Original Article

Red Cell Distribution width in Type 2 Diabetic Patients.

Aml Mohamed Nada, Maha Hammouda.

Endocrine Unit, Department of Internal Medicine, University of Mansoura, Department of Biochemistry, University of Mounofyia, Egypt .

Abstract:

Aim: To study the indices of some elements of the complete blood count in type 2 diabetic patients on treatment in comparison with non-diabetic healthy controls and to find out the effects of glycemic control and different medications on these indices. To the best of our knowledge this study is novel in our environment and will serve as a foundation for other researchers in this field. **Patients and Methods:** A retrospective study included 260 type 2 diabetic patients on treatment and 44 healthy control subjects. All data including gender, age, weight, height and blood pressure were available for all the study population. For diabetic patients, duration of diabetes and all medications were available. Complete blood count, fasting plasma glucose, HbA1c and lipid profile, were available for all participants. **Results:** Red cell distribution width (RDW) was significantly higher in diabetic patients than controls (p= 0.008). It was also higher in patients with uncontrolled glycaemia (HbA1c >7%) than those with good control (HbA1c ≤ 7%) [p= 0.035]. Mean platelet volume (MPV) was comparable in both diabetics and healthy controls (p= 0.238). Red cell distribution width and MPV did not significantly correlate with any of the fasting plasma glucose, HbA1c or duration of diabetes. Both aspirin and clopidogrel did not show a significant effect on mean platelet volume (MPV). Both insulin and oral hypoglycemic agents in our study did not show a significant effect on RDW, MPV or any of the studied indices. Diabetics treated with indapamide or the combined thiazides and angiotensin receptor blockers showed no significant difference in RDW when compared with the controls. **Conclusion:** RDW which is recently considered as an inflammatory marker with a significant predictive value of mortality in diseased and healthy populations, is significantly higher in diabetic patients than healthy subjects, and is particularly higher in uncontrolled glycaemia. None of the studied hypoglycemic agents showed a significant effect on RDW. Patients receiving antihypertensive therapy in the form of indapamide or the combined therapy of thiazides and angiotensin receptor blockers have RDW values comparable to those of the healthy population.

Keywords: Red cell distribution width, mean platelet volume, menopausal, diabetes, inflammation

Introduction:

The prevalence of type 2 diabetes has been increasing rapidly throughout the world[1]. It is estimated that over three hundred million people worldwide will become diabetic by year 2025 [2,3]. It is a global health problem because of its associated high morbidity and mortality. The primary cause of mortality in diabetic patients is cardiovascular diseases[4] while the major cause of morbidity is microvascular complications[5].

The evidence associating red cell distribution width (RDW) with a higher risk of mortality has been expanding since the initial report of its prognostic utility in heart failure patients. Red cell distribution width has also been shown to independently predict overall and cardiovascular mortality in the general population and various high-risk populations[6-10]. It is also a strong predictor of mortality in in many conditions such as obesity, malignancies, and chronic kidney diseases[11]. Being of an independent predictive value for various diseases makes it imperative to be studied in diabetes mellitus.

The red cell distribution width is a quantitative measure of the heterogeneity of the volume of red blood cells (RBCs) with higher values reflecting greater heterogeneity in cell sizes (anisocytosis)[12]. It is originally used together with the mean corpuscular volume (MCV) in clinical practice to differentiate between causes of anemia[13-15].

Inflammation has been proposed as a component of diabetes and its complications[16] Diabetic patients show high levels of chronic subclinical inflammation and oxidative stress, which play key roles in the progression of atherosclerotic diseases[7] Researchers showed RDW to be strongly associated with markers of chronic subclinical inflammation, higher oxidative stress and under-nutrition[13,17]. This may postulate an association between RDW and diabetes.

Platelets; another element of the complete blood count (CBC), play a key role in the development of atherothrombosis, a major contributor of cardiovascular events[18] which represent the major cause of mortality in diabetes[19]. Platelet aggregation and adhesion play a major role in intravascular thrombosis on top of atherosclerosis resulting in cardiovascular and cerebrovascular events. They may also be involved as a causative agent in the development of micro- and macrovascular disease in diabetes, with respect to altered platelet morphology and function[20,21].

Platelet hyperactivity has been reported in diabetics both in vivo *and* in vitro[22,23]. Mean platelet volume (MPV) is an indicator of the average size and was suggested by some authors to be an indicator of the platelet activity[24] and the state of thrombogenesis[20,22]. Antiplatelets have been demonstrated to be very effective at decreasing myocardial infarction, stroke, and death[25].

