RESEARCH ARTICLE

Assessment of red cell distribution width, glycaemic control and diabetes related complications - the ARDENT Study

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Abstract

Objective: To assess the association of red cell distribution width with glycaemic control and the presence of complications in diabetes patients.

Methods: The cross-sectional study was done at the Pakistan Institute of Medical Sciences, Islamabad, Pakistan, from September to November 2017, and comprised patients with type 2 diabetes. Clinical and demographical characteristics were documented and they were subjected to complete blood count, red cell distribution width, glycated haemoglobin, fasting and random blood glucose, lipid profile, urea and creatinine. The presence of complications were assessed during clinical examination. SPSS 20 was used for data analysis.

Results: There were 349 patients with a mean age of 53.14±11.77 years. The mean duration of diabetes was 8.36±6.64 years and mean glycated haemoglobin was 9.05±1.93. Red cell distribution width was significantly associated with the duration of diabetes, hypertension, macrovascular and microvascular complications and extent of glycaemic control ($p<0.0001$ each). A statistically significant linear relationship was observed between red cell distribution width and the number of macrovascular and microvascular complications ($p<0.0001$) and glycated haemoglobin ($p<0.0001$). Mean red cell distribution width was 13.94±1.66, 14.72±1.38, and 15.76±1.55 for optimal control, borderline control and poor control respectively. This linear incremental pattern was statistically significant ($p<0.0001$).

Conclusion: The linear association of red cell distribution width with glycated haemoglobin may enable its use as a measure of the extent of hyperglycaemia.

Keywords: RDW, HbA1c, Diabetic complications, Glycaemic control, Type 2 diabetes mellitus.

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Introduction

Red blood cell distribution width (RDW) is a quantitative measurement of erythrocyte size variability. Automated haematology analysers provide RDW levels as part of the routine complete blood count (CBC). It is calculated by dividing the standard deviation of erythrocyte volume by the mean cell volume (MCV) and converting it into a percentage.[1,2]

The results of study data have linked elevated levels of RDW to poorer outcomes in the general population.[3,4] There is an established association between raised RDW and cardiovascular disease, particularly coronary artery disease,[5-8] stroke,[9] heart failure[10-18] and the metabolic syndrome.[19] The documented associations extend beyond cardiovascular disease, with studies highlighting correlations between elevated RDW and Crohn's disease,[20] hypothyroidism and hyperthyroidism,[21] and chronic kidney disease.[22] Thus it is not surprising that researchers have termed RDW an inflammatory marker with a significant predictive value of mortality in diseased and healthy populations.[23,24] The findings of a strong, graded association between RDW and C-Reactive Protein (CRP) and the erythrocyte sedimentation rate (ESR) further establishes the use of RDW as a marker of inflammation.[25] Elevated RDW in patients with diabetes has been found to be significantly higher than in non-diabetic controls[23] and that longitudinal changes in RDW were significant in patients with diabetes versus non-diabetic counterparts.[26] The current study was planned to evaluate RDW in patients with type 2 diabetes mellitus (T2DM) and to assess the relationship between RDW and glycaemic control and the presence of both microvascular and macrovascular complications.

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Patients and Methods

The cross-sectional study was done at the Pakistan Institute of Medical Sciences (PIMS), Islamabad, Pakistan, from September to November 2017, and comprised T2DM patients. Since local data was not available, an international study[27] had to be relied upon for the calculation of sample size. With a 95% confidence level, 90% power and least extreme odds ratio (OR) of 2.06, the sample size was 336 patients. Using non-probability consecutive sampling technique, T2DM patients were enrolled from among those presenting to the diabetic out-patient department (OPD). Written informed consent was taken from each participant. Those included were aged 18-85 years, with a T2DM diagnosis for at least one year who were on regular medication and were undertaking regular follow-up visits. Patients were excluded if they had proven anaemia (Haemoglobin [Hb]<12 g/dL in males and <11 g/dL in females), had received blood transfusions, haematinics (iron, vitamin B12 or folic acid supplementation), erythropoietin treatment or were current or former smokers.

Demographic and clinical parameters including gender, age, height, weight, body mass index (BMI), duration of T2DM, treatment being taken for T2DM (oral agents, injectable therapy including insulin, or a combination of both) were documented. The presence of co-morbidities, like hypertension and ischaemic heart disease (IHD), diabetes-related macrovascular complications, like peripheral vascular disease, cerebrovascular accidents and myocardial infarctions, were assessed via review of patients' medical records. Microvascular complications were evaluated in the clinic. Neuropathy was assessed by microfilament examination, nephropathy by the presence of microalbuminuria or frank proteinuria, and retinopathy was assessed by detailed fundoscopic examination.

