CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.3692652

Available online at: http://www.iajps.com Research Article

VALUATION OF GLYCEMIC CONTROL, RED CELL DISTRIBUTION WIDTH AND DIABETES RELATED COMPLICATION

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Article Received: December 2019 **Accepted:** January 2020 **Published:** February 2020

Abstract:

Aim: *To assess the relationship between the red blood cells distribution width and glycemic control and the presence of complications in patients with diabetes.*

Study Design: *A Cross-Sectional Study.*

Place and Duration: *In the Medicine Unit of Sharif Medical City Lahore for one year duration from May 2018 to May 2019.*

Methods: *300 total patients with diabetes mellitus type II were selected for the study. Clinical and demographic features were documented and complete blood counts were performed. The distribution width of red blood cells, glycosylated hemoglobin, fasting and random sugar, lipid profile, urea and creatinine. The presence of complications was assessed during a clinical trial. SPSS 21.0 was used for data analysis.*

Results: *There were 300 middle-aged patients with 54.20 ± 12.07 mean age. The diabetes mean duration was 7.40 ± 5.50 years and the mean glycosylated hemoglobin was 8.85 ±1.23. Red blood cell distribution was related with diabetes duration, hypertension, macro vascular and microvascular complications, and glycemic control (each p <0.0001). A statistically significant linear relationship was observed between the distribution of red blood cells and the number of macro vascular and microvascular complications (p <0.0001) and glycosylated hemoglobin (p <0.0001). The mean width of red blood cell distribution was 14.54 ± 1.50, 15.02 ± 1.40 and 14.80 ± 1.60, respectively, for optimal control, border control and weak control. This linear growth pattern was statistically significant (p <0.0001).*

Conclusion: *The linear relationship between the RDW and glycosylated hemoglobin may allow its use as a measure of hyperglycemia.*

Key words: *RDW, HbA1c, diabetic complications, glycemic control, type 2 diabetes.*

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Please cite this article in press Imran Joher et al, ***Valuation Of Glycemic Control, Red Cell Distribution Width And Diabetes Related Complication.,*** *Indo Am. J. P. Sci, 2020; 07(02).*

INTRODUCTION:

The distribution width of red blood cells (RDW) is a quantitative measure of the variability in the size of red blood cells. Automated hematology analyzers provide levels of RDW as part of routine blood count (CBC). It is calculated by dividing the standard deviation of the volume of erythrocytes by the mean cell volume (MCV) and converting it into a percentage[1-3].

Study data results combined higher RDW levels with poorer results in the general population. There is an established relationship between high RDW and cardiovascular disease, especially coronary artery disease, stroke, heart failure and metabolic syndrome[4-5]. Documented connections go beyond cardiovascular disease, and there are studies highlighting the correlation between high WFD and Crohn's disease, hypothyroidism and hyperthyroidism, and chronic kidney disease[6-7]. Therefore, it is not surprising that researchers describe the RDW as an inflammatory marker with significant mortality in a healthy and patient population[8-9]. Strong and gradual correlation results between RDW and C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) also allow the use of RDW as a marker of inflammation. It was found that high RDW in diabetic patients was significantly higher than in non-diabetic patients, and longitudinal changes in RDW in diabetic patients were significant compared to their non-diabetic counterparts. This study was planned to assess RDW in patients with type 2 diabetes (T2DM) and assess the relationship between RDW and glycemic control as well as the presence of microvascular and macrovascular complications.

PATIENTS AND METHODS:

This Cross-Sectional Study was held in the Medicine Unit of Sharif Medical City Lahore for one year duration from May 2018 to May 2019. A total of 300 patients with type 2 diabetes were selected for the study. As local data are not available, an international survey should be used to calculate the sample size. The sample size was 300 patients, with a 95% confidence level, 90% strength and 2.06 lower endpoints (OR). Using non-probability sampling technique, patients with T2DM patients were enrolled from among those presenting to the diabetic out-patient department (OPD). Informed written consent was obtained from each participant. Among them were people aged 18 to 85, as well as those who regularly received medications with a regular diagnosis of T2DM and had regular follow-up visits for at least a year. Proven anemia (hemoglobin in men [Hb] <12 g / dl and <11 g / dl in women), blood transfusions, hematinic (iron, vitamin B12 or folic acid supplements), if treated, patients were excluded from erythropoietin or currently or former smokers.

