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The evaluation of the efficacy of C-reactive protein-to-albumin ratio as a marker for Hashimoto's thyroiditis

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Abstract

Aim: Hashimoto's thyroiditis (HT), the leading cause of hypothyroidism in developed nations, is an autoimmune condition characterized by the progressive destruction of the thyroid gland through various cell- and antibody-mediated immune mechanisms. C-reactive protein-to-albumin ratio (CAR) is a known inflammatory marker easily obtained from a routine blood test. In this context, this study aims to investigate the efficacy of CAR instead of conventionally used thyroid antibodies in predicting the diagnosis and prognosis of HT.

Materials and Methods: The participants in this prospective cross-sectional study were adults aged 18 years and above diagnosed with Hashimoto's thyroiditis (HT), seeking medical care at the Internal Medicine and Family Medicine Departments of Recep Tayyip Erdoğan University Training and Research Hospital in Rize, Turkey, during the period from April to July 2022. An age- and gender-matched control group was created from healthy individuals who applied to the outpatient clinics for routine check-ups. The patient and control groups were compared based on C-reactive protein (CRP), hemoglobin, and albumin serum levels of free triiodothyronine (FT3), free thyroxine (FT4), and thyroid stimulating hormone (TSH).

Results: The patient and control groups comprised 142 HT patients and 62 healthy individuals. CRP level and CAR value were significantly higher. However, albumin and hemoglobin levels were significantly lower in the patient group than in the control group. [1.5 (0.4-5.6) mg/dL vs. 0.98 (0.3-2.6) mg/dL, $p<0.001$; 58 (11.5-193.1) vs. 29.5 (8.1-72.2) $p<0.001$; 2.9 (2.1-4.1) g/dL vs. 3.3 (2.3-4.2) g/dL, $p<0.001$; and 12±1.1 g/L vs. 12.7±1.760 g/L, $p=.005$; respectively]. The multivariate analysis revealed CRP, CAR, albumin, FT3, and hemoglobin as significant predictors of HT, with CAR being the most promising one among them [Odds Ratio (OR): 1.11, 95% confidence interval (CI): 1.38-1.19, $p=0.003$].

Conclusion: This study's findings indicated that CAR is an easily measurable, reliable, and cost-effective marker of HT that can be used as an alternative to conventional thyroid antibodies in primary care centers.

Introduction

Hashimoto's thyroiditis (HT) was first defined as an autonomous pathology of thyroid tissues approximately 100 years ago, and later, with the isolation of anti-thyroglobulin (anti-Tg) antibodies, it was accepted as a specific clinical entity [1-4]. Numerous studies show the relationship between autoimmune thyroiditis and inflammation [5]. HT usually presents with hypothyroidism, while Graves' disease, another type of autoimmune thyroiditis, usually presents with thyrotoxicosis [6]. HT is characterized by histopathologically defined diffuse lymphocytic infiltration of thyroid tissues, lymphoid follicle formation, damage to epithelial cells, Ashkenazy cells, and fibrosis [7]. Many studies on HT pathology and autoimmunity have suggested that diagnosing HT is primarily established by the presence of thyroid antibodies in the bloodstream, such as anti-thyroglobulin (anti-Tg) and anti-thyroid peroxidase (anti-TPO)[8]. Additionally, histopathological changes in thyroid tissue, morphological changes in thyroid ultrasonography (USG), and abnormalities in thyroid functions are also considered to indicate the diagnosis of HT. As is known, C-reactive protein (CRP) and albumin are defined as acute-phase reactants. In inflammatory conditions, the decrease in serum albu-

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min levels and the increase in serum CRP levels indicate the severity of inflammatory conditions, such as infection, ischemia, and trauma [9,10]. CRP stimulates various cytokines to respond to inflammatory conditions [11]. However, albumin is described as a negative acute phase reactant; hence, serum albumin levels decrease in inflammatory conditions [12, 13]. CRP-to-albumin ratio (CAR) combines both parameters and has recently been used as a novel inflammation marker in many diseases such as cancer, sepsis, pancreatitis, and Takayasu's arteritis [14, 15, 16]. In this context, we aimed to investigate the efficacy of CAR instead of conventionally used thyroid antibodies in predicting the diagnosis and prognosis of HT.

