Red Blood Cell Distribution Width is a Reliable Marker of Inflammation in Plaque Psoriasis

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ABSTRACT Psoriasis is a systemic inflammatory disease accepted as an independent risk factor for cardiovascular diseases (CVD). Elevated levels and correlation of red cell distribution width (RDW) with inflammatory markers has recently been shown in studies investigating CVD risk and prognosis in rheumatoid arthritis and ankylosing spondylitis. The aim of this study was to evaluate levels and correlation of RDW with inflammatory markers in patients with plaque psoriasis. Data including demographics, disease severity indices, laboratory parameters, and bioelectrical impedance analysis was collected from medical charts of patients who were diagnosed with plaque psoriasis at the Hacettepe University Department of Dermatology between March 2014 and August 2015. Patients were evaluated for major CVD risk factors defined by international guidelines. 199 patients with psoriasis and 73 volunteers were included. Patients had statistically significant higher values of metabolic age, visceral fat rating, body-mass index (BMI), red blood cells (RBC), white blood cells (WBC), red blood cell distribution width (RDW), alanine aminotransferase (ALT), uric acid, low-density lipoprotein (LDL), and C-reactive protein (CRP) (p=0.044, p=0.047,p=0.029, p= 0.005, p=0.02, p<0,01, p=0.001, p=0,016, p=0,014, p<0.01). A statistically significant relationship and positive correlation between RDW and CRP levels was found in the patient group (p=0.01, r=0.396). Patients without major CVD risk factors (n=79) had significantly higher values of RDW, LDL, and CRP (p=0.01, p=0.031, p=0.03, respectively). Patients with psoriasis who had one or more CVD risk factors (n=120) had significantly higher values of BMI, RDW, thrombocytes, ALT, and CRP (p=0.038, p=0.01, p=0.017, *p*=0.02, p=0.01, respectively). RDW, which is elevated as well as CRP, reflects the systemic inflammatory burden and can be used for prediction of CVD in psoriasis. In fact, patients with psoriasis who do not have any major CVD risk factors still have high levels of CRP and RDW, supporting the hypothesis that psoriatic inflammation itself can simultaneously cause CRP and RDW elevation. Coexistence of CVD risk factors is associated with ALT elevation since additional CVD risk factors may predict psoriatic comorbidities such as nonalcoholic fatty liver disease.

KEY WORDS: red cell distribution width, C-reactive protein, psoriasis, cardiovascular disease

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INTRODUCTION

Psoriasis is an immunologically mediated, chronic, recurrent, systemic inflammatory skin disease (1). Cardiovascular diseases (CVD) are one of the most important comorbidities of psoriasis (1-5). Psoriatic inflammation leads to development of CVD (2,4-6). In fact, psoriasis has been shown to be an independent risk factor for CVD (5,6). The increased incidence of CVD in psoriasis is caused by underlying systemic inflammation together with increased incidence of traditional CVD risk factors, which are frequently found in patients with psoriasis (2-6).

The red cell distribution width (RDW) is a coefficient and shows the variation between erythrocyte corpuscle volumes calculated as standard deviation (SD) of red blood cell (RBC) volume/mean corpuscular volume (MCV) ×100 (normal range: 11.5-14.5%) (7). Increased RDW is claimed to indicate CVD risk and prognosis. Elevated levels of RDW and the correlation with inflammatory markers have recently been demonstrated in studies investigating CVD and other chronic inflammatory diseases such as rheumatoid arthritis and ankylosing spondylitis (7-9). The increase in RDW, i.e. the increase in the difference among the sizes of RBC, is suggested as a consequence of the inflammatory effects of circulating cytokines that modulate erythropoiesis (10-12). Inflammation impairs erythroid cell maturation and reduces erythrocyte circulatory half-life (13,14). Iron metabolism is proven to be influenced by inflammatory cytokines (15). Furthermore, downregulation of erythropoietin receptor expression and altered erythropoietin secretion is caused by systemic inflammation (12-16). Moreover, interleukin 6 (IL-6) and interferon alfa (IFN-α), which are also known to increase and play key roles in the etiopathogenesis of psoriasis, have also been shown to be associated with RDW (13,14,16)

Therefore, the aim of this study was to evaluate the levels and correlation of RDW with inflammatory markers in patients with plaque psoriasis. RDW levels and other markers of inflammation were also evaluated according to the presence of CVD risk factors. We hypothesized that the burden of psoriatic inflammation can be reflected in elevated RDW levels.