Demographic and clinical parameters for sex, age, height, weight, body mass index (BMI), duration of T2DMand its treatment (including oral agents, insulin therapy containing injections or combinations thereof) have been documented). Macro-vascular complications associated with diabetes, such as the presence of comorbidities such as hypertension and ischemic heart disease (IC), peripheral vascular disease, stroke, and myocardial infarction, were evaluated by reviewing the patient's medical records. Microvascular complications were evaluated in the clinic. Neuropathy was assessed by detailed examination of nephropathy and retinopathy based on microfilament examination, micro-albuminuria or pure proteinuria.

CBC, including RDW, was measured using a Sysmex XP 100 automated analyzer (Sysmex Corporation, Kobe, Japan). According to the hospital laboratory, the normal reference range for WFD was 11-14%.

During fasting glucose (FBG) and random blood glucose (RBG) measurements, glycosylated hemoglobin (HbA1c) was measured using a Cobas 6000 e601 series analyzer (Roche / Hitachi Diagnostics, Tokyo, Japan), urea and creatinine, alanine aminotransferase (ALT) and fasting lipid profile were measured using a Cobas 6000 series analyzer (Roche / Hitachi Diagnostics, Tokyo, Japan). The collected data was analyzed using SPSS 21. Descriptive statistics expressed as frequency and percentage as well as continuous variables presented as mean ± standard deviation (SD) were used for qualitative variables. The variables were compared using an independent sample test for mean RDW, sex and presence of complications. An analysis of variance (ANOVA) was used to compare the number of complications, age groups, duration of diabetes, and magnitude of glycemic control. Pearson's correlation coefficient was used to assess the correlation between RDW and clinical and laboratory parameters. Statistical analysis was considered significant with conventional $p < 0.05$.

RESULTS:

195 (65%) of the 300 patients were women. The overall mean age was 54.15 ± 12.07 years (range: 26-85 years, mean T2DM duration was 7.40 ± 5.50 years, and mean HbA1c was 8.85 ±1.23. Macro vascular and complications were observed and other conditions.

The clinical features, mean red cell distribution width (RDW) and Demographic data given in Table-1.

	RDW Mean ±SD	**n**	**p-value**		**RDW Mean ±SD**	**n**	**p-value**
Sex				**Presence of Macro vascular Complications**			
Male	15.30±1.79	105	0.37	Yes	16.70±1.60	55	<0.0001
Female	15.09±1.50	195		No	14.90±1.49	245	
Age Group (years)				**Number of Macro vascular Complications**			
26 - 35	14.89±1.50	20	0.049	None	14.90±1.50	240	<0.0001
36 - 45	14.95±1.48	60		1	16.29±1.50	43	
46 - 55	15.02±1.50	100		2	17.30±1.15	15	
56 - 65	15.30±1.80	80		3	18.85±2.70	2	
66 - 75	15.09±1.39	30		**Neuropathy**			
76 - 85	16.50±2.40	10		Yes	15.69±1.49	180	
Duration of T2DM				No	14.09±1.30	120	
< 5 Years	14.69±1.45	135	<0.0001	**Nephropathy**			<0.0001
6 -10 Years	15.50±1.44	85		Yes	16.19±1.50	190	
11 - 15 Years	15.40±1.20	35		No	14.39±1.29	110	
16 -20 Year	15.90±2.00	25					
> 20 Years	15.70±2.50	20					
Medical Treatment for T2DM				**Retinopathy**			
Insulin alone	14.89±1.50	30	<0.0001	Yes	16.10±1.40	160	<0.0001
Oral agents alone	15.50±1.55	190		No	14.39±1.40	140	
Insulin plus oral agents	15.80±1.68	80					
Hypertension				**Presence of Microvascular Complications**			
Yes		130	<0.0001	Yes	15.59±1.48	220	<0.0001
No		170		No	13.70±1.15	80	
Ischemic Heart Disease				**Number of Microvascular Complications**			
Yes	15.49±1.50	40	<0.0001	None	13.80±1.20	60	<0.0001
No	14.90±1.66	260		1	14.69±1.18	70	
Peripheral Vascular Disease				2	15.65±1.10	65	