Materials and Methods

This prospective cross-sectional study was approved by Recep Tayyip Erdogan University Non-Invasive Research Ethics Committee (2022/98). Individuals aged 18 years and above diagnosed with HT who sought treatment at the Internal Medicine and Family Medicine Departments of Recep Tayyip Erdoğan University Training and Research Hospital in Rize comprised the study population. Turkey between April and July 2022. HT diagnosis was based on relevant medical history, physical examination findings, USG findings, and/or elevated levels of serum thyroid autoantibodies, i.e., anti-TPO and anti-Tg. None of the HT patients with HT included in the study were using levothyroxine or anti-thyroid medication. Patients with other inflammatory and chronic diseases, such as recent infectious diseases, rheumatological diseases, malignancies, renal failure, liver diseases, coronary artery disease, and hematological diseases, were excluded. Ultimately, the study sample consisted of 142 HT patients. An age- and gender-matched control group was created from 62 healthy individuals who applied to the outpatient clinics for routine check-ups.

Laboratory measurements

The serum albumin levels were measured using an Abbott C8000i automatic photometry commercial kit (Abbott Park, Illinois), and the serum CRP levels were measured via the nephelometric method (UniCel DxC 800 System; Beckman Coulter Inc., Brea, California). CAR was calculated by multiplying the CRP level to albumin level ratio by 100. Patients' anti-TPO and anti-Tg levels were evaluated regarding their normal ranges (0-60 U/mL for anti-TPO and 0-4.5 IU/mL for anti-Tg).

Statistical analysis

Statistical analyses were conducted using the software package SPSS 22.0 (Statistical Product and Service Solutions for Windows, Version 22.0, IBM Corp., Armonk, NY, U.S., 2013). Descriptive statistics were expressed as median with minimum and maximum values for non-normally distributed continuous variables, while for normally distributed continuous variables, mean ± standard deviation values were used. Additionally, categorical variables were presented as frequencies and percentages (%). Visual methods such as histograms and analytical methods, including the Kolmogorov-Smirnov and Shapiro-Wilk tests, were employed to analyze the normal distribution characteristics of numerical variables. Student's t-test was used to compare normally distributed variables between two independent groups, while the Mann-Whitney U test was employed for non-normally distributed variables. To identify the independent predictors of HT, univariate and multivariate logistic regression analyses were performed. The odds ratio (OR) and 95% confidence interval (CI) values were utilized to assess any correlations between the patient and control groups across the analyzed variables. Receiver operating characteristic (ROC) curve analysis was then employed to determine the optimal cutoff values for independent variables identified as significant predictors of HT. Statistical significance was defined as a probability (p) value of ≤ 0.05.

Results

The study comprised 142 participants, with the patient group of 80 HT patients and the control group of 62 healthy individuals matched for age and gender. The mean age of the patient group was 43.5±10 years, and that of the control group was 40.9±7 years (p=0.102). Women accounted for 90% of the patient group and 77.4% of the control group. No significant differences were observed between the patient and control groups regarding age and gender (p>0.05). Similarly, there was no significant difference between the patient and control groups in free thyroxine (FT4) levels (1.09±7 ng/dL vs. 1.22±0.35

Table 1. Baseline clinical and laboratory characteristics of the and univariate analysis of the variables.

Study Population			
Variable	Hashimoto thyroiditis (N= 80)	Control (N=62)	P value
Age, years	43.5±10	40.9±7	.102
Sex, female %	90	77.4	.060
Diabetes, %	3.8	3.2	.867
Smoking, %	12	10	.665
Dyslipidemia, %	14	9.2	.334
TSH (uIU/mL)	6.3±8.58	3.5±1	**.011**
Anti TPO (U/mL)	295.4 (22-2417)	NA	
Anti TG (IU/mL)	16.4 (15-1000)	NA	
FT3 (pg/mL)	2.72±0.65	3.05±0.59	**.002**
FT4 (ng/dL)	1.09±7	1.22±0.35	**.179**
C-reactive protein, mg/dL	1.5(0.4-5.6)	0.98(0.3-2.6)	**<.001**
Albumin, g/dL	2.9 (2.1-4.1)	3.3(2.3-4.2)	**<.001**
CAR, ×100	58 (11.5-193.1)	29.5(8.1-72.2)	**<.001**
Hemoglobin, g/dL	12±1.1	12.7±1.76	**.005**
WBC, k/mm^3	9.8±2.4	9.4±2.4	.384
Fasting glucose,mg/dL	101±16	103±15	.411
Total cholesterol, mg/dL	214±50	220±39	.280
LDL cholesterol, mg/dL	140±31	142±34	.758
HDL cholesterol, mg/dL	34±13	35±8	.901
Triglyceride, mg/dL	202±104	175±110	.133
GFR,mL/min	74±18	78±14	.143
BMI (kg/m^2)	28.2±3	26.5±5	.169

