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A routine but overlooked parameter for impaired glucose control: red cell distribution width

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Abstract. – OBJECTIVE: Red cell distribution width (RDW), an index of erythrocyte size, is recently found to be associated with inflammation and a high risk for cardiovascular disease. Hyperglycemia, the hallmark of prediabetes (PDM) and diabetes mellitus (DM), causes endothelial dysfunction and a proinflammatory state. We investigated the relationship between RDW and hs-CRP in patients with prediabetes and overt DM.

PATIENTS AND METHODS: A total of 155 patients were categorized into 3 groups according to the 2007 guideline for American Diabetes Association: "Type 2 DM" group (n = 45), "PDM" group (n = 60) and "Control" group (n = 50). RDW and hs-CRP levels were measured.

RESULTS: PDM group had higher hs-CRP and RDW levels than the control group (14.3 ± 0.84 *vs.* 12.7 ± 0.8, $p < 0.001$ for RDW; (0.91 ± 0.49 *vs.* 0.55 ± 0.37, $p < 0.001$ for hs-CRP). Similarly, when compared with the PDM, RDW and hs-CRP levels were higher in the DM group (14.8 ± 0.87 *vs.* 14.3 ± 0.84, $p = 0.002$ for RDW; 1.15 ± 0.59 *vs.* 0.91 ± 0.49, $p = 0.03$ for hs-CRP).

CONCLUSIONS: Prediabetes and diabetes were associated with elevated RDW levels which may be attributed to a subclinical inflammatory background.

Key Words:
Diabetes mellitus, hs-CRP, Inflammation, Prediabetes, RDW.

Introduction

Diabetes mellitus (DM) is a significant health concern that is associated with increased mortality and morbidity for cardiovascular diseases, stroke, kidney failure, and blindness[1]. The best coping strategy with diabetes is early diagnosis and prevention rather than dealing with complications[2]. Since the progressive nature of impairment in insulin secretion and loss of beta-cells, only about 50% percent of beta-cell function remains at the time of diagnosis in type 2 DM[3]. Therefore, prediabetes, a clinical condition with higher glucose levels than usual, is of great clinical importance in early diagnosis and prevention of DM. There is solid evidence that glycemic control in prediabetes can prevent or delay the development of overt DM and its complications[4,5].

Red cell distribution width (RDW) is a routine parameter of complete blood count analysis (CBC) which reflects the variability of circulating red blood cell sizes. Traditionally RDW is used in the differential diagnosis of anemia[6]. A high RDW value can be seen not only in hematological disorders (Iron, vitamin B12 or folate deficiency, impaired red blood cell production due to hemolysis), but also in some clinical conditions such as prehypertension, hypertension, thrombotic thrombocytopenic purpura (TTP), and pregnancy[7-10]. Recently, it has been reported that higher RDW values mean poor outcomes in acute myocardial infarction, coronary artery disease, and heart failure[11-14].

In our study, our aim is to research the relationship between RDW and hs-CRP in patients with prediabetes and overt DM.

Patients and Methods

A total of 155 patients of outpatient clinics were included in this prospective randomized controlled study. The subjects were categorized into three groups: 45 patients with Type 2 DM, 60 patients with prediabetes and 50 age-, and sex-matched subjects without prediabetes or DM. Prediabetic and diabetic patients were determined according to the 2007 guidelines in American Diabetes Association[15]. Those criteria are as follows.

Prediabetes

(1) Impaired fasting glucose:
Fasting plasma glucose 100-125 mg/dL (5.6-6.9 mmol/L)

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(Fasting = no caloric intake for ≥ 8 hours)

(2) Impaired glucose tolerance:
2-hour plasma glucose 140-199 mg/dL (7.8-11.0 mmol/L)

(Measured by oral glucose tolerance test using a 75-g glucose load)

Diabetes

(1) Fasting plasma glucose:
≥126 mg/dL (≥ 7.0 mmol/L)

(2) 2-hour plasma glucose:
≥200 mg/dL (≥ 11.0 mmol/L)

The subjects were included in the prediabetes group in the presence of impaired fasting glucose, impaired oral glucose tolerance test (OGTT) or both.

Exclusion Criteria

The exclusion criteria were: prehypertension or HT (according to JNC-7 guideline), coronary artery disease, manifest heart disease, hepatic failure, TTP, chronic obstructive lung disease, renal failure, pregnancy, hyperthyroidism, anemia, any prior blood transfusion, any hypertensive medication.

