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2018 Adana

THE RELATIONSHIP BETWEEN HYPOTHYROIDISM-INDUCED AUTOANTIBODIES, TSH LEVELS, AND RDW, AS AN INFLAMMATION MARKER

Kemal Aygun[1], Ozden Gokdemir[2], Ali Riza Sisman[3], Tevfik Demir[4]

1. *İzmir Provincial Health Directorate, Atatürk Education and Research Hospital, İzmir, Türkiye*
2. *İzmir University of Economics, Faculty of Medicine, İzmir, Türkiye*
3. *Dokuz Eylul University, Faculty of Medicine, Department of Medical Biochemistry, İzmir, Türkiye*
4. *Dokuz Eylul University, Faculty of Medicine, Department of Internal Medicine Endocrinology and Metabolic Diseases, İzmir, Türkiye*

Abstract

Aim: Serum RDW grades were detected in patients with Hashimoto's thyroiditis. We aimed to use RDW to detect increased cardiovascular events in patients, increased oxidative stress, and inflammation without the need for an additional cost.

Methods: We collected 904 persons results, 462 patients which have Hashimoto's thyroiditis, and 442 age and sex-matched control cases were comprised in our study. From the laboratory measurements of the patients' records were utilized such as hemogram, hs-CRP, fasting blood glucose, insulin, C-peptide, kidney function tests, liver function tests (ALT, AST), serum lipids (total cholesterol, triglyceride, HDL, LDL), anti-Tg, and anti-TPO, FT3, FT4, TSH levels.

Results: RDW was considerably scaled up in case group compared to control group (Hashimoto's thyroiditis =10.08 ± 4.48%, control = 8.95 ± 6.68%, $p < 0.05$). Also, MPV was increased in the study group($p<0.05$). hs-CRP showed a statistically significant positive correlation between the level of RDW.

Conclusions: Although the exact mechanism is still not fully understood, increased RDW levels in individuals with Hashimoto's thyroiditis, possibly related to ongoing subclinical inflammation, neurohumoral activation, and changes resulting from oxidative stress in such patients.

RDW is potentially a valuable tool for assessing cardiovascular diseases among patients diagnosed with Hashimoto's thyroiditis.

Keywords: *RDW, Hashimoto's thyroiditis, MPV, inflammation, hs-CRP, thyroid auto antibodies*

Corresponding Author: Ozden Gokdemir, e-mail: ozden.gokdemir@ieu.edu.tr

Received: 28.11.2022, Accepted: 12.01.2023, Available Online Date: 13.03.2023

Cite this article as: Aygun K, Gokdemir O, Sisman AR, Demir T. The Relationship Between Hypothyroidism-Induced Autoantibodies, TSH Levels, and RDW, as an Inflammation Marker. J Cukurova Anesth Surg. 2023;6(1):56- 66.