PATIENTS AND METHODS

Study population

Data was collected from medical charts of patients who were on follow-up for plaque psoriasis at Hacettepe University Department of Dermatology between March 2014 and August 2015. Inclusion criteria for the study consisted the following: 1) existence of moderate to severe plaque psoriasis; 2) absence of any topical treatment for the past month and any systemic treatment for 3 months prior to evaluation for the study; 3) hemoglobin levels higher than >13.6 g/dL, mean corpuscular hemoglobin (MCH) levels higher than 29.3 pg/cell, and mean corpuscular hemoglobin concentration (MCHC) levels higher than 33.6 g/dL, confirming absence of anemia.

Patients and methods

Severity of psoriasis was determined by the psoriasis area severity index (PASI) score and body surface area (BSA) involvement. Patients with a PASI score of 5-10 and a BSA between 5-10% were classified as having moderate psoriasis, while those with a PASI score higher than 10 and BSA >10% were classified as severe psoriasis. Patients were evaluated for major CVD risk factors defined by international guidelines. Hypercholesterolemia and dyslipidemia were defined as total cholesterol 240 mg/dL or greater, low-density lipoprotein (LDL) cholesterol 160 mg/dL or greater, or high-density lipoprotein (HDL) cholesterol less than 40 mg/dL (for persons with and without diabetes) or receiving cholesterol-lowering medication. Hypertension was defined as systolic blood pressure 140 mmHg or greater, diastolic blood pressure 90 mmHg or greater, or receiving antihypertensive medication. Obesity was defined as a body-mass index (BMI) of 30.0 or greater. Diabetes mellitus was defined as fasting plasma glucose 126 mg/dL or greater, 2-hour-post load plasma glucose 200 mg/dL or greater, hemoglobin A1c (HbA1c) 6.5% or greater, or use of antihyperglycemic medications. Smoking was defined as currently smoking cigarettes. Prevalent CVD was defined as a self-reported history of myocardial infarction, coronary bypass surgery, balloon angioplasty, or stent placement in coronary arteries. Prevalence of stroke was ascertained from self-reported history of stroke. Weight, height, waist circumference, BMI, and body composition parameters including fat %, fat mass, fat-free mass, muscle mass, total body water (tbw), tbw %, bone mass, basal metabolic rate (BMR), visceral fat rating, ideal body weight, and degree of obesity were assessed by bioelectrical impedance analysis (Tanita body composition analyzer SC-33OST). Laboratory examinations consisted of total blood count (RBC, hemoglobin, hematocrit levels, MCV, MCH, MCHC, RDW, white blood cell (WBC), lymphocyte, monocyte, neutrophil, eosinophil, basophil, thrombocyte, MPV, neutrophil/lymphocyte ratio (NLR)) biochemistry (ALT, AST, ALP, GGT, BUN, creatinine, uric acid), fasting glucose, serum fasting lipid profile (total cholesterol, LDL, VLDL, triglyceride, HDL), folic acid, vitamin B12, homocysteine, and C-reactive protein. An age and sex-matched control group was chosen from patients

without a chronic inflammatory disease who were admitted to dermatology outpatient clinic for diagnoses such as contact dermatitis, superficial cutaneous fungal infections, and xerosis.

Statistical analysis

The t-test was used for continuous variables with normal distribution, and the Mann-Whitney U test was used for continuous variables without normal distribution. The chi-square test was used for categorical variables. Pearson correlation analysis was used to assess the relationships. A *P* value <0.05 was accepted as statistically significant.