CBC, including RDW, was measured with Sysmex XP 100 automated analyzer (Sysmex Corporation, Kobe, Japan). The normal reference range for RDW was 11-14% as per the hospital laboratory.

Glycated haemoglobin (HbA1c) was measured with the use of Cobas 6000 series analyser e601 (Roche/Hitachi Diagnostics, Tokyo, Japan) while fasting blood glucose (FBG) and random blood glucose (RBG) measurements, urea and creatinine, alanine aminotransferase (ALT) and the fasting lipid profile were measured with Cobas 6000 series analyser (Roche/Hitachi Diagnostics, Tokyo, Japan).

Data collected was analysed using SPSS 20. Descriptive statistics were employed for qualitative variables, expressed as frequencies and percentages, and continuous variables, presented as means ± standard deviations (SD). Variables were compared using independent samples t-test for mean RDW, gender and presence of complications. Analysis of variance (ANOVA) was applied to compare the number of complications, age groups, duration of diabetes and extent of glycaemic control. Pearson correlation coefficient was applied to assess correlations between RDW and clinic-laboratory parameters. Statistical analysis was considered significant at the conventional $p<0.05$.

Results

Of the 349 patients, 213(61%) were females. The overall mean age was 53.14±11.77 years (range: 26-85 years. Mean T2DM duration was 8.36±6.64 years and mean HbA1c was 9.05±1.93. Macrovascular and complications as well as other conditions of the sample was noted (Table 1)

Mean RDW was 15.194±11.77% and it was be significantly associated with T2DM duration, hypertension, macrovascular and microvascular complications of diabetes and the extent of glycaemic control ($p<0.0001$ each). No significant association was found between RDW and age or gender ($p>0.05$ each). A statistically significant linear relationship was observed between RDW and number of macrovascular complications ($p<0.0001$), number of microvascular complications ($p<0.0001$) and HbA1c ($p<0.0001$). Weaker but statistically significant correlations were also observed for RDW and fasting blood glucose, random blood glucose, serum total cholesterol and serum creatinine ($p<0.0001$). No significant correlations were seen between RDW and ALT, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglycerides (TG). RDW value was also not significantly associated with any of the other CBC parameters (Table-2).

Comparisons were analysed between different levels of glycaemic control and RDW. The mean value for RDW was 13.94±1.66, 14.72±1.38, 15.76±1.55 for optimal control (HbA1c <7%), borderline control (HbA1c 7-8.5%) and poor control (HbA1c >8.5%) respectively. This linear incremental pattern was statistically significant ($p<0.0001$). Poor glycaemic control was associated with smaller values for MCV than optimal control ($p<0.0001$). Both total cholesterol and TG levels were found to increase as glycaemic control worsened ($p<0.0001$) (Table-3).

Table-1: Demographic and clinical features and mean red cell distribution width (RDW).

