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Original Research Article

Autoimmune thyroiditis CRP association

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ABSTRACT

Background: C-reactive protein (CRP) is an acute phase reactant and its serum levels may be risen during many diseases. Hypothyroidism is a clinical disease state accompanied by mild inflammation that is known to be significantly associated with atherosclerosis. In this study, we aim to determine and compare serum CRP levels in overt and subclinical hypothyroidism subgroups and research their association with autoimmune markers.
Methods: Around 79 patients who are diagnosed with overt and subclinical hypothyroidism in our polyclinic were included in this study. Patients' morning blood samples were collected after 8hours of fast and thyroid functions, CRP, sedimentation rate, anti TG and anti TPO antibody levels were studied. Thyroid ultrasonography was planned for each patient.
Results: We found significant differences regarding age, sT3, sT4, TSH, anti-TPO, anti-TG and CRP levels between overt and subclinical groups. There was no significant difference between the groups in thyroxin use, nodularity and sedimentation rate. No significant difference was found between CRP levels and autoimmunity markers anti-TPO and anti-TG among the groups as well. A significant cut-off value was determined for CRP in overt hypothyroidism by using Roc analysis and this value was also considered for being a possible cardiovascular risk marker.
Conclusions: In this study, we found out that CRP levels were high in both overt and subclinical subgroups, CRP levels were increased during progression of the disease from subclinical to overt and this increase may be related with higher inflammation and tendency to cardiovascular diseases.

Keywords: Autoimmunity, C-reactive protein, Hypothyroidism, Overt, Subclinical

INTRODUCTION

First stage of autoimmune thyroiditis development is activation of thyroid specific CD4-T helper cells (CD4 positive helper T lymphocytes). The cytokine secretion of these cells leads to activation of cytotoxic T cells and B lymphocytes' autoantibody production.[1]

Mc Corty also found that CRP is a prototype of acute phase proteins and its serum levels are actually very low in normal conditions, but inflammation increases its concentration (34). Plasma levels and increase pattern as an acute phase protein of CRP shows variations in different species. For example, its normal level is 0.02µg/ml in mice whereas over 500µg/ml in rats. In inflammatory conditions it shows a dramatic increase in humans, rabbits and monkeys while showing slight changes in mice.[2] CRP concentration begin rising on the 4th hour of tissue damage and reaches its peak levels in between 48th-72nd hours.[3] CRP in blood plasma is synthetized by hepatocytes in major and it's under the effect of humoral mediators.[4,5] CRP levels go up quicker then sedimentation rate just after tissue damage and begin falling down rapidly as recovery goes on. Limitation of CRP use is that it is nonspecific; it may rise in many diseases.[6,7]

In this study, we aim to define and compare serum CRP levels in overt and subclinical hypothyroidism patients. We also wanted to specify if there is a correlation between CRP levels and thyroid autoantibodies or not and investigated if it can be used as an autoimmune marker.

METHODS

Around 79 patients who are diagnosed with overt and subclinical hypothyroidism in between September 2007 and January 2008 in our polyclinic were included in this study. Patients who also have an infection, malignity and inflammatory systemic disease were excluded. Also, patients with history of diabetes mellitus, hypertension and coronary artery disease were excluded from this study.

Patients' morning blood samples were collected after 8 hours of fast and thyroid functions, CRP, sedimentation rate, anti TG and anti TPO antibody levels were studied. Thyroid ultrasonography was planned for each patient. Patients with thyroiditis and thyroid nodules were identified by their ultrasonographic images.

Patients were divided into 2 subgroups as overt and subclinical hypothyroidism according to their thyroid function tests. History of L-thyroxine use was questioned in medical anamnesis. Serum CRP levels were measured by immunonephelometric method. Electrochemiluminescence immunoassay (ECLIA) was used for Anti-TPO and anti-TG antibody levels. Each patient was recorded into the patient data form created for this study.

SPSS 11.0 software was used for statistical calculations. Student's t-test, Mann-Whitney U test and Chi-Square test was used for comparison between the subgroups. Parametric variables were presented as mean ± standard deviation while nonparametric variables were presented as median (minimum and maximum). In order to analyze the differences between the groups, student's t test was used for parametric variables and Mann Whitney U test for nonparametric variables. Spearman's rho test was used for multiple correlation analysis. Roc analysis was chosen in the interest of determining a cut-off value. $P<0.05$ was referred as statistically significant.

