



ORIGINAL ARTICLE

Levels of hs-CRP as a Cardiovascular Risk Factor in Different Groups of Patients with Hypothyroidism

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Abstract

Introduction: It is known that thyroid function disorders negatively affect all systems, especially the cardiovascular system. In our study, we investigated hs-CRP levels and their relation with metabolic syndrome components between hypothyroid patients who are taking thyroid hormone replacement therapy (THR) and those who are newly diagnosed and haven't started treatment yet.

Methods: 124 subclinical and overt hypothyroid patients, 53 healthy controls without known disease, admitted to the Internal Medicine outpatient clinic were enrolled in this cross-sectional, controlled study. Patients were divided into 3 groups. Group 1: taking THR and having normal thyroid test results, Group 2: taking THR but not having targeted thyroid tests, Group 3: Newly diagnosed with hypothyroidism. Blood pressure, body mass index (BMI), waist circumference, glucose, sT4, sT3, TSH, lipid profile, and hs-CRP (nephelometric method, Beckman Coulter Image800 device) were measured.

Results: There was a negative correlation between HDL cholesterol and hs-CRP levels in patients with hypothyroidism ($p < 0.05$). When patients and controls were divided into groups according to their BMI ($< 25 \text{ kg/m}^2$ and $\geq 25 \text{ kg/m}^2$) and waist circumference (a border of 88 cm for women, 102 cm for men), there was a statistical difference in hs-CRP levels ($p < 0.05$).

Discussion and Conclusion: In both subclinical and overt hypothyroidism (with/without THR), hs-CRP levels are higher compared to controls, and cardiovascular risk increases. The difference detected in mean hs-CRP levels between the control and patient groups is not correlated with the increase in LDL-cholesterol levels, whereas it is negatively correlated with HDL-cholesterol levels. Both in control and patient groups, hs-CRP levels are affected by obesity. It is important to detect and follow hs-CRP levels in hypothyroidism for cardiac risk, but it is not independent of BMI and waist circumference.

Keywords: Cardiovascular risk; cholesterol; hypothyroidism; hs-CRP

The globally increasing incidence of thyroid function disorders and their adverse impact on various systems, especially the cardiovascular system, have prompted research in this field for the determination of treatments and risks.

Numerous studies in the literature investigate the relationship between hypothyroidism and cardiovascular

risk. These studies generally examine the associations between hypothyroidism and the development of atherosclerosis, lipid metabolism disorders, hypertension, obesity, and endothelial dysfunction, emphasizing that cardiac risk in hypothyroidism patients could be higher compared to the healthy population^[1-3].

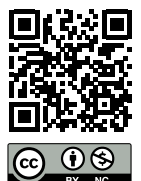
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C-reactive protein, a polymeric protein synthesized in the liver, is an acute-phase reactant and is carried in the blood attached to polysaccharides. CRP is a nonspecific indicator of inflammation and tissue damage. The primary conditions leading to an increase in CRP include infections, malignancy, autoimmune diseases, and hormone replacement therapy. Additionally, CRP has recently begun to be used in diagnosing cardiovascular diseases. However, to employ CRP in diagnosing cardiovascular diseases and determining risk, methods that measure CRP levels at lower concentrations more sensitively, specifically, and with higher accuracy are needed. For this purpose, high-sensitivity CRP (hs-CRP) measurement methods have been developed.

It has been demonstrated that hs-CRP levels are a significant marker in assessing the risk of the first myocardial infarction^[4]. Similarly, notable and rapid increases in hs-CRP levels during the post-infarction period have been shown to be associated with increased morbidity and mortality^[5,6]. hs-CRP levels also rise in the presence of stroke and peripheral artery disease^[7]. Additionally, in healthy individuals, hs-CRP levels have been identified as an independent risk factor for predicting future myocardial infarction, stroke, and peripheral vascular disease^[8,9].

These findings, which support an increase in cardiac risk in hypothyroidism, suggest that hs-CRP levels could be significantly higher in hypothyroid patient groups compared to the general population, leading to further studies in this area. However, the results have been inconsistent^[10-13].