doi: 10.36516/jocass.1210920

Introduction

Thyroid hormones have a significant role in the progress of atherosclerotic cardiovascular disease. Subclinical hypothyroidism and hypothyroidism accelerate atherogenesis. Subclinical hypothyroidism is an independent risk factor for cardiovascular illness. Additively, Hashimoto's thyroiditis is a risk factor for cardiovascular illness unincorporated of thyroid hormones [1]. Hashimoto's thyroiditis is the most common autoimmune disease, characterized by lymphocytic infiltration of thyroid tissue. Although its prevalence varies, approximately 15-20% of the population in any society has Hashimoto's thyroiditis. This is a more prevalent problem in women. In areas where iodine is not deficient, autoimmune thyroiditis is the most frequent cause of hypothyroidism [2]. The immunological diagnosis of Hashimoto thyroiditis is made by detecting anti-thyroid peroxidase (anti TPO) and anti-thyroglobulin (anti Tg) antibodies in serum by various methods. Anti-thyroid peroxidase (Anti TPO) antibody is the most appropriate laboratory test. Autoimmune thyroiditis includes a broad spectrum, ranging from Hashimoto's disease (with goiter) to atrophic lymphocytic thyroiditis (without goiter). These diseases differ in the types of antithyroid antibodies produced [3]. Many genetic and environmental parameters founded in etiology of Hashimoto's thyroiditis, caused by T cell-mediated autoimmunity [4]. Pathologically, the disease is characterized by infiltration of lymphocytes, plasma cells and, more rarely, multinuclear giant cells of the thyroid gland [5]. In USG, reduction in thyroid echogenicity and pseudonodules are observed in Hashimoto's thyroiditis [6]. Immunological diagnosis of Hashimoto's thyroiditis involves using various methods to detect anti TPO and anti Tg antibodies in serum. Antithyroid peroxidase (Anti TPO) antibody is the most appropriate laboratory test. However, antithyroid antibodies with low titers can be found in other thyroid diseases, and even in normal individuals. Initial needle aspiration biopsy, although not routinely required for diagnosis, supports diagnosis in patients with negative antibodies. It is also necessary to rule out malignancy in patients with a single nodule [7]. As in all autoimmune diseases, there is harmful interaction of internal (genetic) and external (environmental) factors in the formation of Hashimoto's thyroiditis [6].

Red cell distribution width (RDW) is a parameter usually found in routinely measured complete blood count and indicates the heterogeneity in the size of circulating erythrocytes. High RDW level indicates an increased change in erythrocyte volume. RDW is the expression of the erythrocyte volume as a percentage, when divided by the mean corpuscular volume (MCV). RDW is classically used in the differential diagnosis of anemia [8]. Thyroid hormones increase the erythropoietic activity of the bone marrow and the serum erythropoietin level and the amount of erythrocyte 2,3 diphosphoglycerate and facilitates oxygen delivery to the tissues. In hyperthyroidism, bone marrow activity increases and erythrocytosis. It can be seen that anemia is common in hypothyroidism. In hypothyroidism, due to decreased iron absorption, microcytic, B12 and Folate malabsorption may cause macrocytic or normocytic anemia. However, in recent studies, it has been determined that RDW height is associated with increased cardiovascular disease[9-11]. In cardiovascular diseases, peripheral artery disease, acute heart failure and chronic heart failure, increased RDW level has been found to be associated with mortality and morbidity[12,13]. Although the relationship between cardiovascular events and high RDW has been demonstrated in many studies, there is no clear understanding of the physiopathological mechanism of this relationship. However, it is thought that chronic inflammation may cause an elevated RDW in cardiovascular diseases. Hashimoto's thyroiditis progresses with a low degree of systemic inflammation, and this inflammation accelerates the progression of atherosclerosis[14-16]. Hs-CRP is a very important marker in evaluating chronic inflammation [12]. In a cohort

study handeled by Veeranne et al., the predictive value of RDW in terms of cardiovascular mortality was found to be stronger than hs-CRP [13]. In another study examining the relationship between RDW and microalbuminuria, which is an independent predictor of cardiovascular events, high RDW level was found to be associated with microalbuminuria as an independent variable [14]. Despite a lack of understanding of the exact mechanism, RDW has recently been used as an indicator of chronic inflammation, oxidative stress and cardiovascular diseases[9,20].

As the thyroid hormones are important regulators of the CVS, and T3 nuclear receptor after binding to proteins, it mediates the expression of several important cardiac genes. It also transcribes alpha myosin heavy chain and sarcoplasmic reticulum ATPase gene. While increasing beta myosin heavy chain and decreases the transcription of the phospholamban gene. In hyperthyroidism, cardiac contractility and cardiac output increase, cardiac hypertrophy develops, systemic vascular resistance decreases, and there is an increased frequency of supraventricular tachyarrhythmia, similar to atrial fibrillation. The visa vera situation is also correct (in hypothyroidism, the opposite is the case) [15].