RESULTS

Among 79 patients included in this study, 70 (88.6%) were female and 9 (11.4%) were male. 55 patients (69.6%) were diagnosed with subclinical hypothyroidism and 24 (30.4%) with overt hypothyroidism. 4 out of 55 patients with subclinical hypothyroidism were male (7.27%) and 51 (92.7%) were female. In 24 patients with overt hypothyroidism, 5 (20.83%) were male and 19 (79.17%) were female. Table 1 shows gender ratio in hypothyroidism subgroups. There was no statistically significant difference between subgroups ($p>0.05$).

Table 1: Gender ratio in hypothyroidism subgroups.

		Gender		Total
		Male	Female	
Hypothyroidism	Subclinical (Gender %)	4 (44.4%)	51 (72.9%)	55 (69.6%)
	Overt (Gender %)	5 (55.6%)	19(27.1%)	24 (30.4%)
Total	Number (Gender %)	9 (100%)	70 (100%)	79 (100%)

Table 2: Mean values in subclinical and overt hypothyroidism subgroups.

	Subclinical	Overt	p
Age (Years)	44.85±11.79	52.38±15.04	0.036
sT_3 (pg/ml)	3.18±0.42	1.61±0.62	<0.001
sT_4 (ng/dl)	1.25±0.22	0.58±0.32	<0.001

Patients were aged between 23 and 79 and mean age was 47.14±13.23. Mean age was 52.22±16.40 in men and 46.49±12.76 in women. Subclinical hypothyroid 55 patients' mean age was 44.85±11.79 when overt hypothyroid 24 patients' mean age was 52.38±15.04. There was statistically significant difference in between these two groups considering age (p:0.036). Mean sT4 value of all the cases included was 1.04±0.40. This value was 1.25±0.22 in subclinical hypothyroidism subgroup and 0.58±0.32 in overt hypothyroidism. Table 2 shows mean values of the subgroups.

The median TSH for all patients, subclinical and overt hypothyroidism subgroups were 10.09uIu/ml (min:0.14uIu/ml; max:163.22uIu/ml), 7.48uIu/ml (min: 4.58uIu/ml; max: 56.40uIu/ml), 35.93uIu/ml (min: 0.14uIu/ml ; max: 163.22uIu/ml) respectively and there was statistically significant difference in between ($p<0.001$).

The median anti TG value was 52.1IU/ml (min:3.18IU/ml-max:9700IU/ml) in all patients, 28.1 IU/ml (min:3.18IU/ml-max:5860.0IU/ml) in subclinical subgroup, 184.5IU/ml (min:20,0IU/ml-max:9700IU/ml) in overt hypothyroid subgroup. There was statistically

significant difference in comparison of the subgroups (p<0.01).

The median value of anti TPO for all patients was 292IU/ml (min:5.70IU/ml-max:4972IU/ml), for subclinical subgroup 107.0IU/ml (min:5,70IU/ml-max:2300IU/ml) and 568.5IU/ml (min:10.0IU/ml-max:4972.0IU/ml) for overt and there was statistically significant difference according to Mann-Whitney U test (p<0.05).

Sedimentation rate and CRP median values for the study group , subclinical subgroup and overt subgroup were 18.0mm/hour (min:4.0mm/hour, max: 64.0mm/hour) and 4.10mg/L (min: 2.0mg/L, max:130.0mg/L); 15.0mm/hour (min: 4.0mm/hour, max: 64.0mm/hour) and 3.40mg/L (min:2.0mg/L, max:33.25mg/L); 21.0mm/hour (min: 6.0mm/hour, max:60.0mm/hour) and 7.51mg/L (min:2.86mg/L, max:130.0mg/L) respectively. When two subgroups were compared, there was no statistically significant difference in sedimentation rate (p>0.05) where there was in CRP values (p<0.001). Table 3 shows median values and p values for subgroups.

Table 3: Median values for subgroups.

	Subclinical	Overt	p
TSH	7.48uIu/ml	35.93uIu/ml	0.000
CRP	3.40mg/L	7.51mg/L	0.000
Sedimentation rate	15.0mm/saat	21.0mm/saat	0.208

Comparison of sT3 and CRP values showed statistically significant correlation (p<0.05). However, correlation tests did not show statistically significant correlation in between CRP values and sT4 and TSH (p values were 0.595; 0.594, respectively).

Around 19 patients (24.1%) had history of thyroxine use. 60 patients (75.9%) did not have any history of thyroxine use. Among 19 patients with thyroxine use, 3 (15.8) were diagnosed with overt and 16 (84.2%) were diagnosed with subclinical hypothyroidism. In subclinical subgroup, 16 (29.1%) patients had thyroxine use while in overt subgroup 3 patients (12.5%) had history of thyroxine use. Subgroups showed no statistically significant difference for thyroxine use (p>0.05).