All participants included in the study were informed about the study and their verbal and written consent was obtained to participate in the study voluntarily. This study was approved by the Research Ethics Review Board of Mustafa Kemal University (Approval #2016-1/3).

After questioning the clinical history of risk factors such as age, gender, hypercholesterolemia, smoking and family history, previous medications, height and weight were measured for each participant. BMI was calculated by dividing weight in Kilograms by size in square meters (kg/m^2). The glomerular filtration rate (GFR) was estimated by the simplified Modification of Diet in Renal Disease Equation. White blood cell (WBC), Hemoglobin (Hb), and RDW count were evaluated as part of the automated complete blood count analyzed by the Beckman-Coulter Gen-S system device (Beckman-Coulter Inc., California, CA, USA). Anemia was defined as a baseline Hb < 12 g/dL in women and Hb < 13 g/dl in men by the criteria of the World Health Organization (WHO).

Serum total cholesterol, TG, LDL, HDL, glucose, urea, creatinine, levels and hs-CRP were evaluated from venous blood samples taken in the morning after eight hours of fasting. Serum creatinine, Blood urea nitrogen, levels of high-density lipoprotein, triglycerides, low-density lipoprotein, and thyroid-stimulating hormone (TSH) were recorded. hs-CRP was evaluated in serum by EIA (Image hs-CRP EIA kit, Beckman Coulter Inc., California, CA, USA). Transthoracic echocardiography was performed before coronary angiography and biplane Simpson ejection fraction (%) was calculated. Our study was approved by the local ethics committee.

Statistical Analysis

Statistical analysis was conducted with SPSS 13 (SPSS Inc, Chicago, IL, USA) software package program. Whereas categorical variables were presented as percentages, continuous variables were expressed as mean ± standard deviation. Chi-square (x^2) test was employed for the comparison of categorical variables. Differences in numerical variables were evaluated with the Mann-Whitney U test or Kruskal-Wallis analysis of variance, as appropriate. To determine the independent predictors of prediabetes, uni- and multivariate analyses were performed. Parameters found to be significant (p<0.10) in univariate analysis were evaluated with stepwise logistic regression analysis. Ninety-five percent confidence intervals and odds ratios (OR) are presented. An exploratory assessment of additional breakpoints was performed using receiver operating characteristics (ROC) curve analysis. A p < 0.05 was considered statistically significant.

Results

In total, 155 patients (42.4 ± 3.0 years, 62.6% comprised of males) were included in the study. Baseline clinical and laboratory characteristics relative to groups were shown in Table I. Age, sex, smoking status, HDL-C, LDL-C, triglyceride, hemoglobin, GFR, and TSH levels were not different between the groups. Glucose levels, HbA1c, and BMI were higher in the prediabetic group.

The patients with DM had serum hs-CRP and higher RDW levels than the prediabetic patients (14.8 ± 0.87 *vs.* 14.3 ± 0.84, p = 0.002 for RDW; 1.15 ± 0.59 *vs.* 0.91 ± 0.49, p = 0.03 for hs-CRP) and control subjects (14,8 ± 0.87 *vs.* 12.7 ± 0.8, p < 0.001 for RDW; 1.15 ± 0.59 *vs.* 0.55 ± 0.37, p < 0.001 for hs-CRP). In addition, the RDW levels were higher in the prediabetic group than the control group (14.3 ± 0.84 *vs.* 12.7 ± 0.8, p < 0.001) (Figure 1). Similarly, serum hs-CRP levels were higher in prediabetic group than the control group, as well (0.91 ± 0.49 *vs.* 0.55 ± 0.37, p < 0.001) (Figure 1). Uni-

Table I. Comparison of the basic clinical and laboratory characteristics of the groups.

