Red Cell Distribution Width as a Marker of Inflammation in Type 2 Diabetes Mellitus

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Abstract: Background: Red cell distribution width (RDW) is considered a prognostic marker which may reflect an underlying inflammatory process. This marker can be used as a predictor for macrovascular and microvascular complications of diabetes mellitus. **Aim of the study:** was to investigate the relation between RDW and vascular complications in patients with type 2 diabetes and it is relation to other inflammatory marker high sensitivity C-reactive protein (hs-CRP). **Subjects and methods:** This study is a cross-sectional study of 75 subjects with type 2 diabetes mellitus and 15 healthy controls. All subjects underwent thorough history, clinical examination and investigations including measurement of hs-CRP and calculation of RDW. **Results:** In the present study RDW was found to be elevated in diabetic patients with macrovascular complications (15.251±1.77) as compared to those without macrovascular complications with statistically significant difference (p =0.04). Also RDW was found to be elevated in diabetic patients with microvascular complications but this was not statistically significant (p= 0.87). Hs-CRP was elevated in diabetic patients with macro- and microvascular complications (3.12±4.06) with statistically significant difference as compared to control group (p =0.02). There was significant positive correlation between hs-CRP and HbA1c. Also positive correlations were found between RDW and hs-CRP. **Conclusion:** High levels of RDW are associated with increase risk of macrovascular complications in type 2 diabetes mellitus.
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Introduction:

Diabetes mellitus is a group of metabolic disorders characterized by hyperglycemia which results from either defect in insulin secretion, insulin action, or both. Chronic hyperglycemia of diabetes mellitus is associated with long term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart and blood vessels **(1)**.

The primary cause of mortality in diabetic patients is cardiovascular diseases (CVD) **(2)**, while major cause of morbidity is microvascular complications **(3).**

Inflammation has been proposed as a component of conditions such as hypertension, DM and metabolic syndrome causing their complications, but the role of inflammation as an independent factor is still uncertain **(4).** Detection of markers for macrovascular and microvascular disease could supply new data about pathogenesis of diabetic complications which may help early diagnosis and help to take decisions in terms of prevention and treatment. RDW is a measure of variation in size of circulating erythrocytes (anisocytosis) **(5)** which is routinely obtained in standard complete blood cell counts (CBC) without more costs and has been used in differential diagnosis of anemia. RDW is calculated mathematically [standard deviation (SD) of red cell volume /mean cell volume] x 100. The normal value of RDW ranging between 11.5 and 14.5 %, while higher values indicate greater variations in cell sizes **(5).** High RDW indicate the presence of anisocytosis which is related to impairment of erythropoiesis and degradation of erythrocytes **(5)**, reflecting chronic inflammation and increased level of oxidative stress **(6).** However the underlying biological mechanism remain unclear, RDW is recognized as global marker of chronic inflammation and oxidative stress **(7).**

There was strong and independent association of RDW level with risk of all-cause and cardiovascular (CV) mortality in patients with cardiovascular disease (CVD) **(8)** and in the general population **(9)**. Increase risk to recent cardiovascular insult in patient with previous myocardial infarction (MI) has been related to (RDW) **(8)**.

However the relationship between RDW and macrovascular complication was not investigated in any studies, moreover no published data were reported on the relationship between RDW and microvascular complication in selected diabetic persons **(10).**

The aim of the study was to study the relation between RDW and vascular complications in patients with type 2 diabetes and it is relation to other inflammatory marker hs-CRP.

2. Subjects and methods:

Patients:

This study is a cross-sectional study, it was conducted on 75 patients with type 2 diabetes mellitus selected from departments of internal medicine of Cairo University Hospital and endocrinology outpatient clinic and 15 matching healthy controls over 12 month period (January-December 2011). All subjects provided written consent for data collection which was approved by our institutional ethical committee. They were classified into the following groups:

Group I: include 75 subjects with type 2 diabetes mellitus.

Group II: include 15 subjects matching healthy controls.