TSH: Thyroid stimulating hormone, FT3: free Triiodothyronine, FT4: free Thyroxine, CAR: C-reactive protein to albumin ratio, BMI: body mass index, GFR: glomerular filtration rate, LDL: low-density lipoprotein, HDL: high-density lipoprotein, TGAb; anti-thyroglobulin autoantibody, TPOAb; anti-thyroid peroxidase autoantibody.

Table 2. Univariate and multivariate analysis in patients with Hashimato thyroid (multivariate p value, OR with 95% CI).

	Predictors of patientswith Hashimato thyroid			
	Univariableanalysis		Multivariableanalyzes	
	OR (95% CI)	p	OR (95% CI)	p
C-reactive protein	2.64 (1.62-4.31)	<.001	0.30 (0.009-0.793)	.030
Albumin	0.23 (0.11-0.50)	<.001	0.92 (0.14-5.92)	.093
CAR	1.03 (1.01-1.04)	<.001	1.11(1.38-1.19)	.003
FT3	0.42 (0.23-0.75)	.003	0.31 (0.15-0.64)	.002
Hemoglobin	0.70 (0.55-0.91)	.007	0.64 (0.48-0.87)	.004

Abbreviations: FT3: free Triiodothyronine, CAR: C-reactive protein to albumin ratio; CRP: C-reactive protein.

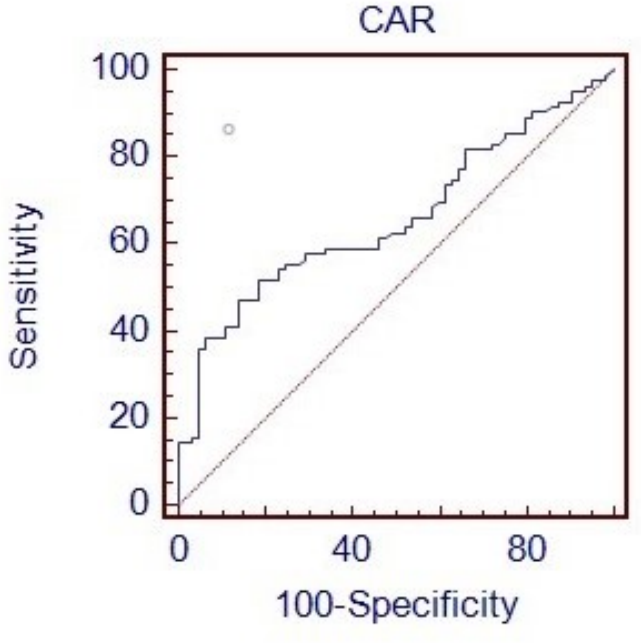

Figure 1. CAR: AUC 0.660(0.577-0.735), P=0.0003 Cut-off value>56. Sensitivity:51.8 Specificity:81.5.

ng/dL, p= 0.179). On the other hand, the free triiodothyronine (FT3) level was significantly lower, and In the control group, the level of thyroid-stimulating hormone (TSH) was significantly lower compared to the control group (2.72±0.65 pg/ml vs. 3.05±0.59 pg/ml, p=0.002; and 6.3±8.58 mIU/L vs. 3.5±1 mIU/L, p=0.011; respectively). Additionally, The patient group exhibited significantly higher levels of CRP and CAR value while displaying significantly lower levels of albumin and hemoglobin compared to the control group [1.5 (0.4-5.6) mg/dL vs. 0.98 (0.3-2.6) mg/dL, p<0.001; 58 (11.5-193.1) vs. 29.5 (8.1-72.2) p<0.001; 2.9 (2.1-4.1) g/dL vs. 3.3 (2.3-4.2) g/dL, p<0.001; and 12±1.1 g/L vs. 12.7±1.760 g/L, p=.005; respectively]. No significant differences were observed between the groups in the other analyzed parameters. (Table 1). Univariate analysis followed by multivariate analysis revealed CAR value (OR: 1.11, 95% CI: 1.38-1.19, p=0.003), CRP (OR: 0.30, 95% CI: 0.009-0.793, p=0.030), FT3 (OR: 0.31, 95% CI: 0.15-0.64, p=0.002) and hemoglobin (OR: 0.64, 95% CI: 0.48-0.87, p=0.004) levels as significant predictors of HT. Albumin (OR: 0.92, 95% CI: 0.14-5.92, p=0.093) level, which was found to be a significant predictor of HT in univariate analysis, was not found to be significant in multivariate analysis (OR: 0.92, 95% CI: 0.14-5.92, p=0.093) (Table 2). ROC curve analysis revealed 56 as the optimum cutoff value of CAR in predicting HT. Accordingly, CAR values >56 predicted HT with a sensitivity of 51.8% and specificity of 81.5% [Area under the curve (AUC): 0.660; 95% CI, 0.577-0.735; p < 0.0003] (Figure 1).