It is not recommended to use routine evaluation for checking. If chronic lymphocytic thyroiditis is suspected in a patient with high TSH levels, anti TPO and anti Tg are important in the diagnosis. These autoantibodies are positive in 95-100% of Hashimoto's thyroiditis. Anti TPO is the most determinant antibody that can predict the development of hypothyroidism. The risk of developing explicit hypothyroidism in a person with subclinical hypothyroidism and antibody positivity is approximately 4% per year [16].

This study involves a retrospective examination of the RDW levels of patients with Hashimoto's thyroiditis and without (control group). The hypothesis is that RDW level, used as an indicator of chronic inflammation, oxidative stress, and cardiovascular events, is high in patients with Hashimoto. If, as in our hypothesis, RDW level is found to be high in patients with Hashimoto, RDW level can be used as an indicator of increased cardiovascular risks, increased oxidative stress and inflammation in this group of patients, avoiding the need for additional cost or testing.

Dokuz Eylül University Ethical Committee has approved the study (2013/44-09).

Materials and Methods

Study design and participants

The universe of the study was the 3788 patients in endocrinology outpatient clinics. The study sample were patients with Hashimoto's thyroiditis who applied to Dokuz Eylül University Endocrinology Outpatient Clinic between 2013-2014, and the control group, those without. By searching over admission logs from the available medical records, patients were identified. Data were retrieved from regional servers by qualified research physician. Data on pre-existing comorbidities, laboratory values, complications, treatments were collected. According to this retrospective evaluation, there were a total of 904 patients, 462 of whom were diagnosed with Hashimoto's thyroiditis, and 442 of whom were in the control group.

1. Inclusion criteria:

• Being over 18 years old,

• Patients whose hemogram, anti-T, anti-M, FT3, FT4, TSH were checked.

• Patients who are anti-Tg and / or anti-TPO positive will be considered Hashimoto thyroiditis, and those negative for both thyroid autoantibodies were included in the study as a control group.

2. Exclusion criteria:

• Patients with acute and chronic renal and hepatic insufficiency.

• Patients with liver or kidney transplantation.

Patients with a history of cancer,

Patients with anemia, female haemoglobin value <12 mg / dL, male haemoglobin value <13 mg / Dl

3.Parameters Used During Evaluation and Monitoring:

In our retrospective study, the following patient data were monitored: the demographic

characteristics (age, gender), detailed disease history, history, blood pressure, waist circumference, weight, and height. From the patients' laboratory measurements, records were made of hemogram, all sub-parameters of hemogram, hs-CRP, fasting blood glucose (FBG), insulin, C-peptide, kidney function tests (BUN, creatinine), liver function tests (ALT, AST), serum lipids (total cholesterol, triglyceride, HDL, LDL), anti-Tg, and anti-TPO, FT3, FT4, TSH levels.

Statistical analysis

The Kolmogorov-Smirnov test was employed to examine whether continuous variables adhered to the normal distribution. If two independent groups of variables had a normal distribution, the student's t test was used to compare them; otherwise, the Mann Whitney U Test was applied. Chi-square analysis was used to determine whether categorical variables were related. As descriptive statistics, frequency, percentage, and mean std, deviation values are provided. The statistical analysis was performed using the SPSS for Windows version 22.0 package program, and $p < 0.05$ was considered statistically significant.The relationship between numerical variables was tested with the Pearson correlation coefficient.

Results

The study included 904 people, 462 with Hashimoto's thyroiditis, with a mean age of 34.45 ± 8.43 years, and 442 without Hashimoto's thyroiditis, mean age 33.79 ± 9.97. The demographic and laboratory data of the participants with and without Hashimoto's thyroiditis are characterized in Table 1.