RESULTS

A total of 199 patients with moderate to severe psoriasis and 73 volunteers for the control group were enrolled in the study. The mean age of the patient group was 43.62±14.27 (mean ± SD, while the mean age of the control group was 44.93±14.34. There was no statistically significant difference among the two groups according to their age (*P*=0.502). Of the total patients, 82 (41%) were women and 117 (59%) were men, while 28 (%38) of the controls were women and 45 (62%) were men; there was no statistically significant difference between the patient and control group according to sex (p=0.671). No major CVD risk factors were found in n=64 (32%) of patients and n=24 (33%) of the controls. There was no statistically significant difference between the patient and control group regarding to the presence of major CVD risk factors and the number of CVD risk factors they had (*P*=0.952, *P*=0.280, respectively).

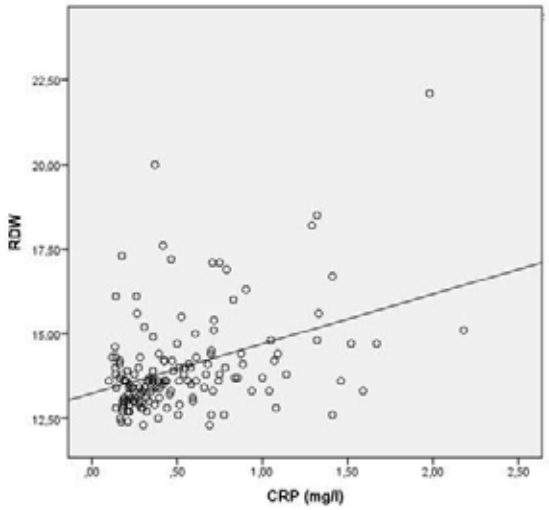

Figure 1. Positive correlation between red cell distribution width (RDW) and C-reactive protein (CRP) levels in patients with psoriasis.

*A statistically significant relationship and a positive correlation between RDW values and CRP levels was found win patients with psoriasis (**p=0.01, r=0.396**).

The body composition parameters, consisting of weight, fat percentage, fat mass, fat-free mass, muscle mass, tbw, tbw percentage, BMR, and obesity degree percentage revealed no statistically significant difference between the patient and control groups respectively (p=0.470, p=0.508, p=0.502, p=0.450, p=0.354, p=0.364, p=0.431, p=0.502, p=0.410, respectively). However, the patient group had statistically significant higher values of metabolic age, visceral fat rating, and BMI than the control group (P=0.044, P=0.047, P=0.029, respectively).

Comparisons of laboratory parameters of the patient and control groups revealed that patients had statistically significant higher levels of RBC, WBC, RDW, ALT, uric acid, LDL, and CRP (p= 0.005, p=0.02, p<0,01, p=0.001, p=0,016, p=0,014, p<0.01). A statistically significant relationship and a positive correlation between RDW values and CRP levels was found in patients with psoriasis (p=0.010, r=0.396)

Patient and control groups were then grouped according to the presence of major CVD risk factors. Patients who did not have any major CVD risk factors

Table 1. Comparison of body composition parameters in patients with psoriasis and controls

Body composition parameters		Mean ± SD	*P*
Weight	P	89.93±93.25	0.470
	C	75.95±22.61	
Fat %	P	27.82±9.86	0.508
	C	26.17±11.21	
Muscle mass	P	53.88±10.67	0.354
	C	51.24±14.36	
BMR**	P	1689.88±17.76	0.502
	C	1630.00±20.82	
Metabolic age	P	46.68±5.29	**0.044**
	C	37.43±5.26	
Visceral fat rating	P	9.23±6.71	**0.047**
	C	6.62±4.86	
BMI***	P	28.65±83.56	**0.029**
	C	25.,98±28.70	
Obesity degree %	P	36.1808±83.56	0.401
	C	20.4952±28.70	

SD: Standard Deviation; P: patient; C: control
**BMR: basal metabolic rate
***BMI: body mass index

Table 2. Comparison of laboratory parameters in patients with psoriasis and controls