Leukocytes are known to participate in the inflammatory process accompanying atherosclerosis[26]. They are recruited at the site of endothelial injury, and form foam cells in the atheromatous plaque[27]. Interleukins and tumor necrosis factor-α are released from activated leukocytes and cause endothelial dysfunction. White blood cell (WBC) count is positively associated with increased cardiovascular mortality, mainly from coronary heart disease[28].

We aimed to use the complete blood count in type 2 diabetic patients as a simple and costless technique that is routinely done to investigate the state of various indices of blood elements especially those, which are claimed to have a role in the disease process and its complications such as RDW, MPV, platelet count and WBC count. We also elucidated the effects of various medications on these indices.

Patients and Methods:

We conducted a retrospective study which included 260 diabetic patients (98 females and 162 males) and forty-four non diabetic healthy controls (16 females and 28 males) from Internal Medicine Department, Diabetes and Endocrinology Clinics in a tertiary care hospital in KSA. The study was approved by the Hospital Ethical Committee. Patients were excluded because of anaemia, chronic liver disease, dialysis, thyroid disease, pregnancy, heart failure, acute or chronic infection or blood disease. Patients with known inflammatory conditions such as rheumatoid arthritis, systemic lupus erythematosus, those receiving anticoagulants or had a diagnosis of malignancy were also excluded.

Age of all participants as well as weight, height, and blood pressure were all available. Body mass index was calculated as follows [weight (kg)/height $(m)^2$]. In diabetic patients; duration of diabetes and medications were all noted.

Laboratory Analysis: All patients and healthy controls had complete blood count on venous blood samples taken into tripotassium EDTA (ethylene diamine tetracetic acid), using a Roche Minos cell counter and automatic blood counter (CELL-DYN 3500) within two hours of sample collection for platelet indices, WBC count and RBC indices. Standardization, calibration of instrument and processing of samples were done according to manufacturer's instructions. The blood glucose level was measured by glucose oxidase method and hemoglobin A1c (HbA1c) by calorimetrical method in the autoanalyser. Total cholesterol (T-Ch), low density lipoprotein (LDL), high density lipoprotein (HDL) and triglycerides (TG) in whole serum were measured enzymatically using a Cobas

autoanalyzer. Reference values were as follows: T-Ch: 3-5.2 mmol/L, LDL: < 3.4 mmol/L, HDL: 0.62-1.55mmol/L, TG: 0.34-2.28 mmol/L. WBC count: (4-11) 10^9/µl, platelet count: (140-440) 10^9/µl, MPV: 7-13 fl, RDW: 11-14%, MCV: 76- 96 fl.

Statistical Analysis:

Collected data were verified prior to computerized data entry. The Statistical Package for Social Sciences (SPSS, version 21.0) was used for the statistical analysis of data. Descriptive statistics (e.g., frequency, mean and standard deviation) were applied. Pearson's correlation coefficient and tests of significance (e.g., unpaired t-test) were applied. A significant p-value was considered at 0.05 or less.

Results:

Patient and healthy control characteristics are available in table (I).

Red cell distribution width was significantly higher in diabetic patients than healthy controls (p=0.008) while MCV was significantly smaller (p=0.036). No statistically significant differences were noted between both groups in MPV, platelet count or WBC count. Comparing diabetics with HbA1c≤ 7% (47 patients) with diabetics with HbA1c> 7% (213 patients) showed higher RDW (p=0.035) and smaller MCV (p =0.016) in the group with HbA1c > 7% otherwise no other significant differences were noted. Table (II)

In the patient group no statistically significant correlations were noted between RDW and FPG, A1c (p= 0.22, 0.781), blood pressure or duration of diabetes. RDW was strongly and directly associated with the body mass index (p<0.0001). MCV showed to be inversely associated with BMI (p=.016) and HbA1c (p=0.048). Platelet count inversely correlated with age (p=0.035) while the WBC count was directly associated with the duration of diabetes (p=0.049). MPV showed direct but insignificant correlation with FPG and HbA1c (p=0.057, 0.164 respectively). Table (III)

In the diabetic patients RDW, MCV and MPV did not correlate significantly with any of the components of the lipid profile. Platelet count correlated inversely with triglycerides (r= -0.14, p=0.015) and directly with HDL (r= 0.153, p= 0.008). White cell count inversely correlated with both T-Ch and LDL (r=-0.155, -0.152, p= 0.007, 0.008 respectively). Mean platelet volume was inversely correlating with platelet count (r= -0.368, p <0.001). White blood cell count was directly correlating with platelet count (r=0.16, p= 0.01) and RDW although the second correlation did not reach a statistical significance (r= 0.118, p=0.059).Table (III)