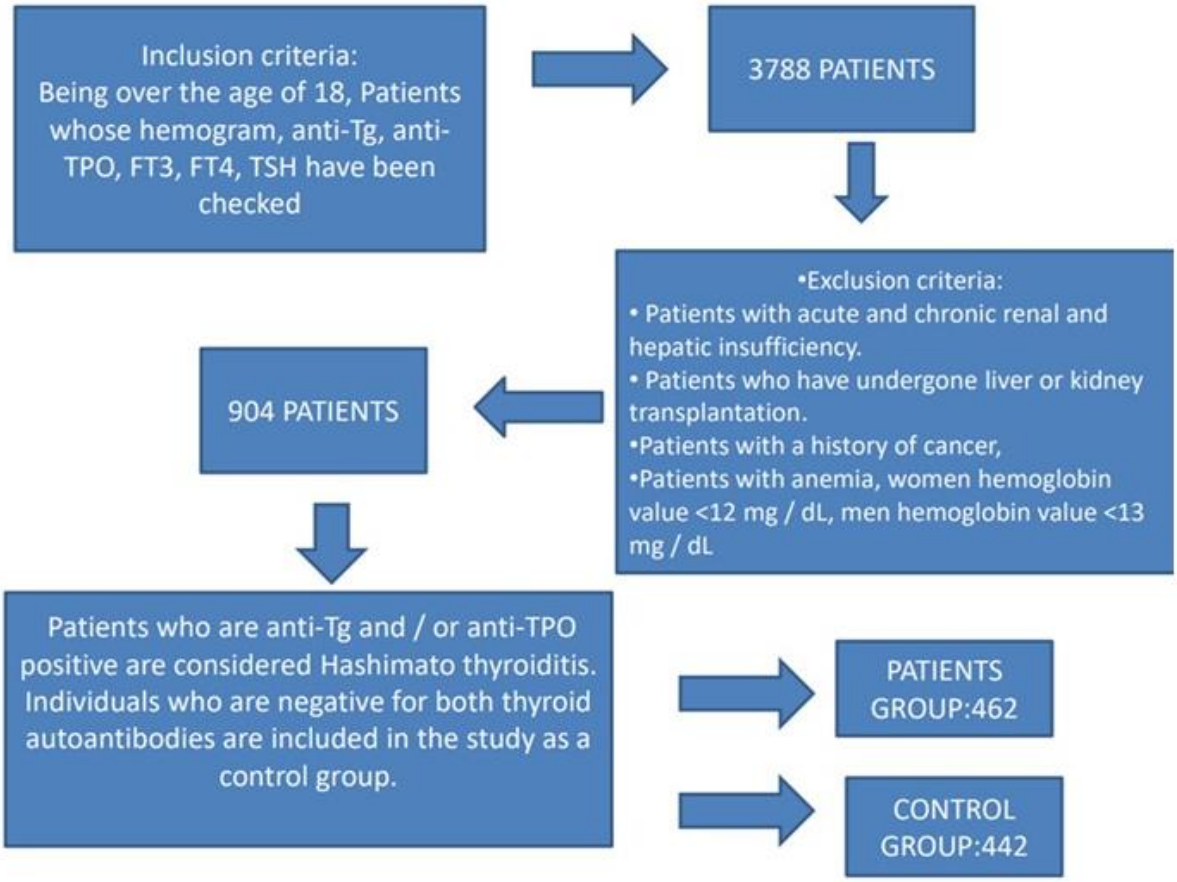

Figure 1. Flowchart

Table 1. Comparison of demographic and laboratory data of individuals with and without Hashimoto's thyroiditis