Laboratory parameters		Mean ± SD	*P*
RBC (10^6/µl)	P	4.97±0.52	**0.005**
	C	4.77±0.04	
Hemoglobine (g/dL)	P	14.45±1.93	0.770
	C	14.53±1.45	
MCV (fL)	P	8657±6.46	0.161
	C	87.85±5.00	
RDW (%)	P	13.98±1.43	**0.000**
	C	13.25±0.59	
Leucocyte (10^3/µl)	P	7.91±1.92	**0.020**
	C	7.27±1.64	
NLR	P	2.51±2.38	0.369
	C	2.18±1.16	
Platelet (10^3/µl)	P	258637.81±74311.17	0.243
	C	246142.86±79890.56	
MPV (fL)	P	8.59±0.99	0.074
	C	9.65±7.75	
Cholesterol (total) (mg/dL)	P	2003.96±21093.48	0.516
	C	199.16±43.95	
HDL (mg/dL)	P	47.87±12.40	0.319
	C	50.10±14.26	
LDL (mg/dL)	P	146.18±35.99	**0.014**
	C	132.48±35.36	
TG (mg/dL)	P	2969.61±33469.96	0.516
	C	155.42±85.95	
VLDL (mg/dL)	P	33.21±18.89	0.349
	C	29.52±14.67	
Glucose (mg/dL)	P	100.11±28.63	0.606
	C	97.26±21.56	
Sedimentation (mm/hr)	P	18.50±25.16	0.524
	C	9.38±6.37	
C reactive protein (mg/dL)	P	0.52±0.39	**0.000**
	C	0.31±0.23	
ALT (U/L)	P	27.46±16.73	**0.001**
	C	20.98±10.60	
AST (U/L)	P	24.71±8.81	0.114
	C	22.52±7.15	
Uric acid (mg(dL)	P	5.63±1.57	**0.016**
	C	4.99±1.27	

SD: Standard Deviation; P: patient; C: control

(n=79) were compared with control group cases who also did not have any major CVD risk factors, whereas patients who had one or more CVD risk factors (n=120) were compared with controls with one or more CVD risk factors. Among these subgroups, patients without any major CVD risk factors had significantly higher values of RDW, LDL, and CRP (p=0.010, p=0.031, p=0.030, respectively). Patients with one or more CVD risk factors had significantly higher values of BMI, RDW, thrombocytes, ALT, and CRP (p=0.038, p=0.010, p=0.017, p=0.020, p=0.010, respectively).

Table 3. Comparison of body composition and laboratory parameters in patients with psoriasis and controls without any major CVD risk factors.

Body composition parameters		**Mean±SD**	**P**
Muscle mass	P	51,02±14,34	**0.006**
	C	43,93±3,98	
Tbw	P	50,12±9,84	**0.012**
	C	41,71±3,78	
BMR	P	53,54±6,14	**0.049**
	C	55,31±7,70	
Laboratory parameters			
RBC^ (x10^6/µl)	P	4,87±0,54	**0.015**
	C	4,61±0,28	
RDW^^ (%)	P	14,00±1,58	**0.01**
	C	13,24±0,67	
LDL+ (mg/dL)	P	125,55±24,88	**0.031**
	C	118,73±25,18	
C reactive protein (mg/dL)	P	0,40±0,27	**0.03**
	C	0,25±0,20	

SD: standard deviation; P: patient; C: control
* Tbw: total body water
**BMR: basal metabolic rate
^RBC: red blood cell count
^^RDW: red cell distribution width
+ LDL: low density lipid

DISCUSSION

In this study, patients with moderate to severe psoriasis were shown to have significantly higher levels of RDW, which was positively correlated with CRP levels. CRP is a well-known marker of inflammation and a generally accepted predictor of CVD which has been shown be associated with BMI and other inflammatory markers in patients with psoriasis (1-6,17). RDW levels rise when there is a difference in the sizes of RBC, which can be due to inflammatory effects of circulating cytokines that modulate erythropoiesis (7-9). IL-6 and IFN-α are cytokines associated with RDW elevation which cause keratinocyte proliferation and T-cell chemoattraction in the etiopathogenesis of psoriasis (13,14,16). Elevated RDW has been suggested as a risk marker in CVD, chronic hepatitis, and metabolic syndrome (18-20). In a recent study by Kim *et al*., RDW was shown to increase in moderate to severe psoriasis; however in this study the associated

Table 4. Comparison of body composition and laboratory parameters in patients with psoriasis and controls with at least one major CVD risk factor.