The objective of our study was to determine hs-CRP levels in clinical and subclinical hypothyroid patient groups receiving thyroid hormone replacement therapy (THR), not receiving THR, and those newly diagnosed, and to investigate the relationship between hs-CRP levels and the components of metabolic syndrome.

Materials and Methods

This study is a case-controlled, cross-sectional study that includes 124 patients diagnosed with subclinical and overt hypothyroidism, aged between 18-65 years, who visited the outpatient clinics of Haydarpaşa Numune Training and Research Hospital, and who did not have any other additional diseases. It also includes a control group of 53 individuals with similar demographic characteristics. The control group individuals had no known acute or chronic diseases or a history of continuous medication use.

This study was conducted with the permission of the

hospital's scientific committee (ethics committee) and administration.

Inclusion criteria for the study:

- Being above 18 and under 65 years of age.
- Patients previously diagnosed with hypothyroidism and receiving thyroid hormone replacement therapy, or patients diagnosed with subclinical or overt hypothyroidism during the outpatient visit.

Exclusion criteria:

- Known diagnosis of hypertension, coronary artery disease, malignancy, inflammatory bowel disease, arthritis, autoimmune disease, pelvic inflammatory disease.
- Detected acute infection and/or symptoms of infection.
- Pregnancy.
- Recently undergone surgical procedure.
- Oral contraceptive use.
- Known diagnosis of any other systemic additional disease.

Patients included in the study were further divided into three groups. Group 1 consisted of patients diagnosed with hypothyroidism, undergoing thyroid hormone replacement therapy, and having free T3, free T4, and TSH values within the desired normal ranges (n=64). Group 2 comprised patients diagnosed with hypothyroidism, receiving replacement therapy, but with free T3, free T4, and TSH values not within the normal ranges (n=31). Group 3 consisted of patients diagnosed with hypothyroidism but not on medication (n=29). Patients in all three groups were not taking any medication other than thyroid drugs. Cases in Group 2 were further categorized into overt hypothyroidism, subclinical hypothyroidism, and subclinical hyperthyroidism.

In the study, the age, gender, height, weight, body mass index, waist circumference, smoking status, and systolic and diastolic blood pressures of the cases were recorded. After 12 hours of fasting, venous blood samples were taken from the patients to measure fasting blood glucose (FBG), free T3 (sT3), free T4 (sT4), TSH, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and hs-CRP. Electrocardiograms (EKGs) of the patients were taken to exclude major cardiac pathologies. Routine blood tests were conducted in the biochemistry laboratory using the Roche-Hitachi Modular device, and hs-CRP was measured in the microbiology laboratory using the nephelometric-turbidimetric method with the Beckman-Coulter Immage 800 device.

For determining the normal hs-CRP value in the cases, the upper limit of the standardized hs-CRP value in our hospital, which is 0.74 mg/dL, was considered. hs-CRP levels above this value were deemed high. The normal range for sT3 was accepted as 2.3 pg/mL to 3.9 pg/mL, for sT4 as 0.58 ng/dL to 1.64 ng/dL, and for TSH as 0.34 μ IU/mL to 5.60 μ IU/mL. Both patient and control groups were further divided internally based on their biochemical parameters into three groups for LDL cholesterol: <130 mg/dL, 130-160 mg/dL, and \geq 160 mg/dL; into two groups for HDL cholesterol: below and above 50 mg/dL for women and 40 mg/dL for men; into two groups for triglycerides: below and above 150 mg/dL; into two groups for waist circumference: below 88 cm for women and 102 cm for men (normal waist circumference) and above 88 cm for women and 102 cm for men (increased waist circumference); and into two groups for BMI: <25 kg/m² (normal BMI) and \geq 25 kg/m² (increased BMI). All patients and controls included in the study were normotensive.

Statistical analysis was conducted using the SPSS 16.0 for Windows software. The Student's t-test was used as a parametric test, and the Mann-Whitney U test as a non-parametric test for comparing means between two groups. The Kruskal-Wallis analysis was utilized for comparing the means of more than two groups. The distributions between groups were analyzed using the Chi-square test. Pearson's correlation coefficient was employed in the correlation analysis. Values of $p < 0.05$ were considered statistically significant.