Demographic and laboratory data	Hashimoto's thyroiditis Group n=462	Control Group n=442	*P*[a]
Age (year)	34.45 ± 8.43	33.79 ± 9.97	0.304
Gender (Female)	399, % 86.1	385, % 87.1	0.585
Fasting Glucose (mg/dL)	85.13 ± 9.89	85.71 ± 12.08	0.462
Creatinine (mg/Dl)	0.74 ± 0.37	0.73 ± 0.13	0.966
BUN (mg/dL)	12.47 ± 7.93	11.66 ± 3.36	0.075
ALT (u/L)	20.74 ± 14.11	20.40 ± 12.24	0.701
Total cholesterol, (mg/dL)	209.93 ± 40.83	200.10 ± 44.37	0.002*
HDL (mg/dL)	54.88 ± 13.69	56.67 ± 13.02	0.067
LDL (mg/dL)	130.12 ± 35.07	122.89 ± 37.93	0.007*
Triglyceride (mg/dL)	123.72 ± 89.60	105.86 ± 65.86	0.002*
TSH (µIU/mL)	3.80 ± 1.34	1.76 ± 1.13	0.003*
Free T4 (ng/dL)	1.02 ± 0.31	1.87 ± 0.68	0.040*
Free T3 (pg/mL)	3.02 ± 0.80	5.41 ± 1.91	0.072
Anti-TPO (IU/mL)	376.24 ± 351.41	2.04 ± 5.09	-
Anti-TG (IU/mL)	143.57 ± 372.55	2.15 ± 5.01	-
WBC (µL)	7.07 ± 1.75	6.97 ± 1.73	0.373
Hgb (g/dL)	13.46 ± 0.99	13.47 ± 0.98	0.913
Htc (%)	40.41 ± 3.42	40.09 ± 4.20	0.205
RBC (µL)	4.62 ± 0.37	4.58 ± 0.36	0.091
MCV (fl)	87.36 ± 5.30	87.59 ± 7.51	0.589
PLT (µL)	252.39 ± 49.72	248.33 ± 53.67	0.239
MPV (fL)	10.51 ± 1.12	9.57 ± 0.72	0.013*
RDW (%)	10.08 ± 4.48	8.95 ± 6.68	0.003*
PTC (%)	0.31 ± 0.37	0.27 ± 0.14	0.024*

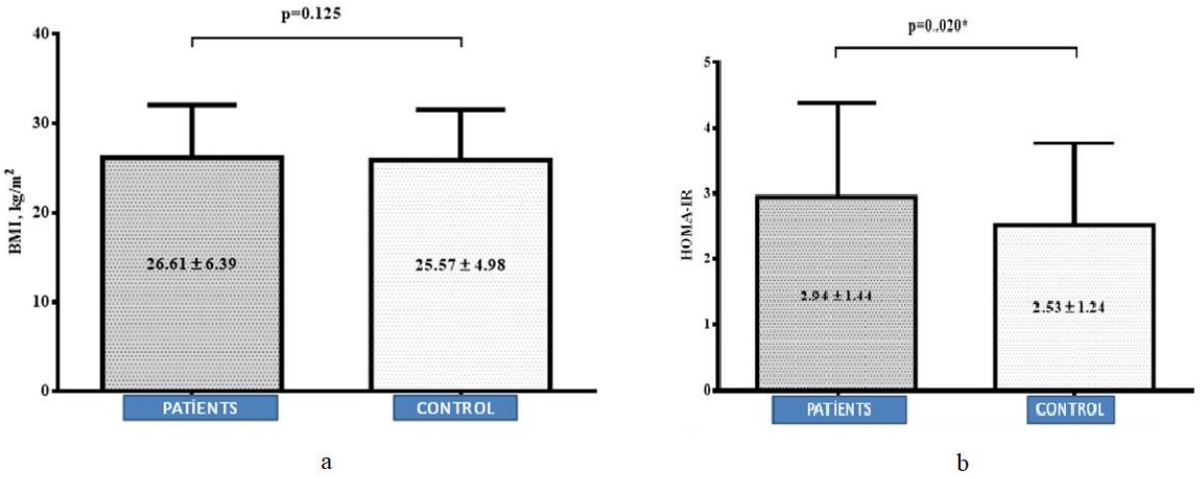

Figure 2a. Comparison of BMI between two groups
2b. Comparison of HOMA-IR between two groups

Age and gender also do not statistically differ significantly from one another. In terms of PLT, Hgb, HTC, RBC, and MCV, there was no statistically significant difference between the two groups (p> 0.05). Regarding the levels of serum urea, creatinine, and ALT, there was no discernible difference between the two groups (p> 0.05). Comparing the two groups' serum RDW levels revealed that the patient group's RDW level was statistically significantly higher than the control group's (Hashimoto's thyroiditis = 10.08 ± 4.48%, control = 8.95 ± 6.68%, p <0.05).