In the study group, ultrasonography found nodules in 19 patients (24.1%) and did not in 60 (75.9%). 14 patients (25.6%) had nodules in subclinical subgroup while 5 patients (20.8%) showed nodules in overt hypothyroidism subgroup and there was no statistically significant difference in between subgroups (p>0.05). Among 19 patients with thyroid nodules, 14 (73.7%) had subclinical, 5 (26.3%) had overt hypothyroidism. 8 (42.1%) out of 19 patients with thyroxine use had thyroiditis and 5 (26.3%) had multinodular goiter.

Spearman's test did not show statistically significant correlation between CRP levels and anti TPO or anti TG values; p values 0.458 and 0.960, respectively. On the other hand, there was no statistically significant correlation between sedimentation rates and anti TPO or anti TG (p values 0.584 and 0.609, respectively).

Distinctive CRP level was found to be 4.655 mg/L for overt hypothyroidism by ROC analysis and this level was statistically significant (p<0.001). Area under curve (AUC) can be seen in Table 4 for this value.

Table 4: AUC values for CRP cut-off level.

Area	Std deviation	Asymptomatic 95% confidence interval	
		Lower limit	Upper limit
0.765	0.058	0.651	0.879

Specificity and sensitivity of this cut-off CRP level were 72.7% and 75%, respectively (Table 5). Negative predictive value was 87% and positive predictive value was 54.5%. In patients with overt hypothyroidism, risk of having a CRP level above this cut-off value was found to be increased by 8 times (OR:8.0). 95% confidence interval was 2.67-23.99 (p<0.001).

Table 5: Comparison of hypothyroidism groups and CRP levels.

		CRP Value (mg/L)		
		CRP≤4.655	CRP>4.655	Total
Hypothyroidism	Subclinical	40 (72.7%)	15 (27.3%)	55 (100%)
	Overt	6 (25%)	18 (75%)	24 (100%)
Total	Total	46 (100%)	33 (100%)	79 (100%)

When patients were divided into two groups depending on CRP cut-off value 4.655mg/L which was found statistically significant for overt hypothyroidism, mean age was 43.87±12.75 years for the group with CRP≤4.655mg/L while it was found 51.70±12.71 years for the group with CRP≥4.655mg/L and there was statistically significant difference between them (p:0.009).

Mean sT3 and sT4 values were respectively 2.97±0.74pg/ml and 1.12±0.31ng/dl in the group with CRP levels below the cut-off value while 2.31±0.92pg/ml and 0.93±0.48ng/dl in the group with levels above the cut-off value and there was statistically significant difference between them for both sT3 and sT4 (p values 0.001 and 0.038, resp.).

However, there was no statistically significant difference between groups divided by CRP levels for TSH, anti TG and anti TPO (p values 0.245;0.714;0.438, resp.).

When all the cases were divided as autoimmune and non-autoimmune related, mean CRP values were 7.23±5.11mg/L in autoimmune related group and 6.25±5.04mg/L in non-autoimmune. Between the groups, there was no significant difference in CRP levels (p:0.618). Table 6 shows mean CRP values for both groups.

Table 6: Mean CRP values in autoimmune and non-autoimmune related groups.

Cause	n	Mean CRP	SD	p
Autoimmune	42	7.23 mg/L	5.11 mg/L	0.618
Other	36	6.25 mg/L	5.04 mg/L	

DISCUSSION

In a recent study of 77 patients with subclinical hypothyroidism, it was found out that patients had statistically significant higher CRP levels when compared with controls and this reveals mild inflammation that occur in subclinical hypothyroidism.[8] Similarly, our study shows that subclinical hypothyroidism group has CRP levels above normal. We found that as severity of thyroid hormone insufficiency increases, CRP levels rise up accordingly and both subclinical and overt hypothyroidism groups have CRP levels above normal while overt hypothyroidism patients present statistically significantly higher CRP levels then subclinical group. We also determined a cut-off value for CRP which could be significant for overt hypothyroidism. Sensitivity and specificity being around 75% was thought to be due to limited size of this study and we suggest that this value may be studied in wider series. Because of the fact that hypothyroidism has known correlation with morbidities due to cardiovascular events, this cut-off value of inflammation marker CRP is considered for also being a marker of cardiovascular risk in overt hypothyroidism.