Results

A total of 177 individuals were included in the study, consisting of 53 controls (29.9%) and 124 patients (70.1%). Of these, 156 were women (88.1%) and 21 were men (11.9%).

The demographic, clinical, and laboratory value averages of the control and patient groups, and their comparisons, are presented in Table 1 and Table 2.

Significant differences were found in hs-CRP levels between the control and patient groups ($p < 0.05$). The average hs-CRP level of the control group was 0.25 ± 0.16 mg/dL, while that of the patient group was 0.45 ± 0.47 mg/dL. The average hs-CRP levels of the groups are shown in Table 3.

No significant difference was found between Group 1 and Group 2, Group 1 and Group 3, or Group 2 and Group 3 in the patient groups in terms of hs-CRP.

The average body mass index (BMI) of the patient group (27.9 ± 4.9) was significantly higher than that of the control group (25.6 ± 4.3) ($p < 0.05$).

When the patient group was divided into two subgroups based on BMI (<25 kg/m² and \geq 25 kg/m²), a statistically significant difference in hs-CRP levels between these groups was observed (the average hs-CRP level was 0.19 ± 0.14 mg/dL in the group with BMI <25 kg/m², and 0.29 ± 0.17 mg/dL in the group with BMI \geq 25 kg/m²) ($p < 0.05$).

The average waist circumference of the patient group (90.6 ± 12.0 cm) was significantly higher than that of the control group (86.0 ± 12 cm) ($p < 0.05$).

When the patient group was divided into two based on waist circumference, with women <88 cm, men <102 cm and women \geq 88cm, men \geq 102 cm, a statistically significant difference in hs-CRP levels between these groups was observed (the average hs-CRP value was 0.31 ± 0.40 mg/dL in the group with women <88 cm, men <102 cm and 0.56 ± 0.49 mg/dL in the group with women \geq 88cm, men \geq 102 cm) ($p < 0.05$).

No significant difference was found between the control and patient groups in terms of total cholesterol and LDL cholesterol values ($p > 0.05$).

Table 1. Demographic and Clinical Characteristics of Control and Patient Groups

Parameter	Control Group (n=53)	Patient Group (n=124)	p*
Age (years)	40.15 \pm 12	43.6 \pm 11.3	>0.05
Gender (M/F)	16 / 37	5 / 119	<0.05**
Height (cm)	164.1 \pm 9.03	159.0 \pm 5.99	<0.05
Weight (kg)	68.8 \pm 11.5	70.5 \pm 12.4	>0.05
BMI (kg/m ²)	25.6 \pm 4.3	27.9 \pm 4.9	<0.05
Waist circumference (cm)	86.0 \pm 12	90.6 \pm 12.0	<0.05
Smoking (n, %)	9, 17%	17, 13.7%	>0.05**
Systolic blood pressure (mmHg)	115.8 \pm 11	120.8 \pm 10.7	<0.05
Diastolic blood pressure (mmHg)	71.5 \pm 7.6	72.9 \pm 8.0	>0.05

BMI: Body Mass Index; *Student's t-test; **Chi-square test.

Table 2. Laboratory Data of Control and Patient Groups

Parameter	Control Group (n=53)	Patient Group (n=124)	p*
Fasting Blood Sugar (mg/dl)	87.0±7.4	89.5±8.5	>0.05
sT3	3.09±0.32	2.96±0.41	>0.05
sT4	0.85±0.12	0.82±0.23	>0.05
TSH	1.74±0.85	9.69±16.92	<0.05
Total Cholesterol (mg/dl)	194.9±37.6	200.6±43.8	>0.05
LDL Cholesterol (mg/dl)	119.1±33.9	122.5±38.0	>0.05
HDL Cholesterol (mg/dl)	52.5±15.8	54.9±12.7	>0.05
Triglycerides (mg/dl)	123.4±81.8	116.8±55.5	>0.05
hs-CRP (high-sensitivity C-reactive protein)	0.25±0.16	0.45±0.47	<0.05

*Student's t-test.