Body composition parameters		Mean±SD	P
BMI*	P	29,76±6,97	**0.038**
	C	27,10±4,74	
Laboratory parameters			
Plt^ (x10^3/µl)	P	259307,54±82433,89	**0.01**
	C	231065,22±61384,91	
RDW^^ (%)	P	13,99±1,38	**0.017**
	C	13,25±0,55	
ALT (U/L)	P	29,50±17,60	**0.02**
	C	23,07±11,65	
C reactive protein (mg/l)	P	0,58±0,42	**0.01**
	C	0,34±0,25	

SD: standard deviation; P: patient; C: control

* BMI: body mass index

^Plt: platelet

^^RDW: red cell distribution width

CVD risk factors were not evaluated, and thus the attribution of RDW elevation solely to psoriasis remained controversial (16). In the current study, even patients with psoriasis who did not have any major CVD risk factors were shown to have higher levels of CRP and RDW than the controls lacking any major CVD risk factors. This important finding indicates that psoriatic inflammation itself can cause CRP and RDW elevation simultaneously without any concomitant CVD risk factor presence. Additionally, patients with psoriasis had higher values of metabolic age, BMI, and visceral fat rating than the age and sex matched control group with a similar profile of CVD risk factors. Thus, evaluation of patients with psoriasis for CVD risk is mandatory and RDW seems to reflect the systemic inflammatory burden which is predictive for CVD.

Another important result of this study was the finding that BMI, visceral fat rating, LDL, and ALT levels were higher in patients with psoriasis. We think that the presence of major CVD risk factors along with psoriasis causes significant differences in these parameters. Synchronous elevation of ALT, which is a specific enzyme elevating for liver pathologies, and visceral and blood lipid parameters brings to mind a probable association with non-alcoholic steatohepatitis (NASH). NASH is a well-known comorbidity of psoriasis and is a part of the spectrum of non-alcoholic fatty liver disease (NAFLD) (21). Chronic inflammation has been shown to play a significant role in the progression of simple fatty liver disease to NASH, advanced fibrosis, and cirrhosis, which are the endpoints of this spectrum. A recent study showed that patients with biopsy-proven NASH have higher values of RDW compared with patients with simple steatosis and healthy controls (22). We believe that the increase of RDW in psoriasis may also be associated with possible NAFLD, as the patients were also shown to have increased visceral fat rating, LDL, and ALT levels.

CONCLUSION

In conclusion, RDW was elevated in patients with moderate to severe psoriasis even in the absence of major CVD risk factors; it can be accepted as a reliable marker of inflammation correlating with CRP levels in patients with plaque psoriasis.

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References:

1. Menter A, Griffiths CE, Tebbey PW, Horn EJ, Sterry W; International Psoriasis Council. Exploring the association between cardiovascular and other disease-related risk factors in the psoriasis population: the need for increased understanding across the medical community. J Eur Acad Dermatol Venereol 2010;24:1371-7.
2. Horreau C, Pouplard C, Brenaut E, Barnetche T, Misery L, Cribier B, *et al*. Cardiovascular morbidity and mortality in psoriasis and psoriatic arthritis: a systematic literature review. J Eur Acad Dermatol Venereol 2013;27:12-29.
3. Prey S, Paul C, Bronsard V, Puzenat E, Gourraud PA, Aractingi S, *et al*. Cardiovascular risk factors in patients with plaque psoriasis: a systematic review of epidemiological studies. J Eur Acad Dermatol Venereol 2010;24:23-30.
4. Hugh J, Van Voorhees AS, Nijhawan RI, Bagel J, Lebwohl M, Blauvelt A, *et al*. From the Medical Board of the National Psoriasis Foundation: The risk of cardiovascular disease in individuals with psoriasis and the potential impact of current therapies. J Am Acad Dermatol 2014;70:168-77.
5. Miller IM, Skaaby T, Ellervik C, Jemec GB. Quantifying cardiovascular disease risk factors in patients

with psoriasis: a meta-analysis. Br J Dermatol 2013;169:1180-7.