The serum ALT and MPV levels did not significantly differ from one another (p <0.05). It was found to be 10.51 ± 1.12 in the patient group, and 9.57 ± 0.72 in the control group.

Serum total cholesterol, triglyceride, and TSH levels were found to be statistically significantly higher in patients with Hashimoto's thyroiditis, while FT3 and FT4 levels were observed to be statistically significantly lower. (Table 1)

Using an independent variables t test to compare the BMI levels of 177 Hashimoto's thyroiditis patients and 177 controls, it was found that there wasn't significant difference among the two groups. (Figure 2a)

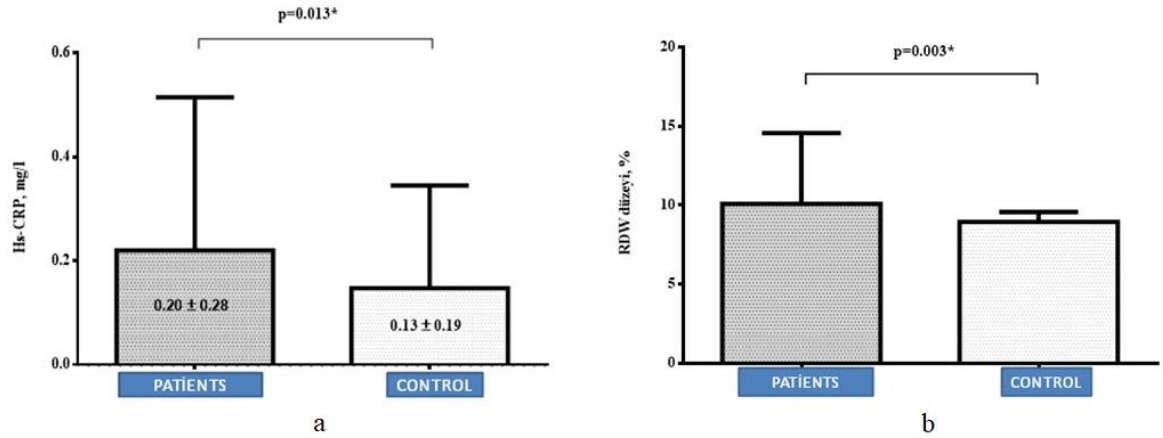

Figure 3a. Comparison of Hs-CRP between two groups
3b. Comparison of RDW between two groups

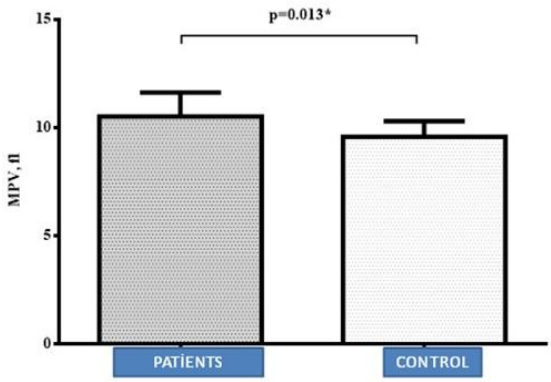

Figure 4. Comparison of MPV between two groups

Independent variables were used to compare the HOMA-IR levels of 177 patients with Hashimoto's thyroiditis and 177 controls. The t test revealed a statistically significant difference between the two groups (p = 0.02). (Figure 2b)

Between HOMA-IR and RDW level, a statistically significant positive correlation was observed (r = 0.265, p = 0.003 *).

Results are compared of hs-CRP levels between 177 Hashimoto's thyroiditis patients and 177 individuals in the control group using independent variables A significant difference between the two groups was shown by the t test. (p = 0.013). (Figure 3a)

It was found that the patient group's serum RDW level was statistically significantly higher. (p = 0.003) (Figure 3b)

The patient group's serum MPV level was found to be statistically significantly higher (p = 0.003). A statistically significant positive correlation was found between Hs-CRP and RDW level. (r = 0.344, p <0.001 *) (Figure 4)

The following pairs of variables did not have a statistically significant relationship with one another: anti-TPO, anti-thyroglobulin, total cholesterol and LDL and RDW levels, triglyceride and HDL and RDW levels.

