dL). This study was approved by the local ethical committee of Medical School, Dicle University. All subjects gave written voluntary consent to participate in the study.

B-Methods

1-Anthropometric measurements

Body weights (kg) and heights (cm) were measured without shoes and/or cap. BMI was expressed as weight per height square (kg/m^2). Waist and hip circumference were measured and recorded (cm).

2-Biochemical evaluations

All blood samples were taken between 08.00–08.30 am after 12 hours of fasting period. After collection, serum samples were stored at –40°C until assayed. Total, HDL, and VLDL-cholesterol, glucose and triglyceride levels were determined with Abbott Aeroset auto analyser. LDL-cholesterol was calculated by Friedewald equation (LDL chol. = Total chol. – (HDL + TG/5)). Serum insulin levels were measured by radioimmonoassay (RIA, Diagnostic System Laboratories, Webster, TX, USA, Berthold LB 2111). The intraassay coefficent of variation (CV) were 8.2%, 4.8% and 6.3%, at serum concentrations of 4.75, 17.62 and 54.60 μU/ml, respectively. The interassay CV was 11.2%, 7.5% and 4.7%, at serum concentrations of 4.92, 16.23, and 52.92 μU/ml, respectively. Serum prolactin (analytical sensitivity 10 μIU/ml (0.47 ng/ml)), TSH, T4 (analytical sensitivity 0.42 μg/dl), T3 (analytical sensitivity 0.195 ng/ml), FT4 and FT3 levels were measured by electrochemiluminescence immunoassay (ECLIA) with modular analytics E170 immunoassay analyzers (Roche Diagnostic, Germany). Serum CRP levels were measured with immunometric assay by Immulite 2000 high sensitivity CRP kits (Diagnostic Products Corporation, Los Angeles, CA). A coefficient of variation (CV) of 7.6% was observed from ten replicates of a sample containing 0.41 mg/L of CRP.

3-Assessment of insulin resistance

Homeostasis model assessment (HOMA) index for insulin resistance (HOMA-IR) was calculated with the formula [HOMA-IR = (fasting plasma insulin (μU/mL) × fasting plasma glucose (mmol/L)/22.5].

4-Statistical analysis

Results were shown as mean ± standard deviation. In dependent-t test was used to compare patients with SCH and control group. Pearson correlation test was used to define correlation among hs-CRP, TSH, prolactin, fasting insulin and HOMA-IR values. Chi-square test was used in comparison of gender differences between SCH and control groups. Values $p<0.05$ were accepted as statistically significant.

Results

Mean age, BMI, systolic and diastolic blood pressure, waist and hip circumference, triglycerides, HDL-cholesterol, AST and ALT concentrations in SCH and control group did not differ. Total and LDL cholesterol levels of subjects with SCH were higher than control group. The characteristics of patients and control group subjects are summarized in Table 1. Mean TSH levels of subjects with SCH were significantly higher than control subjects (7.4 ± 2.9 μIU/ml and 1.55 ± 0.78 μIU/ml, respectively, p = 0.0001). On the contrary, FT4 levels were lower than control subjects (1.18 ± 0.22 and 1.38 ± 0.26 ng/dl ng/dl, respectively, p = 0.001). Patients with SCH were not different from the control group in terms of T4, T3 and free T3 levels (Table 2).

Mean serum hs-CRP levels of subjects with SCH was higher than those of control subjects (4.2 ± 0.8 mg/l and 1.05 ± 0.3 mg/l respectively, p = 0.0001). Mean insulin levels of subjects with SCH were also higher with respect to control subjects (8.5 ± 4.3 μU/ml, 7.1 ± 3.1 μU/ml, p<0.02) but HOMA-IR values of the two groups were not significantly different (1.74 ± 0.8, and 1.98 ± 1.25). Serum glucose concentration was not different in the two groups. Mean prolactin levels of the subjects with SCH were higher than control group (p = 0.0001). Patients and control subjects were divided into 4 groups according to their gender (SCH men, control men, SCH women and control women). We found significant differences in hs-CRP levels, prolactin, fasting insulin and TSH level between SCH and control in both men and women. Results are shown in Table 3.

We performed a Pearson correlation test among hs-CRP, insulin, TSH, prolactin, total and LDL-cholesterol in both male and female gender. We found a positive correlation between hs-CRP levels and insulin (r = 0.362, p = 0.002 in men, r = 0.358, p = 0.0001 in women), TSH levels (r = 0.611, p = 0.0001 in men, r = 0.411, p = 0.0001 in women), and prolactin (r = 0.340, p = 0.01 in men r = .553, p = 0.0001 in women). TSH levels were positively correlated with prolactin (r=0.376, p=0.0001 in men, r=0.382, p=0.0001 in women). Prolactin levels were positively correlated with insulin (r = 0.289, p = 0.03 in men, r = 0.267, p = 0.01 in women). The correlations between hs-CRP, TSH, insulin, prolactin, total-cholesterol, LDL-cholesterol are shown in Table 4.