Inclusion criteria:

Type 2 diabetes mellitus with micro and/or macrovascular complications.

Exclusion criteria:

1- Type 1 diabetes mellites.
2-Type 2 diabetes mellitus without micro or macrovascular complications.
3- Type 2 diabetes mellitus with acute complications like diabetic ketoacidosis (DKA) or acute illness (cold, flu, diarrhea, vomiting, pneumonia or ear infections within the last month).
4- Chronic illness such as congestive heart failure or chronic liver disease.

Methods:

Analysis was confined to 75 participants with type 2 DM, 62 females and 13 males, the ages of the patients ranged from 43 to 68 years. Also the study included 15 healthy subjects as control group, 5 females, 10 males with the age ranging from 33 to 63 years.

Thorough history taking and full clinical examination was done for all participants with special emphasis on duration of diabetes, diabetic medication, and complications of diabetes.

Diabetes mellitus (DM) was defined as fasting plasma glucose ≥7.0mmol/l and or 2-hours post-load plasma glucose ≥11.1mmol/l (both determined after overnight fasting for at least 8 hours) and or HbA1c≥6.5%(48mmol/mol) and or self reported use of diabetes medication and or self reported medical diagnosis of diabetes (other than gestational diabetes) at the time of interview **(10).**

Patients were defined to be hypertensive on the basis of known to be hypertensive and or systolic blood pressure ≥ 130 mmHg and or diastolic blood pressure ≥ 80 mmHg **(ADA, 2010) (2)**.

We also studied their anthropometric characteristics by measuring their weight, height and calculating BMI. Waist circumference and hip circumference were measured.

Patients were also assessed as regards presence or absence of diabetic microvascular complications. Fundus examination was done to detect retinopathy. The presence of retinopathy was classified using the Modified Airlie House Classification scheme **(11)**, and then diabetic retinopathy score was determined.

Also patients were examined for the presence of diabetic peripheral neuropathy (DPN); we use modified Neuropathy disability score criteria (NDS) for diagnosis of diabetic neuropathy. NDS of ≥ 6 was used for diagnosis of diabetic PN **(12).**

To assess renal function, we measured, blood urea, serum creatinine, urine analysis was done for proteinuria and detection of microalbuminurea by collection of 24 hours urine sample.

Patients were also assessed as regards presence or absence of diabetic macrovascular complications [cardiovascular and neurological examinations, Electrocardiogram (ECG) and when required echocardiography, Doppler and computed tomography (CT brain)].

Laboratory investigations were done including:

1-Fasting blood sugar, post prandial blood sugar and HbA1c.
2-Lipid profile: total cholesterol, HDL and LDL cholesterol and triglycerides (TGs).
3-Measurement of hs-CRP: The quantitative determination of hs-CRP by a microplate immunoenzymometric assay (Monobind Inc., USA).
4- Measurement of RDW: 2ml of EDTA blood sample was collected into EDTA tubes for complete blood count using an electronic Coulter counter (Sysmex KX-21N) and RDW was calculated.

The instrument and the kits for blood glucose, lipid and kidney functions were supplied by Roche Diagnostics*.

Detection of microalbuminurea using kit supplied by Siemens Healthcare Diagnostics**.

**Roche Diagnostics Boehringer Mannheim GMbH, D-68298 Mannheim, Germany Boehringer Mannheim corporation, Indianapolis in USA customer technical support 1=800-428-2336.*

***Siemens Healthcare Diagnostics Inc. Newark, DE 10714, USA (www.siemens.com/diagnostics).*

Statistical Analysis

Analysis of data was performed using SPSS 17 (Statistical Package for Scientific Studies) for Windows. Data were statistically described in terms of mean ± standard deviation (± SD), median and range, or frequencies (number of cases) and percentages

when appropriate. For qualitative data comparison between two groups was done using chi -square test (χ^2). For comparison between mean of two groups student t-test was used, and one way ANOVA test was used for more than two independent groups. Fisher exact test was used instead of Chi-square test when one expected cell or more were < 5. For comparison between more than two means the F value of analysis of variance and schafee test was calculated. Comparison of numerical variables between the study groups was done using Mann Whitney *U* test for independent samples. Correlation between various variables was done using Pearson moment correlation equation for linear relation in normally distributed variables and Spearman rank correlation equation for non-normal variables. *p* values less than 0.05 was considered statistically significant.