	RDW Mean±SD	n	*p*-value		RDW Mean±SD	n	*p*-value
Sex				Presence of Macrovascular Complications			
Male	15.29±1.83	136	0.366	Yes	16.65±1.65	60	**<0.0001**
Female	15.13±1.49	213		No	14.89±1.48	289	
Age Group (years)				Number of Macrovascular Complications			
26 - 35	14.90±1.49	24	0.051	None	14.89±1.48	289	**<0.0001**
36 - 45	15.02±1.49	71		1	16.361.49	46	
46 - 55	15.16±1.49	115		2	17.37±1.16	12	
56 - 65	15.25±1.79	93		3	18.90±2.67	2	
66 - 75	15.14±1.41	31		Neuropathy			
76 - 85	16.47±2.38	15		Yes	15.74±1.53	231	**<0.0001**
				No	14.13±1.27	118	
Duration of T2DM							
< 5 Years	14.71±1.48	152	**<0.0001**	Nephropathy			
6 -10 Years	15.47±1.43	92		Yes	16.21±1.48	148	**<0.0001**
11 - 15 Years	15.44±1.23	49		No	14.45±1.31	201	
16 -20 Years	15.89±1.99	31					
> 20 Years	15.75±2.49	25					
Medical Treatment for T2DM				Retinopathy			
Oral agents alone	14.90±1.55	217	**<0.0001**	Yes	16.09±1.39	162	**<0.0001**
Insulin alone	15.55±1.54	47		No	14.42±1.42	187	
Insulin plus oral agents	15.74±1.73	85					
Hypertension				Presence of Microvascular Complications			
Yes	15.55±1.56	159	**<0.0001**	Yes	15.64±1.49	266	**<0.0001**
No	14.89±1.63	190		No	13.76±1.18	83	
Ischaemic Heart Disease				Number of Microvascular Complications			
Yes	16.48±1.57	32	**<0.0001**	None	13.75±1.18	82	**<0.0001**
No	15.06±1.58	317		1	14.70±1.20	91	
Peripheral Vascular Disease				2	15.66±1.04	75	
Yes	16.83±1.43	22	**<0.0001**	3	16.50±1.48	101	
No	15.08±1.59	327		Glycaemic Control			
Cerebrovascular Disease				Optimal (HbA1c <7%)	13.93±1.66	38	**<0.0001**
Yes	16.75±1.61	21	**<0.0001**	Borderline (HbA1c 7 - 8.5%)	14.72±1.38	123	
No	15.10±1.59	328		Poor (HbA1c >8.5%)	15.76±1.55	188	
Myocardial Infarction							
Yes	17.01±1.79	33	**<0.0001**				
No	15.01±1.49	316					

p-values in bold are significant at the <0.05 level., SD: Standard deviation, T2DM (Type 2 Diabetes Mellitus), RDW (Red Cell Distribution Width).

Discussion

The current study demonstrated a significant association between raised RDW and T2DM duration, the presence of hypertension, macrovascular and microvascular complications of diabetes and the extent of glycaemic control. A statistically significant linear relationship was found between RDW and number of macrovascular complications, number of microvascular complications and HbA1c. Increasing levels of HbA1c were associated with a rising trend in RDW. Weaker but statistically significant correlations were also observed for RDW and FBG, RBG, serum total cholesterol and serum creatinine.

Our findings corroborate the study[28] which found that RDW was significantly and positively associated with HbA1c, corresponding to an increase in HbA1c of 0.10% per 1 SD increase in RDW. The relationship between RDW and complications of diabetes (microvascular and macrovascular) was investigated by a study[27] which found that higher values of RDW were associated with an increased probability of developing vascular complications, heart failure, myocardial infarction, stroke and nephropathy. T2DM is considered a pro-inflammatory state[29] and it has been suggested[30] that RDW can be used as a marker of inflammation in T2DM.

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

	Pearson Correlation	*p*-value
Age	**0.123**	**0.022**
Weight	-0.009	0.862
BMI	-0.036	0.505
Duration of T2DM	**0.263**	**<0.0001**
HbA1c	**0.438**	**<0.0001**
Random Blood Glucose	**0.366**	**<0.0001**
Fasting Blood Glucose	**0.357**	**<0.0001**
TLC	-0.027	0.616
Hb	0.026	0.626
MCV	-0.038	0.481
MCH	0.045	0.406
Haematocrit	0.041	0.443
Platelets	0.071	0.184
Urea	**0.198**	**<0.0001**
Creatinine	**0.282**	**<0.0001**
ALT	0.093	0.082
Total Cholesterol	**0.134**	**0.012**
LDL-C	0.079	0.141
HDL-C	-0.060	0.260
Triglycerides	0.098	0.067

p-values in bold are significant at the <0.05 level, BMI (Body Mass Index), T2DM (Type 2 Diabetes Mellitus), TLC (Total Leucocyte Count), Hb (Hemoglobin), MCV (Mean Cell Volume), MCH (Mean Cell Hemoglobin), ALT (Alanine Aminotransferase), LDL-C (Low Density Lipoprotein Cholesterol), HDL-C (High Density Lipoprotein Cholesterol).