In comparison to controls, patients receiving indapamide had comparable RDW (14.79±1.25 vs 13.69 ± 1.20, p=0.473) and MPV (8.68±0.85 vs 8.85±0.97, p=0.456). The thiazide group of patients had significantly larger MPV (9.57±0.84 vs 8.85±0.97, p= 0.009) and RDW (p=0.014). Combined indapamide and angiotensin converting enzyme inhibitors (ACEI) had higher RDW (p <0.0001) and comparable MPV (p=0.403) meanwhile the combined angiotensin receptor blockers (ARBs) and thiazides had comparable RDW (14.34±1.56 vs 13.69±1.2, p=0.15) and comparable MPV (8.75±0.8 vs 8.85±0.97, p= 0.77) to controls. Calcium channel blockers did not show specific effects. Table (IV)

Diabetics receiving antiplatelets in form of ASA (8.99±0.95 vs 8.85±0.97, p=0.368) or clopidogrel (8.88±0.76 vs 8.85±0.97, p= 0.894) did not show significant difference in MPV when compared with controls. Statin therapy did not show a significant effect on CBC. Table (IV)

Hypoglycemic agents including insulin, metformin, sulfonylurea, pioglitazone and dipeptidyl peptidase inhibitors (DPP4I) did not show significant effects on any of the studied hematological indices. Table (IV)

Diabetic women showed significantly higher RDW and lower MCV when compared to men. This difference was persistent for women whether pre or postmenopausal. No significant difference between women in the two age groups was noticed. Tables (V,VI)

Table I: Criteria of Patients and healthy controls

	Healthy controls (n=44)	Diabetics (n=260)	p-value
Duration of diabetes	-	10.98± 6.92	-
Age	54.39±12.26	56.80 ± 11.95	0.221
BMI	30.55 ± 4.51	31.49 ± 5.14	0.255
SBP	125.68 ± 7.37	129.10 ± 16.33	0.174
DBP	76.00 ± 7.30	72.68 ± 9.04	0.021
WBC	6.87±1.82	7.07±2.08	0.549
MCV	84.49 ± 6.63	82.21 ± 6.66	0.036
RDW	13.69 ± 1.20	14.27 ± 1.36	0.008
Platelet count	259.66 ± 53.23	256.33 ± 65.90	0.751
MPV	8.85 ± 0.97	9.04 ± 0.99	0.238
TG	1.63 ±0.79	1.57 ± 0.80	0.666
T-Ch	4.94 ± 0.71	4.4 ±1.05	<0.001
LDL	2.81± 0.93	2.55 ± 0.92	0.079
HDL	1.1 ± 0.49	1.08 ± 0.31	0.587

BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure. WBC: white blood cell, MCV: mean corpuscular volume, RDW: red cell distribution width, MPV: mean platelet volume. Measuring units: WBC count: (4-11) 10^9/µl, platelet count: (140-440) 10^9/µl, MPV: 7-13 fl, RDW: 11-14%, MCV: 76- 96 fl. T-Ch: total cholesterol, LDL: low density lipoprotein, HDL: high density lipoprotein, TG: triglycerides. T-Ch: 3-5.2 mmol/L, LDL: < 3.4 mmol/L, HDL: 0.62-1.55mmol/L, TG: 0.34-2.28 mmol/L.

Table II: The studied CBC indices in patients with A1c≤ 7% vs patients with A1c >7%

	≤7 (n=47)	**> 7 (n=213)**	**P-value**
WBC	6.75 ± 1.74	7.17 ± 2.16	0.095
MCV	83.95 ± 6.93	81.94 ± 6.51	0.016
RDW	13.94 ±1.29	14.29 ±1.36	0.035
Platelet Count	254.75 ± 60.80	257.69 ± 65.65	0.706
MPV	8.95 ± 1.05	9.03 ± 0.965	0.524

WBC: white blood cell, MCV: mean corpuscular volume, RDW: red cell distribution width, MPV: mean platelet volume. Measuring units: WBC count: (4-11) 10^9/µl, platelet count: (140-440) 10^9/µl, MPV: 7-13 fl, RDW: 11-14%, MCV: 76- 96 fl.