Table 1. Biochemical and anthropometric properties of patients with SCH and healthy control

	SCH group (n = 77)	Control group (n = 80)	P
Age (yr)	34.6 ± 13.7	33.9 ± 13.3	Ns
Sex (F/M)	41/36	42/38	Ns
Body height (m)	1.62 ± 0.08	1.64 ± 0.09	Ns
Body weight (kg)	65.2 ± 12.6	64.6 ± 12.2	Ns
BMI (kg/m^2)	24.9 ± 4.9	24.0 ± 4.4	Ns
Waist-circ. (cm)	76.3 ± 11.7	76.9 ± 11.9	Ns
Hip-circ. (cm)	94.8 ± 9.2	94.6 ± 8.7	Ns
Waist/hip ratio	0.80	0.81	Ns
SBP (mmHg)	120 ± 12	115 ± 16	Ns
DBP (mmHg)	74 ± 10	73 ± 12	Ns
AST U/l	21 ± 6	20 ± 8	Ns
ALT U/l	15.6 ± 4.2	14.6 ± 5.3	Ns
Total-cholesterol (mg/dl)	181 ± 40	167 ± 39	P<0.02
HDL-cholesterol (mg/dl)	44.6 ± 10.6	42.4 ± 12.1	Ns
LDL-cholesterol (mg/dl)	116 ± 36	99.9 ± 36	P<0.01
Triglycerides (mg/dl)	120 ± 65	125 ± 96	Ns

Table 2. Serum thyroid hormones, prolactin, hs-CRP, fasting glucose, fasting insulin levels and HOMA-IR values of the groups

	SCH group (n = 77)	Control group (n = 80)	P
TSH (μIU/ml)	7.4 ± 2.9	1.5 ± 0.7	0.0001
T4 (μg/dl)	8.24 ± 2.29	8.59 ± 1.83	Ns
T3 (ng/ml)	1.37 ± 0.46	1.29 ± 0.24	Ns
FT4 (ng/dl)	1.18 ± 0.22	1.38 ± 0.26	0.001
FT3 (ng/dl)	0.327 ± 0.03	0.340 ± 0.05	Ns
Prolactin (ng/ml)	20.3 ± 5.8	13.4 ± 4.9	0.0001
Glucose (mmol/l)	5.48 ± 1.39	5.47 ± 1.49	Ns
Insulin (μU/ml)	8.5 ± 4.3	7.1 ± 3.1	0.02
HOMA-IR	1.98 ± 1.25	1.74 ± 0.8	Ns
Hs-CRP (mg/l)	4.2 ± 0.8	1.05 ± 0.3	0.0001

Discussion

Our study showed that patients with SCH (male, female and whole SCH group) had higher hs-CRP level than control group. Plasma CRP levels rapidly increase in a wide variety of pathologic conditions, including febrile illnesses and various inflammatory states [9]. Participants in our study were free of clinically apparent vascular disease and other major inflammatory disorders at the time of study enrollment and blood collection. Therefore, higher hs-CRP levels in SCH group are not the result of such pathologic conditions. This is an interesting finding since atherosclerosis

Table 3. Comparison of hs-crp, prolactin, fasting insulin, glucose, THS and HOMA-IR levels of the subjects in accordance to their gender

	SCH (♂) (n = 36)	Contr. (♂) (n = 38)	P	SCH (♀) (n = 41)	Contr. (♀) (n = 42)	P
Hs-CRP	4.08 ± 3.5	0.91 ± 0.8	0.0001	4.53 ± 2.6	1.18 ± 1.64	0.0001
Prolactin	22.8 ± 11.3	13.9 ± 4.6	0.002	20.0 ± 11.3	12.6 ± 5.0	0.0001
Insulin	9.1 ± 4.6	6.9 ± 2.8	0.04	8.15 ± 4.06	6.21 ± 3.4	0.05
Glucose	5.22 ± 0.77	5.37 ± 1.43	NS	5.55 ± 1.55	5.50 ± 1.27	NS
TSH	6.2 ± 2.4	1.5 ± 0.8	0.0001	8.16 ± 4.18	1.52 ± 0.78	0.0001
HOMA-IR	1.85 ± 1.1	1.66 ± 0.7	NS	2.04 ± 1.33	1.82 ± 0.89	NS

Table 4. Correlation between Hs-CRP, insulin, TSH, prolactin, total, LDL-cholesterol in both genders

	MEN			WOMEN		
	Hs-CRP	Insulin	TSH	Hs-CRP	Insulin	TSH
TSH	0.611 (p = 0.001)	0.297 (p = 0.003)	–	0.411 (p = 0.0001)	0.044 (NS)	–
Insulin	0.362 (p = 0.002)	–	–	0.358 (p = 0.0001)	–	–
Prolactin	0.340 (p = 0.01)	0.289 (p = 0.03)	0.376 (p = 0.004)	0.553 (p = 0.0001)	0.267 (p = 0.01)	0.382 (p = 0.0001)
Total-chol.	0.176 (NS)	0.119 (NS)	0.341 (p = 0.001)	0.138 (NS)	0.15 (NS)	0.303 (p = 0.0001)
LDL-chol.	0.188 (NS)	0.072 (NS)	0.328 (p = 0.002)	0.028 (NS)	–0.124 (NS)	0.246 (p = 0.01)