Yes	16.50± 1.56	25	<0.00 01	3	16.49±1.50	10 5	<0.00 01
No	15.10± 1.60	27 5		**Glycemic Control**			
Cerebrovascular Disease				Optimal (HbA1c <7%)	13.89±1.65	30	
Yes	16.79± 1.40	40	<0.00 01	Borderline (HbA1c 7 - 8.5%)	14.69±1.40	11 0	<0.00 01
No	15.09± 1.60	26 0		Poor (HbA1c >8.5%)	15.80±1.60	16 0	
Myocardial Infarction							
Yes	17.02± 1.80	45	<0.00 01				<0.00 01
No	14.95± 1.50	25 5					

The average RDW was 15.194 ± 11.77% and duration of T2DM, hypertension was considerably related with complications of microvascular and macrovascular diabetes and the degree of glycemic control (each p <0.0001) There was no important association between RDW and gender or age (p <0.05 each). A statistically noteworthy linear association was observed between the number of microvascular complications (p <0.0001) and HbA1c (p <0.0001) WFD and the weakest, but statistically significant correlations for fasting blood sugar, random blood sugar, cholesterol, serum and serum such as creatinine (p <0.0001) RDW and high density lipoprotein (HDL), ALT, LDL and no significant relationship those observed between triglycerides (TG). The RDW value was also not significantly related to any other CBC parameter (Table 2).

Correlations between clinical, laboratory parameters and red cell distribution width (RDW) in Table-2

	Pearson Correlation		**p-value**
Age	0.119		0.021
BMI	-0.035		0.49
Weight	-0.008		0.8
HbA1c	0.44		<0.0001
Duration of T2DM	0.259		<0.0001
Fasting Blood Glucose	0.36		<0.0001
Random Blood Glucose	0.37		<0.0001
Hb	0.025		0.63
TLC	-0.026		0.61
MCH	0.043		0.41
MCV	-0.04		0.49
Hematocrit	0.039		0.439
Urea	0.199		<0.0001
Platelets	0.069		<0.0001
ALT	0.089		0.079
Creatinine	0.279		
Total Cholesterol	0.129		0.01
HDL-C	-0.059		0.259
LDL-C	0.08		0.139
Triglycerides	0.097		0.065

Various levels of glycemic control and RDW comparisons were analyzed. The average RDW value was 14.54 ± 1.50, 15.02 ± 1.40 and 14.80 ± 1.60 respectively, for optimal control (HbA1c <7%) and border control (HbA1c 7-8.5%, respectively) and poor control (HbA1c> 8.5%). This linear growth pattern was statistically significant (p <0.0001). Weak glycemic control has been associated with values less than the optimal control for MCV (p <0.0001). Both total and TG cholesterol levels were found to increase when glycemic control deteriorated (p <0.0001) (Table 3).