Table 3. hs-CRP Averages of Groups 1, 2, 3, and Control Group

	Group 1 (n=64)	Group 2 (n=31)	Group 3 (n=29)	Control Group (n=53)	p
hs-CRP (mg/dL) Min-Max	0.44±0.40 (0.26-1.12)	0.55±0.69 (0.34-1.25)	0.36±0.29 (0.28-0.88)	0.25±0.16 (0.19-0.79)	<0.05

Mann-Whitney U test; Kruskal-Wallis analysis.

Table 4. Lipid Profile Values of Groups 1, 2, 3, and Control Group

	Group 1	Group 2	Group 3	Control Group 4	p (1-4)	P (2-4)	P (3-4)	P (1-2)	P (1-3)	P (2-3)
Total Chol. (mg/dL)	197.3±40.3 (180-220)	217.5± 47.4 (189-241)	200.3±42.3 (178-225)	190.4±34.6 (168-212)	>0.05	<0.05	>0.05	<0.05	>0.05	<0.05
LDL Chol. (mg/dL)	117.2±36.5 (90-125)	138.5± 48.4 (92-137)	122.8±38.7 (88-131)	115.7±31.2 (88-128)	>0.05	<0.05	<0.05	<0.05	<0.05	<0.05
HDL-Chol. (mg/dL)	55.2±12.7 (46-63)	55.4±12.4 (46-68)	54.6±11.8 (45-61)	52.1±15.4 (48-57)	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
Triglyceride (mg/dL)	116.8±55.5 (86-152)	119.7±56.2 (93-172)	117.5±54.6 (91-168)	120.0±79.3 (89-155)	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05

Mann-Whitney U test; Kruskal-Wallis analysis.

In the patient group, there was a significant difference in hs-CRP levels among the groups divided according to LDL cholesterol values (the average hs-CRP was 0.40±0.38 mg/dL in the group with LDL cholesterol <130 mg/dL, 0.56±0.40 mg/dL in the group with LDL cholesterol 130-160 mg/dL, and 0.47±0.78 mg/dL in the group with LDL cholesterol ≥160 mg/dL) (p<0.05). However, there was no correlation between hs-CRP and LDL cholesterol values.

There was no significant difference between the control and patient groups in terms of average HDL cholesterol levels (p>0.05).

In the patient group, there were 40 individuals (32.3%) with HDL cholesterol values of <40 mg/dL in men and <50 mg/dL in women, and 84 individuals (67.7%) with HDL

cholesterol values of ≥40 mg/dL in men and ≥50 mg/dL in women. There was a significant difference in the average hs-CRP levels between these two groups (the average hs-CRP was 0.60±0.41 mg/dL in the group with low HDL cholesterol and 0.38±0.48 mg/dL in the group with high HDL cholesterol) (p<0.05). A significant negative correlation was found between HDL cholesterol and hs-CRP in the patient group (p<0.05, r= -0.22).

There was no significant difference in the average triglyceride levels between the control and patient groups (p>0.05).

In the patient group, there were 95 individuals (76.6%) with triglyceride values <150 mg/dL and 29 individuals (23.4%) with triglyceride values ≥150 mg/dL. There was no

significant difference in the average hs-CRP levels between these groups ($p>0.05$).

The lipid profile averages of the control and patient groups are shown in Table 4.

Discussion and Conclusion

Thyroid function disorders are increasingly prevalent worldwide due to various causes and are gaining significance in the development of atherosclerosis. Consequently, numerous studies have been conducted on the treatment of thyroid function disorders and the early determination of cardiac risk. The potential importance of hs-CRP in determining cardiac risk has been considered, leading to research in this area.

Studies have shown that in addition to the criteria used in the Framingham risk scoring for determining cardiovascular events, the diagnostic criteria for metabolic syndrome, and the lipid profile used for screening purposes, hs-CRP is an independent risk factor. It can serve as a good indicator for both primary and secondary prevention of cardiac events^[14-17]. In a study conducted by Jiang et al.^[18] in China in 2009, it was found that elevated hs-CRP levels in individuals without cardiovascular disease were an effective factor in predicting cardiovascular disease risk.