3. Results

Our study included 75 type 2 diabetic participants 62 were females (82.7%) & 13 were males (17.3%) and 15 healthy controls, 5 were females (33.3%) & 10 were males (66.7%). Twenty nine patients (38.7%) had both microvascular& macrovascular complications while 41 patients (54.67%) had microvascular complications only & 5 patients (6.7%) had macrovascular complications only. Collectively 63 patients (84.0%) had microvascular complications (52 were females & 11 were males), mean age 55.03 years and 34 patients (45.3%) had macrovascular complications (30 were females & 4 were males) with mean age 53.41years.

Among the studied diabetic patients; 43 patients (57.3%) were hypertensive, 17 patients (22.7%) had history of chest pain,

Among Patients with microvascular complications (63 patients), 33 patients (44%) had nephropathy, 17 patients (22.66%) had retinopathy [15 cases had mild non proliferative diabetic retinopathy (NPDR), 2 cases had moderate NPDR], 53 patients (70.66%) had neuropathy while 37 patients (49.3%) had more than one microvascular complications.

Among Patients with macrovascular complications (34 patients) , 23 patients (30.66%) had ischemic heart diseases (IHD), 19 patients (25.33%) had peripheral vascular diseases (PVD), 3 patients (4%) had cerebrovascular stroke (CVS), while 10 patients (13.3%) had more than one macrovascular complications.

Table (1): Qualitative and quantitative measures of diabetic patients and controls

Variable	Microvascular complications	Macrovascular complications	Controls
NO	63	34	15
Sex			
Female	52	30	5
Male	11	4	10
Age	55.03	53.41	46.6
Blood Pressure			
SBP	142.06	129.7	130.67
DBP	83.96	86.47	80.67
BMI	32.23	41.5	29.23
Waist circumference	103.51	104.03	102.33
Hip circumference	110	109.53	103.33
Fasting Blood Sugar	175.7	167.18	98.53
Post Prandial Sugar	235.48	232.94	104.27
HbAlc	7.45	7.44	5.58
Blood urea	32.11	31.91	27.27
Serum Creatinine	0.95	0.89	0.77
Triglycerides	155.33	174.42	101.73
Total Cholesterol	221.95	228.53	179.40
HDL	53.3	48.2	46.2
LDL	138.34	143.99	106.73
RDW	15.22%	15.65%	15.25%

BMI: Body mass index, HbA1c: Glycosylated hemoglobin, HDL: High density lipoprotein, LDL: low density lipoprotein, RDW: Res cell distribution width, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

Table (2): Comparison of hs-CRP and RDW among cases and controls

	Cases		Controls		*P* value
	Mean	±SD	Mean	±SD	
hs-CRP	3.12	4.06	0.693	0.35	0.02*
RDW	15.251	1.77	15.247	0.83	0.98

*Significant

As shown in table (2): There was significant difference between hs-CRP among cases and controls with *P* value= 0.02 but no significant difference was found between RDW among cases and controls with *P* value= 0.98.

Table (3): Comparison of RDW, between cases with macrovascular and microvascular complications

	Number	RDW		*P* value
		Mean	±SD	
Macrovascular complications	34	15.65	1.44	0.04*
No macrovascular complications	41	14.93	1.71	
Microvascular complications	63	15.22	1.87	0.87
No microvascular complications	12	15.16	0.97	
Microvascular complications	63	15.22	1.87	0.25
Macrovascular complications	34	15.65	1.44	

**Significant*

As shown in table (3): It shows that there was a significant difference between RDW in patients with macrovascular complications as compared to those without macrovascular complications (*P* value= 0.04) but there was no significant difference between RDW in patients with microvascular complications as compared to those without microvascular complications (*P* value= 0.87). However by comparison between RDW in patients with microvascular and macrovascular complications, we found no significant difference with *P* value= 0.25.