In the sense that hypothyroidism patients included in our study have etiologically heterogeneous distribution, patients were divided into two groups as autoimmune and non-autoimmune related hypothyroidism thinking CRP elevation could result from inflammatory thyroiditis. In comparison, there was no statistically significant difference between these groups considering CRP levels. In this study, we revealed that elevated CRP does not originate from autoimmunity and CRP does not have a correlation with autoimmunity. Besides, we could not find a significant correlation between CRP and autoimmunity markers anti-TPO and anti-TG.

In a study including 353 cases with inflammatory and non-inflammatory thyroid diseases, Pearce et al, found out that CRP values do not have a significant correlation in differential diagnosis of thyroid diseases (52). In this study, they could only show significant CRP increase in subacute thyroiditis while showing no significant correlation in the rest of inflammatory conditions. Besides, they revealed that there is no significant difference in CRP levels in the subgroup of Hashimoto's disease which supports lack of correlation between CRP and autoimmunity in our study.

Previous studies suggest that cases with subclinical hypothyroidism which have history of atherosclerotic events have high anti-thyroid antibodies increased by 3.5 times in frequency.[9] A population-based study conducted just when these data made researchers think of a possibility of a significant relationship between CRP values and thyroid autoantibody levels in present patient group, a significant correlation could not be found between thyroid autoantibodies and CRP in subclinical hypothyroidism which supports our data.[10]

In a study conducted by Christ-Crain et al, it was found out that CRP levels were increased significantly in both subclinical and overt hypothyroidism when compared with controls, but there was a weak correlation between CRP values and thyroid hormone indicators. Also, about autoimmunity, a significant relationship could not be found between patients' anti-TPO, anti-TG values and CRP.[11] In our study, there was a weak correlation between CRP and sT3 values shown by correlation tests which could not be shown for TSH and sT4 values.

Although our study shows increased CRP values in both groups, there was no significant correlation between CRP and TSH or sT4, only showing a significant relation with sT3. Therefore, the relationship between CRP values and thyroid hormone levels can only be described as weak. Also, in many other studies, the relationship between CRP values and thyroid hormone levels, if present, interpreted as a possible weak relation.[11-13] In contrast, in a study of Jublanc et al, a negative correlation was found between CRP and sT4 values.[14]

Similarly, in a study based on hypothyroidism co-existence with increased morbidity due to cardiovascular diseases which was conducted by Nagasaki et al, a group of 46 patients with hypothyroidism showed significantly increased CRP levels when compared with controls. Relationship with arterial wall stiffness was also found and it was also suggested that CRP may be a good sign of improvement in arterial wall stiffness in patient group with hypothyroidism.[12]

In a study conducted by Lee et al, 412 patients with hyperthyroidism, hypothyroidism, subclinical hypothyroidism, subclinical hyperthyroidism and control group, there was no significant difference between CRP and lipoprotein a values suggesting that there is no correlation between thyroid hormones and atherosclerosis risk factors.[13] However, we found out that CRP values were high in both subclinical and overt hypothyroidism groups; also, significantly higher CRP values in overt hypothyroidism when compared with subclinical.

In a study including larger patient groups, in contrast with our findings, CRP was found to be in similar levels in both subclinical hypothyroidism and euthyroid patient group suggesting that subclinical group cannot be considered to have higher cardiac inflammation.[15]

In a similar manner, in another study in which 38 subclinical hypothyroidism cases were compared with controls, significant difference could not be found among groups in CRP, homocysteine and fibrinogen values and it was considered that subclinical hypothyroidism may be related with cardiovascular disease not because of mild inflammation but due to impairments in lipid profiles.[16]

In a study of acute (caused by total thyroidectomy) and chronic hypothyroidism cases, endothelial and non-endothelial mediated vascular dysfunction was found in both acute and chronic hypothyroidism groups when compared with healthy controls and serum CRP and TNF alpha levels were found to be similar in both groups, suggesting that thyroid hormone insufficiency is adequate for vascular homeostasis revealing that inflammation markers do not have a contribution in process.[17]

CONCLUSION

Although there are conflicting findings in literature, our study shows as thyroid hormone insufficiency deepens CRP values show a clearer increase, also showing a weak correlation between CRP and thyroid diseases due to lack of significant relation between thyroid tests and CRP. Besides, it was found that CRP cannot be used as an autoimmune marker in thyroid diseases. In this study, a cut-off value was determined for CRP indicating overt hypothyroidism which was not present in literature before that can also be considered as a cut-off value which increases risk of cardiovascular diseases in hypothyroidism cases.

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