Variables	Control (n=50)	Prediabetes (n=60)	Diabetes (n=45)	*p*-value
Age (years)	42.8±2.8	42.6±3.1	43.0±2.7	0.09
Sex, male (%)	30(60%)	36 (60%)	31 (68.9%)	0.58
BMI (kg/m^2)	24.4±2.9	26.8±5.4	26.9±5.1	0.004
Smoking (%)	22 (44%)	28 (46.7%)	20 (44.4%)	0.95
Ejection Fraction (%)	63.2±2.1	62.4±3.1	61.5±4.4	0.22
Medications (%)				
Aspirin	5 (16%)	5 (17%)	10 (16.9%)	0.62
Statin	10 (25.8%)	8 (27.5%)	16 (27.1%)	0.22
Metformin	-	10 (16.7%)	35 (78%)	-
Sulfonylurea	-	-	8 (18%)	-
Thiazolidinedion	-	-	16 (36%)	-
Heart ate(beats/minute)	70.5±8.2	67.3±6.5	71±4.4	0.30
Systolic BP (mmHg)	110.4 ±9.8	111.3±9.9	114.6±14.5	0.45
Diastolic BP (mmHg)	72.4±9.8	73.3±9.9	71.8±9.8	0.73
FPG (mg/dL)	86.9±11.5	100.8±13.9	110.5±25.3	<0.001
HbA1c	5.32±0.3	5.9±0.4	7.4±0.9	<0.001
HDL-C (mg/dL)	33.1±9.1	35.5±9.2	34.2±8.9	0.34
LDL-C (mg/dL)	113.2±33.3	123.9±30.7	119.8±34.4	0.38
TG (mg/dL)	163.4.5±80.8	159.3±86.6	184.0±93.5	0.19
Creatinine	0.78±0.32	0.8±0.3	0.9±0.2	0.55
TSH	1.8±1.6	1.3±0.78	1.35±0.83	0.56
Hemoglobin (g/dL)	13.1±1.4	13.5±1.3	13.5±1.2	**0.12**
hsCRP	0.55±0.37	0.91±0.49	1.15±0.59	<0.001
RDW (%)	12.7±0.80	14.3±0.84	14.8±0.87	**<0.001**

Numerical values were expressed as mean ± standard deviation and categorical values were expressed as number (percentage). Comparison between groups were done with Kruskal-Wallis and Chi-square where appropriate. $p < 0.05$ was considered as significant. BMI, body mass index; BP, blood pressure; FPG, fasting plasma glucose; RDW, red cell distribution width; HDL-C, high density cholesterol; LDL-C, low density cholesterol; hs-CRP, high sensitivity C-reactive protein; TG, triglyceride; TSH, thyroid stimulating hormone.

variate correlation analysis revealed a positive correlation between RDW levels and hs-CRP levels (Rho=0.41, $p < 0.001$).

The ROC curve analysis further revealed that RDW was a strong indicator of the "prediabetic or diabetic state" in patients with an AUC of 0.92 (95% CI: 0.88 to 0.97) (Figure 2). The optimal threshold of RDW level that maximized the combined specificity and sensitivity to predict the "prediabetic or diabetic state" was 13.5%. Sensitivity, specificity, positive predictive value, and negative predictive value to identify "prediabetic or diabetic" patients were 88%, 85%, 93%, and 76%, respectively.

For determining the predictors of "prediabetic or diabetic state," uni- and multivariate analysis were performed. For predicting the "prediabetic or diabetic state", the RDW score was dichotomized into high (RDW ≥ 13.5) and low (RDW < 13.5) groups. Parameters showing significance in multivariate analysis, univariate analysis (age, BMI, hs-CRP and TSH) were evaluated by multivariate analysis to determine the independent predictors of "prediabetic or diabetic state". Thus, hs-CRP, BMI, and TSH were found to be independent predictors of "prediabetic or diabetic state" (Table II).

Discussion

In this study, we investigated the relationship between RDW and hs-CRP in prediabetic and diabetic patients. This study showed that prediabetes and diabetes were associated with elevated RDW levels which may be attributed to a subclinical inflammatory background.

DM is a chronic illness caused by defects in insulin secretion and loss of beta-cells, resulting in high glucose levels[3]. It is a significant health concern because of the associated high mortality and morbidity for cardiovascular diseases, stroke, kidney failure, and blindness[1]. Due to the chronic, insidious and progressive course of the disease, many organ systems are affected and irreversibly damaged in the presence of poor glycemic control. Therefore, early diagnosis is crucial for preventing life-threat-