Discussion

In contrast to the control group, patients with Hashimoto's thyroiditis had higher RDW levels, according to our study. Additionally, we discovered that while serum HDL cholesterol levels, FT3 and FT4 levels were found to be statistically significantly lower in patients with Hashimoto's thyroiditis, MPV, PTC serum total cholesterol, triglyceride, and TSH levels were statistically significantly higher.

Red cell distribution width (RDW) is a parameter usually found in routinely measured complete blood count and indicates the heterogeneity in the size of circulating erythrocytes.

Although the exact mechanism is still not fully understood, RDW has recently been used as an indicator of chronic inflammation, oxidative stress, and cardiovascular diseases[9,17]. There are three known reasons why RDW may be elevated in an inflammatory environment. First, the impairment of erythrocyte maturation caused by the desensitization of inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and interleukin-6 (IL-6) against erythrocyte progenitors, second, the entry of juvenile erythrocytes into the circulation, and finally, the formation of anisocytosis [17]. Oxidative stress is known to both predispose to hemolysis and shorten erythrocyte survival [18]. Another factor that increases RDW is anisocytosis resulting from neurohumoral activation [19]. Thyroid stimulating hormone (TSH) can also accelerate atherosclerosis when it is above the upper limit of the reference range[26-28]. In addition, Hashimoto's thyroiditis is a risk factor for cardiovascular disease independent of thyroid hormones[1,29]. In our study, we found that RDW increased in accordance with the literature.

In the study by Aktas G. et al. on Hashimoto's thyroiditis, RDW was found to be lower in the control group. (p = 0.015) This study consisted of 102 patients, (85 females), and a control group of 63, (55 females). There were no difference between the groups for age and gender. In our study, in addition to RDW, significant results were obtained with TSH and FT4; TSH level was higher and FT4 level was lower [22].

In Chang et al.'s meta-analysis of 22 studies involving 80,216 coronary patients, a correlation was found between increased RDW and mortality due to increased coronary artery disease. Furthermore, this research revealed a statistically significant relationship between RDW and BNP levels in which RDW and serum BNP levels were examined in heart failure patients diagnosed with diabetes. RDW levels were found to be higher among heart failure patients diagnosed with diabetes than those without [23]. Bremmer et al. reported the negative correlation of serum T4 levels with RDW [24], while Montagnana et al. showed a positive correlation between serum TSH levels and RDW [25].

RDW, CRP, and ESR were observed to be significantly higher in the patient group compared to controls in another retrospective study that included 165 patients with inflammatory bowel disease ($p < 0.05$) [26].

Between BMI glucose and RDW level, a statistically significant positive correlation was found in this study ($r = 0.320$, $p < 0.001$ *). Yudkin et al., revealed that CRP had a positive relationship with insulin resistance parameters and triglycerides, and a negative relationship with HDL [27]. In our study, we found higher MPV in the patient group. Carlioglu et al. performed a study on BMI with 51 patients diagnosed with Hashimoto's thyroiditis who were euthyroid, and 51 age-matched people in a control group. In the analysis, MPV level was found to be high in the patient group. There was no significant difference in TSH, FT3, FT4 levels, and a positive correlation was found between both thyroid autoantibodies and MPV [28]. Many studies yield similar results. In Jabeen et all's study on diabetic patients, MPV and hsCRP values were found to be significantly higher in diabetics than the control group [29]. An increase in MPV has been shown in diseases such as DM, acute coronary syndrome, stroke, and hypercholesterolemia[38-40]. It has also been suggested that MPV may have an acute phase reactant that correlates with disease activity in rheumatological diseases, such as rheumatoid arthritis and ankylosing spondylitis [31].

