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Correlation of red cell distribution width with inflammatory markers and its prognostic value in patients with diabetes and coronary artery disease

ABSTRACT

Background. Recent studies have shown red blood cell distribution width (RDW) as a marker for severity and prognosis in coronary artery disease patients. Other studies have also correlated RDW with diabetes mellitus and inflammation. However, such correlation and prognosis in patients with concomitant coronary artery disease and diabetes after percutaneous intervention remains unclear.

Material and methods. Our study group comprised of 730 subjects including 700 patients (cases) and 30 normal subjects (control group). Patients who presented with coronary artery disease were divided into diabetic and non-diabetic groups. All patients had RDW measured at admission and percutaneous intervention was done. Follow-up for adverse events was carried out between 6 to 12 months.

Results. RDW was elevated in patients as compared to control group ($p < 0.05$). RDW correlated well with inflammatory markers including erythrocyte sedimentation rate, C-reactive protein, HbA_{1c}, white blood cells and troponin. RDW was higher with more severe atherosclerosis based on SYNTAX and Gensini scores

($p < 0.05$). Prognosis was found to be worse in patients with high RDW as well as in diabetics.

Conclusions. RDW has positive correlation with other inflammatory marker. It may be used as a marker in determining the severity and prognosis in diabetic patients with coronary artery disease. (Clin Diabetol 2020; 9; 3: 174–178)

Key words: red cell distribution width, coronary artery disease, diabetes

Introduction

Guidelines for acute ST elevation myocardial infarction (STEMI) patients recommend primary PCI as the preferred reperfusion strategy [1]. Inflammation plays a critical role in the initiation and propagation of the atherosclerotic process [2, 3]. Numerous inflammatory markers and indices have been studied recently in relation to atherosclerosis. One such marker is red cell distribution width (RDW). Use of RDW has been established in the investigation of the etiology of anemia [4]. Moreover, recent studies are showing an increasing evidence linking elevated RDW with adverse outcomes, in patients with coronary artery disease, heart failure (HF) and with metabolic syndrome. Diabetes mellitus (DM) is an independent risk factor for heart failure (HF) [4–6].

HbA_{1c} is associated with type 2 diabetes patients and is a marker of long term glucose homeostasis as well as adequacy of glycemic control in diabetic patients [7]. HbA_{1c} level increase with age, chronic subclinical

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inflammation and possibly oxidative stress and also in conditions that can adversely affect red blood cell survival. Correlation of RDW and diabetes in coronary artery disease patients has not been studied well.

Therefore, the aim of this exploratory study was to investigate the correlation and prognostic value of RDW in diabetes and coronary artery disease patients.

Patients and methods

It is a retrospective clinical study which included patients admitted to our hospital with coronary artery disease and diabetes. For the purpose of this analysis patients were divided into low RDW, high RDW, diabetic and non-diabetic groups. ST elevation myocardial infarction (STEMI) was defined as typical chest pain lasting for at least 30 min with new ST-segment elevation at the J point in more than two contiguous precordial or inferior leads (> 0.2 mV in V1 through V3 and > 0.1 mV in the other leads) [8]. Diabetes was defined according to definition previously stated elsewhere [9].

Hypertension was defined as repeated SBP measurements at least 140 mm Hg, repeated DBP measurements at least 90 mm Hg or chronic treatment with antihypertensive medications. Diabetes was recorded when it was reported by the patient and appeared in their medical records or if the patient was receiving regular treatment with oral hypoglycemic agents or insulin. Dyslipidemia was defined as a low-density lipoprotein-cholesterol level above the target according to National Cholesterol Educational Program-3 recommendations, as a high-density lipoprotein-cholesterol level below 40 mg/dL, or chronic treatment with lipid-lowering drugs prior to hospitalization [10].

All patients with an ACS received aspirin (325 mg loading dose) on admission and 100 mg daily as well as clopidogrel (300 mg loading dose for patients < 75 years of age and 75 mg for patients > 75 years of age). PCI was done for all STEMI patients.

Blood samples were taken on admission from all patients at the time of hospitalization and prior to the administration of medication. All hematological measurements were performed using Cobas B221 and 6000, Roche-Switzerland. Our hospital ethics committee approved this study and informed consent was obtained from all study participants according to the declaration of Helsinki.

Statistical analysis

Data was analyzed with Statistical Package for the Social Sciences (SPSS 20) for Windows (SPSS Inc., Chicago, Illinois, USA). Continuous data are presented as the mean along with standard deviation. The Kolmogorov-Smirnov test was used to evaluate data normality.