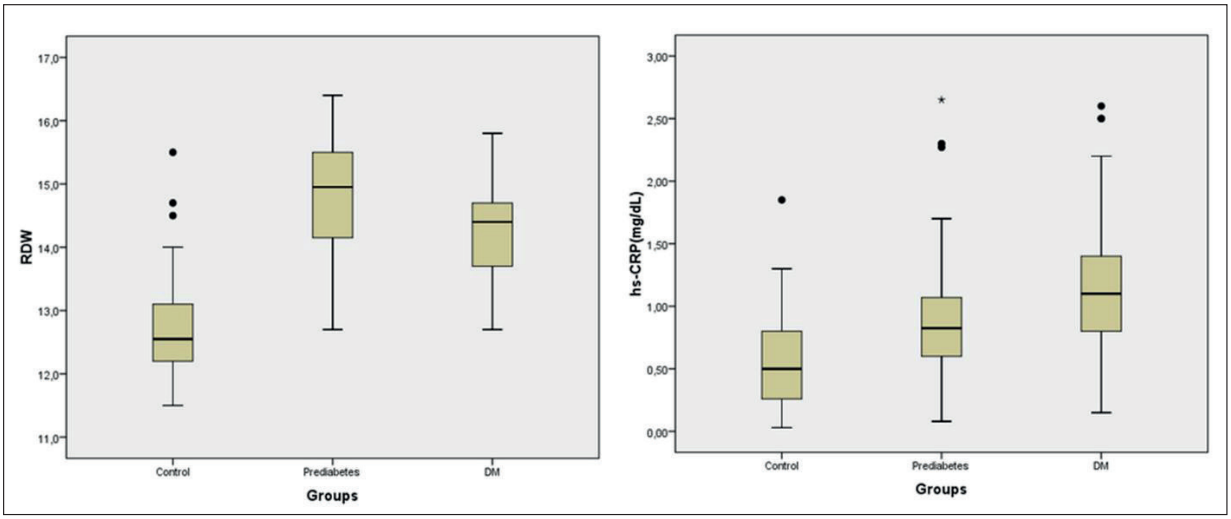

Figure 1. The comparison of RDW and hs-CRP levels in groups.

ening complications because only about 50% percent of beta-cell function remains at the time of diagnosis in type 2 DM[2,3]. Although the exact molecular basis of the end-organ damage is not fully understood, for the time being, the primary target of hyperglycemia appears to be the endothelial cell in which it causes fundamental structural changes, resulting in endothelial dysfunction and microangiopathy[16]. This condition, in turn, causes a prothrombotic and proinflammatory state that predisposes to prediabetes[16]. Because the hallmark of prediabetes and DM is the hyperglycemic state. As mentioned above, hyperglycemia leads to endothelial dysfunction and proinflammatory state, even though overt type 2 DM precedes "prediabetes"[1], an inflammatory background is present at the very beginning of the disease. In the previous studies[17-19], hs-CRP, a well-known inflammatory marker, was associated with prediabetes and elevated blood glucose levels, showing the inflammatory background. Following the literature, in our study, we found that hs-CRP levels were higher in both prediabetic and diabetic patients when compared to normoglycemic subjects. Moreover, diabetic patients had higher hs-CRP levels than the prediabetic subjects. These findings support the idea that inflammation, as a reason or consequence, coexists in all the progression of the disease, and as the disease proceed, more inflammation coexists.

Similarly, RDW values were higher in prediabetic and diabetic patients than in the controls. RDW is an index for the size variability of circulating erythrocytes and is routinely reported by CBC analysis. Although commonly used in the differential diagnosis of anemias[20,21],

Table II. Significant predictors of "Prediabetic and diabetic state" in univariable and stepwise multivariable logistic regression analyses for the RDW cutoff of 13.5%.

	Univariate		Stepwise multivariate	
Variable	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Prediabetic and diabetic state				
Age	1.13 (1.0-1.28)	**0.04**		
BMI	1.13 (1.04-1.24)	**0.003**	1.19 (1.1-1.3)	**0.03**
TSH	0.70 (0.50-0.96)	**0.03**	0.69 (0.48-0.98)	**0.04**
hs-CRP	12.2 (4.2-35.3)	**<0.001**	20.9 (5.7-76.3)	**<0.001**

BMI, body mass index; CI, confidence interval; hs-CRP, high sensitivity C-reactive protein; OR, odds ratio; TSH, thyroid stimulating hormone.