Recently, subclinical hypothyroidism has become considered as a risk factor for cardiovascular diseases, due to the patients' changing lipid profile. In these patients and those with similar conditions, the level of serum total cholesterol is thought to be associated to an increase in LDL cholesterol and a decline in HDL cholesterol [32]. In this study, the group with Hashimoto's thyroiditis had significantly higher levels of total cholesterol, LDL, and triglycerides. In the Rotterdam study, it was found that elderly women's subclinical hypothyroidism played a significant role in the occurrence of atherosclerosis and myocardial infarction [20]. Increased RDW level has been found to be associated with mortality and morbidity in cardiovascular diseases, peripheral artery disease, acute heart failure and chronic heart failure[12,13]. In the NHANES study, conducted between 1988-1994, Perlstein et al. revealed the relationship between RDW and death from all causes, CVD, cancer and lower respiratory tract diseases in 15852 participants [33].

According to Karkoutly et all, hypothyroidism affected hematologic parameters more frequently among women patients, as also reported in our study, this study involved 84 cases [34]. Ahmed and Mohammed reported that, there were 3 groups (control, hypothyroidism, hyperthyroidism) and it was revealed that while thyroid pathologies affected women more than men, the root reason of anemia should be sought, and thyroid pathologies also could be considered [35]. Even low PLT levels could be a predictor for the follow-up of thyroid papillary cancer [36]. Mwafy et all recommend lifestyle modifications not only for the prevention of noncommunicable diseases such as morbid obesity, but also thyroid pathologies, based on laboratory findings of their 94 obese patients [37]. Although Wang et all named their article as "*There is no obvious relationship between red blood cell distribution width and thyroid function.*", in conclusion, among their 8424 male and 5198 female

participants, they reported that “anicocysotis” is crucial. The age and gender difference in RDW have been reported in many studies. The increased anisocytosis and the grade inflammation should also be evaluated as this is a key factor, also for cancers [38]. The potential important point is oxidative stress, which should be carefully noted [39].

As there is a correlation of disease severity with hematology parameters in COVID-19 diagnosed patients, whether diabetics or not[49,50], RDW also could be a predictor for CVS risk. The physiological mechanism between increased mortality and high RDW levels in terms of cardiovascular mortality is not known in detail. Besides, oxidative stress, inflammation, poor pulmonary function has been shown indirectly in other studies, these are not fully understood. Autoimmune diseases and/or infectious diseases such as COVID could also attack CVS. Early recognition of severe diseases is crucial for the optimal use of limited resources.

Conclusion

In this study, the increased RDW level in individuals with Hashimoto’s thyroiditis. This may be related to ongoing subclinical inflammation, neurohumoral activation and changes resulting from oxidative stress in such patients. Also, a correlation was found between increased RDW level and CRP. A positive relationship was found between BMI and RDW.

These results, if confirmed by future studies, suggest that RDW, a parameter of the complete blood count performed as a routine examination as an inflammation marker, may be considered as a parameter to be used in follow-up in patients with Hashimoto’s thyroiditis. In this group of patients, RDW level can be used as a marker of increased cardiovascular event, and increased oxidative stress and inflammation, avoiding the need for additional cost or testing.

The results of our retrospective study, we believe, underline the need for larger-scale prospective studies that can shed further light on Hashimoto's thyroiditis in this regard. A low-cost, “sustainable indicator” could be used to manage patients’ risks, and RDW is one of these parameters for determining risk level, along with BMI, CRP, and other predictors.

Strength of the study

When the literature is evaluated, studies on RDW, although frequent, focused less frequently on the Hashimoto thyroiditis and RDW, and include a small number of participants and/or patients.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Ethical Approval
Dokuz Eylül University Ethical Committee has approved the study (2013/44-09).
During the ethics committee application, the Declaration of Helsinki was approved by all authors.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of Data and Materials
Data available on request from the authors.

Acknowledgement
We would like to thank Simon Edward Mumford, MSc. TESOL, Writing Centre Advisor at the Izmir University of Economics for his great contribution in editing the language of the manuscript.

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