Table (4): Comparison of RDW with different microvascular and macrovascular complications

	RDW		*P* value
	Mean	±SD	
Microvascular			
Nephropathy	15.27	2.04	
Retinopathy	15.60	1.48	0.88
Neuropathy	15.29	1.95	
Macrovascular			
CAD	15.77	1.45	
PVD	15.24	1.41	0.47
CVS	15.87	1.97	

CAD: coronary artery disease; PVD: peripheral vascular disease; CVS: cerebrovascular stroke

As shown in table (4): The highest level of RDW was found in patients with CVS (15.87) however, there was no significant difference between RDW in patients with different diabetic complications.

Table (5): Comparison of RDW between cases with microvascular or macrovascular complications and controls

	RDW		*P* value
	Mean	±SD	
Microvascular complications	15.22	1.87	0.91
Controls	15.25	0.83	
Macrovascular complications	15.65	1.44	0.32
Controls	15.25	0.83	

As shown in table (5): There was no significant difference of RDW between cases with microvascular or macrovascular complications and controls with P value= 0.91 and 0.32 respectively.

As shown in table (6): There was significant positive correlation between hs-CRP and HbA1c. Moreover there were positive correlation between hs-CRP, BMI, SBP, lipid profile, CAD, PVD and CVS but these correlations were not statistically significant.

There were negative correlation between hs-CRP, duration of diabetes, DBP, nephropathy, neuropathy and retinopathy but these correlations were not statistically significant.

Positive correlations were found between RDW and hs-CRP but this correlation was not statistically significant.

Also positive correlations were found between RDW, HbA1c, BMI, DBP, SBP, lipid profile, CAD, CVS, nephropathy and neuropathy while negative correlations were found with duration of diabetes, PVD and retinopathy however, these correlations were not statistically significant.

Table (6): Correlation between hs-CRP and RDW with different variables

	hs-CRP		RDW	
	Correlation	***P* value**	**Correlation**	***P* value**
Duration of DM	-0.112	0.34	-0.013	0.91
HbA1c	0.239	0.02*	0.011	0.92
BMI	0.099	0.35	0.095	0.37
DBP	-0.030	0.80	0.091	0.44
SBP	0.042	0.72	0.158	0.18
hs-CRP			0.083	0.43
Triglycerides	0.12	0.35	0.099	0.35
Cholesterol	0.21	0.08	0.113	0.29
HDL	0.06	0.62	0.048	0.655
LDL	0.21	0.07	0.112	0.292
CAD	0.1	0.41	0.13	0.27
PVD	0.15	0.20	-0.02	0.86
CVS	0.21	0.08	0.30	0.01
Nephropathy	-0.17	0.15	0.07	0.55
Neuropathy	-0.07	0.55	0.22	0.06
Retinopathy	-0.1	0.40	-0.15	0.21

** Significant hs-CRP: high sensitivity C- reactive protein, RDW: Res cell distribution width HbA1c: Glycosylated hemoglobin, BMI: Body mass index, DBP: Diastolic blood pressure, SBP: Systolic blood pressure,HDL: High density lipoprotein, LDL: Low density lipoprotein, AD: Coronary artery disease, sPVD: Peripheral vascular diseases, CVS: Cerebrovascular stroke,*

4. Discussion

Red cell distribution width (RDW) is considered a prognostic marker which may reflect an underlying inflammatory process **(13).** It is a measure of variation in size of red cell in a blood sample, which is calculated by both impedance and flow cystometric analyzers as a part of the routine complete blood count.