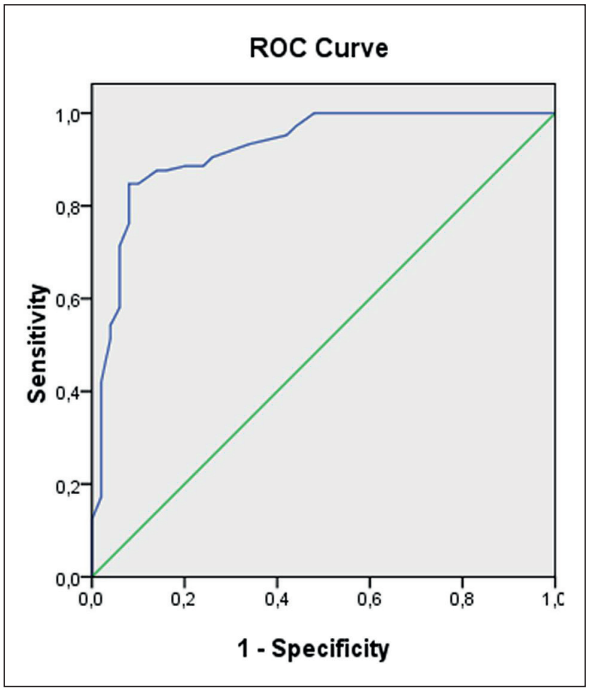

Figure 2. The ROC curve showing the sensitivity and specificity of RDW with regard to "prediabetic and diabetic state" (RDW ≥ 13.5).

it is elevated in many clinical settings, namely prehypertension, hypertension, colon cancer, thrombotic thrombocytopenic purpura (TTP), pregnancy, stroke, and inflammatory bowel diseases (IBDs)[7-10,22,23]. As we found in this study, RDW was found to be correlated with inflammatory markers such as CRP[24]. In addition to that, the independent predictors of high RDW for impaired glycemic control were found to be hs-CRP, BMI, and TSH, all of which are closely related to inflammation. These findings suggest that, beyond being an index parameter for erythrocyte size, an elevated RDW may reflect inflammation, indeed. The reason for the higher RDW levels in hyperglycemic patients may be oxidative stress, which causes cytoskeletal structural changes and endothelial dysfunction[25,26]. In addition, RDW levels such as hs-CRP were found to be higher in diabetic patients than in prediabetic patients. Therefore, elevated RDW levels may even be associated with the degree of inflammation. Although reported routinely in CBC analysis, RDW is overlooked chiefly as an inflammatory marker and the association of RDW with inflammation needs to be more thoroughly investigated.

The first limitation of this study is the lack of subgroup analysis in the prediabetes group. The absence of other inflammatory and biochemical parameters such as IL-6, TNF-alpha, iron, vitamin B12 and folate is another limitation of our study.

Conclusions

RDW, a routine parameter of CBC analysis, is elevated in prediabetic and diabetic patients attributable to a subclinical inflammatory background.

Conflict of Interest

The authors declare that they have no conflict of interests.

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References

1) Bharucha AE, Dunivan G, Goode PS, Lukacz ES, Markland AD, Matthews CA, Mott L, Rogers RG, Z 6 years' therapy of type II diabetes: a progressive disease. Diabetes 1995; 44: 1249-1258.
4) Icks A, Rathmann W, Haastert B, Gandjour A, Holle R, John J, Giani G. Clinical and cost-effectiveness of primary prevention of Type 2 diabetes in a 'real world' routine healthcare setting: model based on the KORA Survey 2000. Diabet Med 2007; 24: 473-480.
5) Jacobs-van der Bruggen MA, Bos G, Bemelmans WJ, Hoogenveen RT, Vijgen SM, Baan CA. Lifestyle interventions are cost-effective in people with different levels of diabetes risk: results from a modeling study. Diabetes Care 2007; 30: 128-134.
6) Salvagno GL, Sanchis-Gomar F, Picanza A, Lippi G. Red blood cell distribution width: A simple parameter with multiple clinical applications. Crit Rev Clin Lab Sci 2015; 52: 86-105.
7) Clarke K, Sagunarthy R, Kansal S. RDW as an additional marker in inflammatory bowel disease/ undifferentiated colitis. Dig Dis Sci 2008; 53: 2521-2523.
8) Shehata HA, Ali MM, Evans-Jones JC, Upton GJ, Manyonda IT. Red cell distribution width (RDW) changes in pregnancy. Int J Gynaecol Obstet 1998; 62: 43-46.
9) Nagajothi N, Braverman A. Elevated red cell distribution width in the diagnosis of thrombotic thrombocytopenic purpura in patients presenting with anemia and thrombocytopenia. South Med J 2007; 100: 257-259.
10) Fukuta H, Ohte N, Mukai S, Saeki T, Asada K, Wakami K, Kimura G. Elevated plasma levels of

B-type natriuretic Peptide but not C-reactive protein are associated with higher red cell distribution width in patients with coronary artery disease. Int Heart J 2009; 50: 301-312.