Independent-samples t-test was used to compare two groups showing normal distribution. Categorical variables were summarized as percentages and compared with the chi-square test. Pearson's and Spearman correlation analysis tests were used to determine the correlation between variables. P value less than 0.05 was considered to indicate a significant difference.

Results

730 subjects were enrolled in this study which included 30 normal and disease free subjects and 700 coronary artery disease patients. Mean RDW in control group was compared to RDW in patients which showed significant difference [(12.4 vs. 14.5) ($p < 0.05$)]. All patients underwent percutaneous intervention at about 8 ± 5 hours after onset of chest pain. The patients were divided into groups according to RDW and diabetic status. The mean age of the patients was 64 ± 7.92 years. Patients were assessed at baseline according to RDW levels (low and high). There was significant difference between low and high RDW groups with regard to hemoglobin, HbA_{1c} , erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), white blood cells (WBC) and troponin levels. Other demographic and clinical baseline characteristics between the two groups did not show any significant difference (Table 1).

Angiographic characteristics and scores of the study groups are presented in Table 2. SYNTAX Score ranged from 5 to 47 and with a mean of 23.75 ± 10.12 while Gensini Score ranged from 8 to 10 and with a mean of 48.31 ± 25.47 . SYNTAX and Gensini score were divided into low and high based on mean values. RDW levels in relation to angiographic scoring were assessed in diabetics ($HbA_{1c} \geq 7$) and non-diabetics ($HbA_{1c} < 7$). RDW levels were significantly higher with high SYNTAX score, Gensini scores and multi-vessel disease and as well as in diabetics ($p < 0.05$) (Table 2).

The Pearson and Spearman correlation coefficients were used to assess the correlations between RDW and various clinical and laboratory variables. Significant positive correlation was found between RDW and age, ejection fraction, ESR, HbA_{1c} , WBC, CRP and troponin while there was significant negative correlation with hemoglobin ($p < 0.05$) (Table 3).

Prognosis was assessed on the basis of five indices (angina, myocardial infarction, heart failure, stroke and death) during a period of 6 months to one year after percutaneous intervention. Comparison was made between low and high RDW groups as well as diabetic and non-diabetics. It showed significant increase in myocardial infarction, heart failure and death in both high RDW and diabetic groups. Moreover, frequency of angina was also more in diabetic group ($p < 0.05$) (Table 4).

Table 1. Baseline characteristics of study groups according to RDW

Variable	RDW < 16 (n = 300)	RDW ≥ 16 (n = 400)
Age (years)	63 ± 7.10	65 ± 8.75
Ejection fraction (%)	50.62 ± 8.65	48.78 ± 8.10
Hypertension	99 (33%)	140 (35%)
Smoking	69 (23%)	108 (27%)
Renal failure	30 (10%)	48 (12%)
Hyperlipidemia	63 (21%)	96 (24%)
HbA _{1c}	5.5 ± 0.5	7.5 ± 1.0*
Erythrocyte sedimentation rate [mm/h]	18 ± 5	39 ± 10*
C-reactive protein [mg/L]	0.7 ± 0.4	1.9 ± 0.6*
Troponin (high sensitivity) [ng/l]	545 ± 370	2360 ± 574*
Hemoglobin [gm/dl]	15 ± 1.0	11 ± 1.5*
White blood cells [$\times 10^9/L$]	9.50 ± 2.32	14.48 ± 2.25*
Aspirin	300 (100%)	400 (100%)
Clopidogrel	291 (97%)	396 (99%)
Beta blocker	285 (95%)	372 (93%)
Renin antagonists	264 (88%)	364 (91%)
Lipid lowering agents	240 (80%)	336 (84%)

*p ≤ 0.05

Table 2. Relationship between RDW and angiographic variables in diabetic (HbA_{1c} ≥ 7) and non-diabetic groups (HbA_{1c} < 7)

Variable	RDW	
	HbA _{1c} < 7	HbA _{1c} ≥ 7
SYNTAX score		
Low (< 23)	12.85 ± 1.10	13.45 ± 1.7
Moderate-high (23–32)	14.24 ± 1.15	17.85 ± 1.14*
Gensini score		
Low (< 47)	12.55 ± 1.18	12.55 ± 1.18
High (≥ 47)	14.37 ± 1.21	18.12 ± 1.11*
No. of vessels involved		
Single vessel disease	11.97 ± 1.25	14.10 ± 1.36
Multi-vessel disease	13.78 ± 1.75	18.82 ± 1.61*