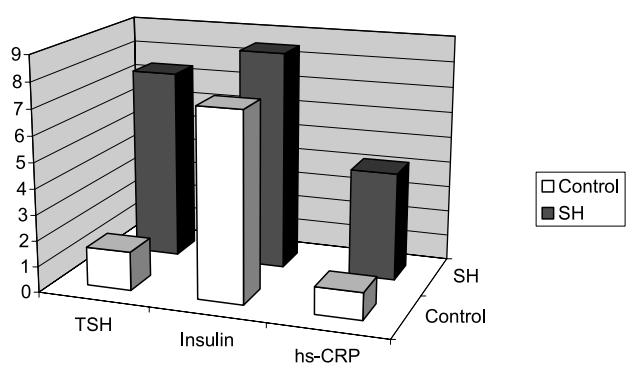

Fig. 1. Comparison of TSH, insulin and hs-CRP levels of the groups.

is presumed to be an inflammatory disease and, CRP, non-specific marker of inflammation, has been proven to be one of the strongest predictors of the risk of cardiovascular diseases [6, 10–12]. Christ-Crain *et al.* [8] showed that CRP levels were elevated in SCH. In addition, CRP may aggravate the atherothrombotic process within activation of complement and monocytes/macrophages [13, 14].

The relationship between SCH and later development of atherosclerosis is unclear [3, 5, 15]. The Whickham survey found no relationship between initial TSH levels and the subsequent development of ischemic heart disease over 20 years of follow-up [5]. On the contrary, in the Rotterdam study, a serum TSH level greater than 4.0 mU/L was found to be associated with a history of myocardial infarction and atherosclerosis of the abdominal aorta [5].

We also found a positive correlation between hs-CRP and insulin levels in male and female patients with SCH. This correlation showed that hs-CRP might induce an interaction with insulin in both genders. Some reports suggested a positive association between components of the insulin resistance syndrome and CRP. The Insulin Resistance Atherosclerosis Study (IRAS) showed that insulin resistance was significantly related to higher CRP levels [16]. In the present study, mean fasting insulin level of SCH group was significantly higher than control subjects. HOMA-IR values were also slightly higher (but not statistically significant) than control group. This result may imply that fasting hyperinsulinemia, even before overt insulin resistance, may play a role in increasing hs-CRP in patients with SCH. A dilemma of our study was the absence of an appropriate thyroxine replacement therapy, since thyroxine replacement therapy may remove probable effects of TRH, TSH and prolactin on fasting hyperinsulinemia. However, it was claimed that CRP levels did not show any improvement after L-thyroxine therapy in patients with SCH [8].

Our study showed that mean prolactin levels of patient with SCH were higher than those of the control group. Prolactin levels were also positively correlated with hs-CRP, insulin and TSH levels in both genders. Prolactin may induce glucose intolerance, hyper-

insulinemia and insulin resistance [17]. We had also previously demonstrated that hyperprolactinemia was associated with insulin resistance [18, 19]. It is still not clear how prolactin deteriorates insulin sensitivity. It was shown that insulin binding to monocytes and erythrocytes significantly decreased in patients with excess prolactin due to decrement in the number of insulin receptors [20]. Therefore, fasting hyperinsulinemia in SCH group may also be the result of hyaperprolactinemia in our study.

In the study, total and LDL-cholesterol levels of patients with SCH were found to be significantly higher than control group, but HDL-cholesterol levels were not different. SCH has been shown to be associated with increased total and LDL cholesterol, and reduced HDL-cholesterol in most, but not all, studies [21]. Some reports have also suggested that even high normal serum TSH values may adversely affect serum lipid and lipoprotein levels [22, 23]. Furthermore, we found a positive correlation between TSH, and total and LDL-cholesterol in both male and female patients with SCH. In addition, it was reported that thyroid hormones stimulate the synthesis and activity of hepatic and peripheral LDL receptors, and thereby induce an increase in LDL-cholesterol clearance in combination with stimulation of HDL-cholesterol synthesis [24]. Mild thyroid failure in SCH may lead to decreasing of LDL-C clearance, and this decrease may be responsible for increased total and LDL-cholesterol levels in subclinical hypothyroid patients. Thus, based on our data, we feel that dyslipidemia and SCH may be associated, and that further studies should clearly identify this association.

Conclusions: 1- Patients with SCH, irrespective of gender, have higher serum hs-CRP, insulin, total and LDL-cholesterol levels than healthy subjects. 2- High hs-CRP level and therefore low grade inflammation may be associated with fasting hyperinsulinemia before obvious insulin resistance in patients with SCH.

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