RDW is effectively a free test which, is reported alongside a complete blood count without extra cost with good prognostic value **(14).**

Why RDW is considered to be a predictor in a wide range of conditions is unclear, it was shown to be a strong predictor of mortality in general population of adults aged 45 years and more **(9)**. High RDW values were associated with deaths from cardiovascular disease (CVD), cancer, and other causes, however the effect was stronger for CVD **(9).**

It was reported that RDW is a strong predictor of mortality in many other conditions such as obesity, malignancies, and chronic kidney disease **(15).**

Atherosclerotic cardiovascular (CV) diseases are a main cause of morbidity and mortality in people with diabetes. Atherosclerosis is a multi factorial disease, involving hemodynamic, metabolic, and lifestyle determinant. As diabetic patients experience accelerated atherosclerosis, so undoubtedly we will require new strategies for risk prediction and primary prevention in diabetic patients. So identification of population at risk for type 2 diabetes mellitus and atherosclerosis at an early stage might prevent or delay the clinical onset of these disorders **(16).**

Recent studies support that chronic subclinical inflammation may be associated with insulin resistance and precede the development of clinically overt type 2 diabetes mellitus **(16)**. However, elevated concentrations of inflammatory markers, as CRP and interleukin-6 (IL-6) have been implicated in the development and progression of long term diabetic macrovascular complications **(17)**.

Inflammation may influence erythropoiesis, circulatory half life and deformability of erythrocytes,

promoting anisocytosis and thus elevating RDW levels **(16)**.

High level of RDW was also associated with the metabolic syndrome **(18),** leading to postulate a possible effect of an underlying inflammatory state (which typically occurred in diabetes and metabolic syndrome **[17])** on increased destruction of erythrocytes.

Similar finding was previously reported by **Acosta *et al.* (2000) (19),** where they reported shortened half life of red blood cell in diabetes mellitus.

However, the Relationship between RDW and diabetic complications has not been investigated **(10).** So the present study was done to study the relation between RDW and vascular complications in patients with type 2 diabetes and it is relation to other inflammatory marker hs-CRP.

In the present study RDW was found to be elevated in all cases (15.251±1.77) and also it was high in controls (15.247±0.83). This could be partially explained by prevalence of iron deficiency anaemia in our population. We exclude iron deficiency anemia by detection of normal levels of MCV and MCH but iron profile study was not done. And as it is stated by **Looker *et al.* (1997) (20)** Iron deficiency anemia was defined by at least two of the following criteria: transferrin saturation <15%, serum ferritin level < 26.9pmol/l and erythrocyte protoporphyrin level >1.24µmol/l **(20).**

By comparison between RDW in patients with macrovascular complications (15.65) and controls (15.25) there was no statistically significant difference (*P* value= 0.32).

While comparing RDW values in patients with and without macrovascular complications it was found to be higher in patients with macrovascular complications (15.65) than those without macrovascular complications (14.93) and this was statistically significant (*P* value= 0.04). This agrees with **Lee, (2005**) **(21)** who stated that chronic vascular inflammation may play a role in the development of macrovascular complications in diabetic patients. Also **Malandrino *et al.* (2012) (10)** suggest that RDW has a role as a predictive marker of macrovascular complications in diabetes mellitus. As they recommended, diabetic patients with raised level of RDW required close monitoring of risk factors as (dyslipidemia, hypertension and albuminuria) even without symptoms of CVD or with normal kidney function. RDW might help to detect patients who will benefit from starting treatment with anti-platelet agents for primary prevention of CVD **(10)**.

There is no significant difference between RDW in patients with microvascular complications (15.22) and controls (15.25) (*P*= 0.91).

In a study done by **Malandrino *et al.* (2012) (10)** no relationship between RDW and retinopathy was found but there was a significant association with nephropathy which can be explained by the fact that in the pathogenesis of diabetic nephropathy underlying macrovascular and microvascular mechanisms take place but diabetic retinopathy is mainly microvascular disease **(10).**

This finding is in agreement with **Felker *et al.* (2007) (22)** who suggested that inflammation has a greater role in macrovascular complications than in microvascular complications.