Correlations between clinical, laboratory parameters and red cell distribution width (RDW) in Table-3

	Optimal (HbA1c <7%)	Borderline (HbA1c 7 - 8.5%)	Poor (HbA1c >8.5%)	p-value
TLC	7665±1609	7839±1850	8578±6100	0.240
RDW	14.04±1.59	14.69±.39	15.80±1.60	<0.0001
MCH	29.3±1.7	28.92±1.9	27.91 ± 1.9	0.569
MCV	85.3±3.6	84.9±3.6	83.5±3.7	<0.0001
Hb	13.7±1.3	13.8±1.2	13.5±1.01	0.070
Urea	34±14	40±30	37±20	0.18
Platelets	261280±82049	270990 ± 91419	281319 ± 89829	0.360
Creatinine	0.99±0.60	1.10±0.60	1.11±0.56	0.243
Total Cholesterol	169±44	170±50	183±53	0.042
ALT	36±23	34±19	35±21	0.310
HDL-C	34±8	36±11	36±9	0.790
LDL-C	91±29	97±38	105±58	0.153
Triglycerides	162±65	180±85	224±173	0.003

DISCUSSION:

The current study has shown a significant relationship between the extended duration of RDW and T2DM, the presence of hypertension, the complications of macrovascular and microvascular diabetes, and the degree of glycemic control. A statistically important linear association was establish between the RDW and the number of macrovascular complications, the number of microvascular complications and HbA1c. Increased HbA1c levels were associated with the upward trend of RDW. Weak but statistically significant correlations were observed for RDW and FBG, RBG, total serum cholesterol and serum creatinine.

Our findings support the study, which the RDW was found to be significant and positively associated with HbA1c, which corresponds to a 0.10% increase in HbA1c for 1 increase in SD in the RDW. The association between diabetes and RDW complications (microvascular and macrovascular) was investigated in a study that found that greater RDW values were related with vascular complications, myocardial infarction, heart failure, the possibility of stroke. DM is considered a proinflammatory condition and it has been suggested that RDW can be used as a marker of inflammation in DM2. The presence of hyperglycemia leads to a decrease in cell deformability, mechanical properties of red blood cells, an increase in adhesion and an increase in osmotic fragility. High glucose leads to a change in the arrangement of erythrocyte membranes, impairment of Hb oxygen binding activity and changes in the mechanical properties of the cell membrane and general aspects of the cell wall. These changes lead to changes in the structure of erythrocytes and changes in the hemodynamic properties of red blood cells. The effect of hyperglycemia goes beyond structural changes with a significant impact on the life of red blood cells. This leads to large variability in erythrocyte volume. Constant glycemic control has been found to cause a small but consistent increase in the half-life of red blood cells compared to poor control. Therefore, it can be understood that there is an interaction between inflammation and the undesirable effect of hyperglycemia on mechanics. The properties of erythrocytes can affect the RDW values.

Another hypothetical mechanism supporting the pathogenic role of high RDW in CVD concerns the physical properties of red blood cells in patients with a high degree of anisocytosis. One study showed that the increase in WFD was significantly and positively associated with a decrease in erythrocyte deformability ($p < 0.003$). Therefore, it makes sense that greater variability in the volume of erythrocytes impairs blood flow by increasing blood viscosity, triggering or increasing the negative consequences of both CVD and pre-existing vascular obstruction.

Deregulation of red blood cell homeostasis, which involves a combination of altered erythropoiesis and abnormal erythrocyte metabolism and survival, is reflected in the increase in RDW. Potentially different factors can be caused by oxidative stress, red blood cell inflammation disorder, shortened telomere length, hypertension, dyslipidemia and

abnormal erythropoietin function. All of these factors have an independent position as important prognostic factors for severe morbidity and death.
Regarding limitations, only correlation can be measured in cross-section of the current study, but not causation. The study was an effort of one center and was not forward-looking. In addition, the results represent the DM2 study population of patients treated in a third-degree public care center. To generalize our results, we need to replicate in many centers to differentiate patient groups. Other inflammatory markers such as ESR, CRP and serum ferritin were also not measured.

CONCLUSION:

RDW is a routine, cheap and widely available marker that correlates well with glycemic control. Its association with hypertension and the presence of macrovascular and microvascular complications may reflect T2DM complications and existing inflammatory load. The linear relationship with HbA1c may allow it to be used as a measure of the degree of hyperglycemia and may justify future prospective studies to further investigate this relationship.

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