How is hs-CRP, generally considered an independent factor in determining cardiovascular risk, related to thyroid function disorders? Many studies have been conducted on this topic as well. In a study by Christ-Crain et al.^[10] in Switzerland in 2003, a significant difference in hs-CRP levels was found between overt and subclinical hypothyroidism cases and healthy individuals. According to this study, elevated hs-CRP levels in patients with hypothyroidism were suggested as a risk factor for future cardiovascular events.

In our study, a significant difference was found in hs-CRP levels between the control group and the patient group ($p<0.05$). As mentioned in the findings section, no significant difference in hs-CRP levels was observed among the three patient groups.

Looking at the results obtained, a statistically significant difference was noted in the waist circumference and body mass index averages between the hypothyroid patients and the control group ($p<0.05$). The waist circumference and body mass index averages were found to be higher in the patient group. The correlation between waist circumference, body mass index, and hs-CRP supports the findings of previous studies on this topic^[19-21].

Research has been conducted examining the relationship between hs-CRP and lipid parameters, yielding varied results^[22-24]. In a study by Retterstol et al.^[22] on twins, hs-CRP levels were found to correlate significantly positively with serum triglyceride levels and significantly negatively with HDL cholesterol. Other studies have emphasized that in patient groups with low HDL cholesterol, higher values of hs-CRP were detected^[25,26]. However, no such correlation was found between total cholesterol and LDL cholesterol and hs-CRP. There are other studies supporting this finding^[23]. In contrast, a study by Tamakoshi et al.^[24] found a negative correlation between hs-CRP levels and HDL cholesterol, while also finding a positive correlation between hs-CRP levels and both triglycerides and total and LDL cholesterol levels^[24]. Similar studies exist^[27].

According to the lipid profile results in our study, no significant difference in LDL cholesterol was detected between the control and patient groups. No correlation was found between LDL cholesterol and hs-CRP levels.

As mentioned in the findings section, cases were grouped based on HDL cholesterol levels, with values below and above 50 mg/dL for women and 40 mg/dL for men. Accordingly, in both the patient and control groups, a significant difference in hs-CRP levels was observed between cases with low and high HDL cholesterol. A statistically significant negative correlation was found between HDL cholesterol and hs-CRP, which is consistent with the results of previous studies^[22,23].

Cases were also grouped based on triglyceride values, as either below or above 150. Unlike previous studies^[22-24], no significant difference in hs-CRP levels was found between cases with low and high triglyceride values in the patient group.

As with the general population, the majority of hypothyroid patients in our study were female. The ratio of women to men in the control and patient groups was not equal. However, when all patients and controls were divided into male and female groups, no statistical difference was found in the average hs-CRP levels between these groups. This suggests that even though the ratio of women to men in the groups was not equal, it did not significantly affect the overall result.

In conclusion, when comparing the 53 controls and 124 hypothyroid patients included in our study, monitoring hs-CRP levels in hypothyroid patients is an important factor in determining cardiac risk. Despite the absence of marked hyperlipidemia in both the control and patient groups,

hs-CRP levels were found to be significantly different in the patient group. This difference does not correlate with an increase in LDL cholesterol levels but is negatively correlated with HDL cholesterol levels. Similarly, hs-CRP levels in both the control and patient groups are affected by obesity (body mass index, waist circumference). Monitoring hs-CRP levels in hypothyroid patients is important for cardiac risk, but this is not independent of body mass index and waist circumference.

Limitations of our study include the small number of patients in each subgroup when patients are divided, and the predominance of female gender in the patient group. Therefore, a gender-based evaluation between patient and control groups could not be distinctly made in our study.

Our study, like others around the world, underscores the importance of monitoring hs-CRP levels in the treatment and cardiac monitoring of thyroid function disorders, which are especially increasing among women in our country. This is in addition to other risk factors such as hypertension, obesity, lipid profile, and smoking.

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