Our result showed positive correlations between RDW and HbA1c however, this was not statistically significant. This Agrees with **Lee, (2005**) **(21)** who observed that some of patients with reasonable glycemic control (HbAlc around 7) but with BMI more than 35 still had a higher RDW than those with lower BMI and this is the case in our study where HbA1c was 7.4 and BMI was 32.48.

In a study done by **Veeranna *et al.* (2012) (23)** reported that RDW was highly significantly correlated with HbA1c ($p < 0.001$), however the correlation itself was relatively mild (Spearman's rho=0.27).

Our result showed positive correlations between RDW and BMI, but this was not statistically significant. This agrees with **Ramana *et al.* (2004) (24)** who stated that a high BMI is associated with increased levels of proinflammatory cytokines, and that obesity is characterized by a state of chronic systemic low grade inflammation **(25).** Studies demonstrate an accumulation of activated macrophages and other immune active cells in adipose tissue from obese subjects **(26)** as possible sources of inflammatory cytokines, determining a link between obesity, low grade inflammation, and insulin resistance. Both obesity and low grade inflammation have been linked with the development of insulin resistance and type 2 diabetes **(27).**

Tanindi *et al.* (2012) (28) reported that higher RDW values were strongly correlated with high SBP and DBP. In our study there was positive correlation between RDW, DBP and SBP but this was not statistically significant.

In the present study hs-CRP levels was higher in cases (3.12±4.06) in comparison with control (0.96±0.35) and this was statistically significant P value= 0.02. There was significant positive correlation between hs-CRP and HbA1c. Positive correlations were found between hs-CRP, BMI, SBP and lipid profile; however these were not statistically significant.

Our results here are in agreement with **Rabkin *et al.* (2013) (29)** who reported that there is an elevation in inflammatory markers CRP, interleukin 18 (IL 18), monocyte chemoattractant protein-1

(MCP1) and amyloid alpha (AA) in population with dyslipidemia and hypertension, however further acceleration of CRP, MCP-1 and AA in presence of DM **(29).**

Rabkin *et al.* (2013) (29) also stated there was significant correlation between systolic but not diastolic blood pressure for CRP **(29)**, this is consistent with respect that CRP is linked to arterial stiffness **(30)**, this is also consistent with the fact that cytokines increases proliferation of smooth muscle cell causing hypertensive vascular changes **(29).**

Karantza *et al.* (2007) (31) documented that in adolescents with type 1 diabetes mellitus, triglycerides (TGs), apoprotein B (apoB), SBP and DBP were all significantly correlated with hs-CRP, after adjusting for age. Total cholesterol and HDL appeared to have positive and negative correlation, respectively with hs-CRP, although this correlation was not statistically significant. HbA1c, LDL and lipoprotein (a) [lp(a)] showed non significant correlation with hs-CRP **(31).**

Lippi *et al.* (2009) (13) found a correlation between high RDW and elevated indexes of inflammation, such as erythrocyte sedimentation rate (ESR) and CRP. This agrees with our study, where there was positive correlation between RDW and CRP but was not statistically significant.

Conclusion

We concluded that high levels of RDW are associated with increase risk of macrovascular complications in type 2 diabetes mellitus. It is applicable, inexpensive test (it is reported with a complete blood count without extra cost).

Limitations in our study included that:

1- Measurement of serum iron, transferrin saturation, iron binding capacity& ferritin to exclude iron deficiency as a cause of high RDW and we relied only on mean corpuscular volume and mean corpuscular hemoglobin concentration.

2- Measurement of serum folate and B12 levels as nutritional deficiency of these is associated with high level of RDW.

Recommendations for further studies to get a bigger number of diabetic patients and divide patients into groups of uncomplicated and complicated diabetics to detect role of RDW in occurrence of diabetic complications. Then patients with diabetic complications should be subdivided into patients with microvascular and macrovascular complications to detect in which type of complications RDW can be used as a predictor. Further studies are needed to examine its relation to other inflammatory markers, ESR and inflammatory cytokines as interleukin 6 and 8 (IL-6, IL-8).

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