*p ≤ 0.05

Table 3. Correlation of RDW with clinical and laboratory variables

Variable	Correlation coefficient (P)
Age	0.487 (0.030)
Systolic blood pressure	0.037 (0.061)
Diastolic blood pressure	0.002 (0.346)
Ejection fraction	0.030 (0.048)
ESR	0.561 (0.001)
Serum creatinine	0.258 (0.979)
BMI	0.003 (0.0686)
Total cholesterol	0.014 (0.725)
Hemoglobin	-0.486 (0.025)
HbA _{1c}	0.529 (0.001)
WBC	0.580 (0.001)
CRP	0.349 (0.029)
Troponin	0.412 (0.017)

ESR — erythrocyte sedimentation rate; BMI — body mass index; WBC — white blood cells; CRP — C-reactive protein

Table 4. Prognosis in relation to RDW and diabetes after percutaneous intervention

	RDW < 16 (n = 300)	RDW ≥ 16 (n = 400)	Non-diabetics (n = 380)	Diabetics (n = 320)
Angina	18 (6%)	28 (7%)	20 (5.26%)	26 (8.12%) [†]
Myocardial infarction	4 (1.33%)	12 (3%)*	5 (1.32%)	11 (3.44%) [†]
Heart failure	3 (1%)	14 (3.50%)*	4 (1.05%)	13 (4.06%) [†]
Stroke	0 (0%)	2 (0.50%)	1 (0.26%)	1 (0.31%)
Death	3 (1%)	10 (2.50%)*	4 (1.05%)	9 (2.81%) [†]

*p ≤ 0.05 comparison between RDW < 16 and RDW ≥ 16 groups; [†]p ≤ 0.05 comparison between non-diabetic and diabetic groups

Discussion

This study showed good correlation of RDW with other inflammatory markers. The underlying pathophysiological mechanisms for the association between a high RDW and atherosclerosis is unknown, but it is believed that inflammation might play a role with cytokines induced changes in the red cell membrane, leading to an increased RDW [11]. Erythrocyte malformation and hence increased RDW may be caused by oxidative stress, inflammation, and increase in cholesterol levels in erythrocyte membrane. Inflammation or oxidative stress may cause increased RDW by impairing iron metabolism, inhibiting the production of or response to erythropoietin, and shortening red blood cell survival [12, 13].

Lippi et al. [14] showed an increase in RDW levels during acute coronary syndrome and its usefulness for the risk stratification. Previous studies have also assessed the relationship between an increased RDW and poor reperfusion results after STEMI, increased risk and morbidity in hospital as well as mortality [15]. A possible explanation for this result is the intense inflammatory response in the setting of STEMI.

In our study, the RDW levels have been shown to be higher in patients with diabetes. A number of risk factors such as age, hypertension, hyperlipidemia, high CRP levels may play a role [12].

Fatemi et al. showed high RDW levels in patients with two or more vessel disease and with early phase of atherosclerosis [16, 17].

Osadnik et al. [18] demonstrated prognostic value of RDW in stable angina pectoris patients undergoing PCI by showing higher mortality in these patients with a high RDW level.

RDW is a marker of inflammation and has prognostic value in diabetic patients [19, 20]. The association between DM and RDW has been initially examined by Subharshree [21] showed correlation between BNP and RDW in diabetic patients with HF. Malandrino et al. [22] demonstrated the relationship between RDW and microvascular and macrovascular complications of diabetes mellitus (DM).

RDW may reflect an underlying inflammatory process and inflammation is considered a vital component in the diabetic disease process as well [4, 23], which led to Sherif et al. [24] suggesting that RDW could be used as a marker of inflammation in type 2 DM.

Elevated glucose levels may affect erythrocytes in multiple ways such as changes in erythrocyte membranes which include increased rigidity, changes in osmotic fragility due to changes in Na⁺/K⁺-ATPase activity and tubulin acetylation and increased aggregation. Other changes include defective oxygen binding

of hemoglobin and alterations in cell as well [25–27]. These changes can result in increase in shear stress on the endothelial wall and increased blood viscosity [28].

Conclusion

RDW has positive correlation with other inflammatory markers. It is an inexpensive and easily accessible marker which can be used in determining the severity and prognosis in diabetic patients with coronary artery disease after percutaneous intervention. More pronounced inflammatory process may be responsible for increased severity and hence poorer prognosis in diabetic patients.

Conflict of interest

The authors declare to have no conflict of interest.

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