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

	Optimal (HbA1c <7%)	Borderline (HbA1c 7 - 8.5%)	Poor (HbA1c >8.5%)	p-value
RDW	13.94±1.66	14.72±.38	15.76±1.55	**<0.0001**
TLC	7676±1614	7842±1846	8580±6097	0.239
Hb	13.5±1.2	13.7±1.0	13.4±1.1	0.071
MCV	86.4±3.7	85.3±3.5	84.0±3.5	**<0.0001**
MCH	29.2±1.6	29.1±2.2	28.9 ± 1.8	0.571
Platelets	261276±82050	270974 ± 91421	281321 ± 89833	0.357
Urea	33±13	41±29	37±21	0.192
Creatinine	0.98±0.57	1.00±0.59	1.10±0.55	0.245
ALT	35±22	33±18	36±22	0.308
Total Cholesterol	168±45	171±49	184±54	**0.043**
LDL-C	92±28	98±39	106±57	0.154
HDL-C	35±7	35±10	35±8	0.798
Triglycerides	163±66	179±86	225±174	**0.004**

p-values in bold are significant at the <0.05 level, RDW (Red Cell Distribution Width), TLC (Total Leucocyte Count), Hb (Hemoglobin), MCV (Mean Cell Volume), MCH (Mean Cell Hemoglobin), ALT (Alanine Aminotransferase), LDL-C (Low Density Lipoprotein Cholesterol), HDL-C (High Density Lipoprotein Cholesterol)

Red blood cells (RBCs) are impacted by hyperglycaemia in ways other than the formation of HbA1c. The presence of hyperglycaemia leads to reduced cellular deformability, altered mechanical properties of RBCs, an increase in adhesion and increased osmotic fragility. High glucose levels lead to rearrangement of erythrocyte membranes, defects in oxygen binding activity of Hb and alterations in the mechanical features of the cell membrane and general aspects of the cell wall.[31,32] These changes lead to an altered erythrocyte structure and changes in the haemodynamic characteristics of RBCs.[33,34] The effect of hyperglycaemia goes beyond structural changes, with a marked effect on RBC lifespan. This leads to high variability in erythrocyte volumes.[35] Tight glycaemic control was found to result in a modest but consistent increase in RBC half-life compared to poor control.[36] It can thus be inferred that the interplay between inflammation and the undesirable effects of hyperglycaemia on the mechanical features of the erythrocytes could impact RDW values.

The question arises whether RDW is simply a marker of inflammation or is also actively involved in the pathogenesis of a variety of disorders. This has been aptly summarised in a review article.[37] Citing a study[38] which showed that a strong and direct relationship exists between the degree of anisocytosis (i.e. the RDW value) and the cholesterol content of erythrocytes membranes ($p<0.001$), and that the cholesterol content of erythrocytes membranes is positively and independently associated with clinical instability in patients with cardiovascular disorders. It also found that the total amount of free cholesterol contained within the necrotic core of advanced atherosclerotic plaques appears to be much greater than that expected from apoptotic death of inflammatory cells. It thus postulated that it is conceivable that the free cholesterol in excess within the primary atherosclerotic lesion may originate from other cellular sources, including RBCs, and that anisocytosis may directly participate in the pathogenesis of cardiovascular disease (CVD) through a variety of mechanisms.

Another postulated mechanism supporting the pathogenetic role of an elevated RDW in CVD relates to the physical properties of RBCs in patients with high degree of anisocytosis. A study[39] showed that an increased RDW is significantly and positively associated with decreased erythrocyte deformability ($p<0.003$). Therefore, it is plausible that a greater variation of erythrocyte volumes would impair blood flow through the microcirculation by increasing blood viscosity, thus triggering or amplifying the adverse consequences of a pre-existing vascular occlusion in both CVD and venous thrombosis.[40]

Deregulation of RBC homeostasis involving a combination

of impaired erythropoiesis and abnormal erythrocyte metabolism and survival is mirrored by an increased RDW. This may potentially be caused by a variety of factors that include oxidative stress, inflammation fragmentation of RBCs, shortening of telomere length, hypertension, dyslipidaemia and abnormal erythropoietin function. All of the mentioned factors have an independent standing as important prognostic factors for severe morbidity and death.[37]

In terms of limitations, the cross-sectional design of the current study can measure only correlation but cannot establish causality. The study was a single-centre effort and was not prospective in nature. Also, the results represent the population of the study who were T2DM patients being managed at a government tertiary healthcare centre. In order for our results to be generalised, a multi-centre replication should be performed to diversify patient groups. Other inflammatory markers such as ESR, CRP and serum ferritin were also not measured.

Conclusion

RDW is a routinely performed, low-cost and widely available marker that correlates well with glycaemic control. Its association with the presence of hypertension and both macrovascular and microvascular complications may reflect the inflammatory burden that exists with T2DM complications. The linear association with HbA1c may enable its use as a measure of the extent of hyperglycaemia and may provide a rationale for use in future prospective studies to further explore this association.

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