6. Späh F. Inflammation in atherosclerosis and psoriasis: common pathogenic mechanisms and the potential for an integrated treatment approach. Br J Dermatol 2008;159:10-7.
7. Danese E, Lippi G, Montagnana M. Red blood cell distribution width and cardiovascular diseases. J Thorac Dis 2015;7:402-11.
8. Rodríguez-Carrio J, Alperi-López M, López P, Alonso-Castro S, Ballina-García FJ, Suárez A. Red cell distribution width is associated with cardiovascular risk and disease parameters in rheumatoid arthritis. Rheumatology 2015;54:641-6.
9. Peng YF, Zhang Q, Cao L, Yang Liu, Dan Chen, Yu-Kun Sun, *et al*. Red blood cell distribution width: a potential maker estimating disease activity of ankylosing spondylitis. Int J Clin Exp Med 2014;7:5289-95.
10. Gerdes S, Osadtschy S, Buhles N, Baurecht H, Mrowietz U. Cardiovascular biomarkers in patients with psoriasis. Exp Dermatol 2014;23:322-5.
11. Rodriguez-Carrio J, Alperi-Lopez M, Lopez P, Alonso-Castro S, Carro-Esteban SR, Ballina-García FJ, *et al*. Red cell distribution width is associated with endothelial progenitor cell depletion and vascular-related mediators in rheumatoid arthritis. Atherosclerosis 2015;240:131-6.
12. Hassan S, Antonelli M, Ballou S. Red cell distribution width: a measure of cardiovascular risk in rheumatoid arthritis patients? Clin Rheumatol 2015;34:1053-7.
13. Vreugdenhil G, Lowenberg B, van Eijk HG, Swaak AJ. Tumor necrosis factor alpha is associated with disease activity and the degree of anemia in patients with rheumatoid arthritis. Eur J Clin Invest 1992;22:488-93.
14. Pierce CN, Larson DF. Inflammatory cytokine inhibition of erythropoiesis in patients implanted with a mechanical circulatory assist device. Perfusion 2005;20:83-90.
15. Beaumont C, Karim Z. Iron metabolism: State of the art. Rev Med Interne 2013;34:17-25.
16. Kim DS, Shin D, Jee H, Kim TG, Kim SH, Kim do Y, *et al*. Red blood cell distribution width is increased in patients with psoriasis vulgaris: A retrospective study on 261 patients. J Dermatol 2015;42:567-71.
17. Dogan S, Atakan N. Is serum amyloid A protein a better indicator of inflammation in severe psoriasis? Br J Dermatol 2010;163:895-6.
18. Wang H, Xu H, Qu L, Wang X, Wu R, Gao X *et al*. Red blood cell distribution width and globulin, noninvasive indicators of fibrosis and inflammation in chronic hepatitis patients. Eur J Gastroenterol Hepatol 2016;28:997-1002.
19. Farah R, Khamisy-Farah R. Significance of MPV, RDW with the presence and severity of metabolic syndrome. Exp Clin Endocrinol Diabetes 2015;123:567-70.
20. Alcaíno H, Pozo J, Pavez M, Toledo H. Red cell distribution width as a risk marker in patients with cardiovascular diseases. Rev Med Chil 2016;144:634-42.
21. Wenk KS, Arrington KC, Ehrlich A. Psoriasis and non-alcoholic fatty liver disease. J Eur Acad Dermatol Venereol 2011;25:383-91.
22. Cengiz M, Candır BA, Yılmaz G, Akyol G, Ozenirler S. Is increased red cell distribution width an indicating marker of nonalcoholic steatohepatitis and fibrotic stage? World J Gastroenterol 2013;19:7412-8.