Discussion

This study aimed to showcase the effectiveness of utilizing CAR as an alternative to conventionally used thyroid antibodies in predicting the diagnosis and prognosis of HT. Analyses for this purpose revealed that HT patients had significantly higher CRP levels and CAR values, while albumin and hemoglobin levels were significantly lower than those of healthy control subjects. Multivariate analysis revealed CAR value, CRP, albumin, FT3, and hemoglobin levels as independent predictors of HT. CAR has stood out as a marker that can predict HT more precisely among these markers.

HT is an autoimmune inflammatory disease that presents with the thyroid gland's lymphocytic infiltration and is characterized by infiltration of mononuclear cells, fibrosis of the thyroid tissue, decreased thyroid follicles, enlarged thyroid tissue, and the presence of thyroid autoantibodies of the thyroid gland, i.e., anti-TPO and anti-Tg [17, 18, 19].

CRP and albumin are acute-phase reactants. CRP levels increase, and albumin levels decrease in inflammatory conditions, including infections and autoimmune and rheumatologic diseases [20, 21, 22].

CRP has been associated with autoimmune thyroiditis [23,24] and subclinical hypothyroidism [25]. However, a comprehensive literature review uncovered no studies investigating the relationship between CAR and HT.

CAR, which combines CRP and albumin, has recently been used as a novel inflammation marker in infections, malignancies, and autoimmune conditions [26, 27]. Kamal et al. investigated the relationship between CAR and Behçet's disease and found that CAR levels were related to disease activation [28]. In another study, Bozkurt et al. reported that CAR was significantly higher in patients with uveitis attacks, an inflammatory condition such as HT, than in healthy volunteers [29]. Similarly, we have demonstrated that CAR is an easily measurable, reliable, and cost-effective marker of HT that can be used as an alternative to conventional thyroid antibodies in primary care centers.

Literature data suggest that increased CAR levels due to increased inflammatory load may be an important marker for inflammatory and autoimmune conditions. Sayar et al. used CAR as a non-invasive, easy, and objective marker for ulcerative colitis, a chronic and idiopathic disease, as well as an inflammatory condition such as HT [30]. In a study investigating the relationship between CAR levels

and mortality in three critically ill patients with coronary artery thrombosis, Park et al. found that increased CAR levels were associated with higher mortality rates [31].

CAR is an independent marker for the prognosis of systemic inflammation in patients with infections, malignancies, and autoimmune and rheumatological diseases [18, 26, 27]. One study reported that CAR was an effective marker for predicting Takayasu's arteritis, a disease with a similar pathophysiology to HT [29]. In the mentioned study, as in our study, CAR levels were significantly higher in patients with Takayasu's arteritis compared to healthy controls. This study's findings, taken together with the relevant findings reported in the literature data, suggest that the CAR level results from serious inflammatory burden. The findings of the aforementioned studies on the relationship between CAR levels and inflammatory conditions such as ulcerative colitis, Takayasu's arteritis, Behcet's disease, and coronary artery diseases with thrombus support our findings.

An important aspect of this study is its pioneering investigation into the correlation between CAR and HT, marking it as the inaugural research endeavor in this Area. Nevertheless, the study had several limitations, notably its relatively small sample size and the lack of histopathological results.

Conclusion

This study's findings indicated that CAR is an easily measurable, reliable, and cost-effective marker of HT that can be used as an alternative to conventional thyroid antibodies in primary care centers. Further studies are needed to corroborate this study's findings and establish the use of CAR as a marker for inflammatory and autoimmune conditions in clinical practice.

Ethical approval

Ethical approval was received for this study from Recep Tayyip Erdoğan University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (Decision no: 2022/98).

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