11) Isik T, Uyarel H, Tanboga IH, Kurt M, Ekinci M, Kaya A, Ayhan E, Ergelen M, Bayram E, Gibson CM. Relation of red cell distribution width with the presence, severity, and complexity of coronary artery disease. Coron Artery Dis 2012; 23: 51-56.
12) Uyarel H, Ergelen M, Cicek G, Kaya MG, Ayhan E, Turkkan C, Yildirim E, Kirbas V, Onturk ET, Erer HB, Yesilcimen K, Gibson CM. Red cell distribution width as a novel prognostic marker in patients undergoing primary angioplasty for acute myocardial infarction. Coron Artery Dis 2011; 22: 138-144.
13) Dabbah S, Hammerman H, Markiewicz W, Aronson D. Relation between red cell distribution width and clinical outcomes after acute myocardial infarction. Am J Cardiol 2010; 105: 312-317.
14) Felker GM, Allen LA, Pocock SJ, Shaw LK, McMurray JJ, Pfeffer MA, Swedberg K, Wang D, Yusuf S, Michelson EL, Granger CB. Red cell distribution width as a novel prognostic marker in heart failure: data from the CHARM Program and the Duke Databank. J Am Coll Cardiol 2007; 50: 40-47.
15) American Diabetes A. Standards of medical care in diabetes--2007. Diabetes Care 2007; 30: 4-41.
16) Grundy SM. Pre-diabetes, metabolic syndrome, and cardiovascular risk. J Am Coll Cardiol 2012; 59: 635-643.
17) Sabanayagam C, Shankar A, Lim SC, Lee J, Tai ES, Wong TY. Serum C-reactive protein level and prediabetes in two Asian populations. Diabetologia 2011; 54: 767-775.
18) Aronson D, Bartha P, Zinder O, Kerner A, Shitman E, Markiewicz W, Brook GJ, Levy Y. Association between fasting glucose and C-reactive protein in middle-aged subjects. Diabet Med 2004; 21: 39-44.
19) Wu T, Dorn JP, Donahue RP, Sempos CT, Trevisan M. Associations of serum C-reactive protein with fasting insulin, glucose, and glycosylated hemoglobin: the Third National Health and Nutrition Examination Survey, 1988-1994. Am J Epidemiol 2002; 155: 65-71.
20) Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function; epidemiology, clinical characteristics, and prognosis. J Am Coll Cardiol 2004; 43: 317-327.
21) Simel DL, DeLong ER, Feussner JR, Weinberg JB, Crawford J. Erythrocyte anisocytosis. Visual inspection of blood films vs automated analysis of red blood cell distribution width. Arch Intern Med 1988; 148: 822-824.
22) Ani C, Ovbiagele B. Elevated red blood cell distribution width predicts mortality in persons with known stroke. J Neurol Sci 2009; 277: 103-108.
23) Spell DW, Jones DV, Jr., Harper WF, David Bessman J. The value of a complete blood count in predicting cancer of the colon. Cancer Detect Prev 2004; 28: 37-42.
24) Lippi G, Targher G, Montagnana M, Salvagno GL, Zoppini G, Guidi GC. Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. Arch Pathol Lab Med 2009; 133: 628-632.
25) Minetti M, Malorni W. Redox control of red blood cell biology: the red blood cell as a target and source of prooxidant species. Antioxid Redox Signal 2006; 8: 1165-1169.
26) Berliner S, Rogowski O, Aharonov S, Mardi T, Tolshinsky T, Rozenblat M, Justo D, Deutsch V, Serov J, Shapira I, Zeltzer D. Erythrocyte adhesiveness/aggregation: a novel biomarker for the detection of low-grade internal inflammation in individuals with atherothrombotic risk factors and proven vascular disease. Am Heart J 2005; 149: 260-267.