Table III: Correlations of CBC indices with various variables

	RDW		MCV		MPV		Platelet Count		WBC count	
	R	P	R	P	R	P	R	P	R	P
Age	0.012	0.853	0.075	0.228	-.061	0.326	-0.131	0.035	0.008	0.9
BMI	0.228	<.0001	-.149	0.016	0.064	0.306	0.097	0.117	0.035	0.572
Duration DM	0.103	0.107	-.051	0.424	0.034	0.6	0.034	0.593	0.125	0.049
SBP	0.109	0.078	-.001	0.984	0.002	0.971	0.032	0.603	0.008	0.898
DBP	-0.094	0.13	.088	0.159	-.067	0.28	-0.024	0.699	0.109	0.08
FPG	-0.076	0.22	-.036	0.564	0.119	0.057	-0.009	0.899	0.044	0.481
A1c	0.017	0.781	-.123	0.048	0.087	0.164	0.005	0.934	0.017	0.786
TG	-0.099	0.086	-0.038	0.504	0.099	0.882	-0.14	0.015	0.001	0.991
T-Ch	-0.01	0.857	-0.026	0.658	-0.054	0.345	0.05	0.39	-0.155	0.007
LDL-c	0.013	0.824	-0.071	0.215	-0.021	0.711	0.028	0.628	-0.152	0.008
HDL-c	0.025	0.667	0.042	0.463	-0.057	0.326	0.153	0.008	-0.094	0.103

BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure. WBC: white blood cell, MCV: mean corpuscular volume, RDW: red cell distribution width, MPV: mean platelet volume. T-Ch: total cholesterol, LDL: low density lipoprotein, HDL: high density lipoprotein, TG: triglycerides. Measuring units and reference ranges: WBC count: (4-11) 10^9/µl, platelet count: (140-440) 10^9/µl, MPV: 7-13 fl, RDW: 11-14%, MCV: 76- 96 fl.T-Ch: 3-5.2 mmol/L, LDL: < 3.4 mmol/L, HDL: 0.62-1.55mmol/L, TG: 0.34-2.28 mmol/L.

Table IV: P values of the effects of different medications in diabetics (in comparison with controls)

	RDW	MCV	MPV	Platelet count	WBC count
Indapamide	0.473	0.214	0.456	0.15	0.716
Thiazides	0.014	0.18	0.009	0.686	0.14
ACEI	0.001	0.028	0.557	0.928	0.493
ARBs	0.023	0.315	0.106	0.317	0.009
CCB	0.003	0.12	0.45	0.458	0.379
ACEI+indapamide	<0.0001	0.002	0.403	0.111	0.623
ARBs+thiazides	0.15	0.567	0.77	0.109	0.143
Metformin	0.12	0.064	0.16	0.91	0.471
SU	0.01	0.17	0.46	0.776	0.293
Insulin	0.022	0.019	0.200	0.899	0.39
Pioglitazone	0.021	0.102	0.247	0.94	0.637
DPP4I	0.043	0.278	0.869	0.788	0.067
ASA	0.009	0.159	0.368	0.951	0.33
Clopidogrel	0.021	0.132	0.894	0.667	0.59
Statins	0.006	0.078	0.435	0.789	0.346

ACEI: angiotensin converting enzyme inhibitor, ARBs: angiotensin receptor blockers, CCB: calcium channel blockers, SU: sulphonylurea, DPP4I: dipeptidyl peptidase 4 inhibitors, ASA: acetyl salicylic acid, WBC: white blood cell, MCV: mean corpuscular volume, RDW: red cell distribution width, MPV: mean platelet volume. Measuring units and reference ranges: WBC count: (4-11) 10^9/µl, platelet count: (140-440) 10^9/µl, MPV: 7-13 fl, RDW: 11-14%, MCV: 76- 96 fl.

Table V: Comparison of the studied CBC indices in pre and post-menopausal females

	Pre (M±SD) n=20	Post(M±SD) n=78	p-value
RDW	15.10 ± 1.67	14.60 ± 1.46	0.183
MCV	77.96 ± 7.63	81.31 ± 6.93	0.061
MPV	9.06 ± 1.04	9.12 ± 1.09	0.831
Platelet count	293 ± 75.29	267.54 ± 70.11	0.156
WBC count	6.96 ± 1.64	6.91 ± 1.79	0.921

Pre: premenopausal, Post: postmenopausal, WBC: white blood cell, MCV: mean corpuscular volume, RDW: red cell distribution width, MPV: mean platelet volume. Measuring units and reference ranges: WBC count: (4-11) 10^9/µl, platelet count: (140-440) 10^9/µl, MPV: 7-13 fl, RDW: 11-14%, MCV: 76- 96 fl.

Table VI: CBC indices in pre and post-menopausal females in comparison with males

	Males (n=162) M±SD	Premenopausal females M±SD	P-value	Postmenopausal females M±SD	P-value
RDW	14.01 ± 1.19	15.1 ± 1.67	<0.0001	14.60 ± 1.4562	0.001
MCV	83.18 ± 6.15	77.96 ± 7.63	0.001	81.31 ± 6.93234	0.035
MPV	8.99 ± 0.94	9.06 ± 1.04	0.77	9.12 ± 1.09	0.365
Platelet count	246.27 ± 60.24	293 ± 75.29	0.002	267.54 ± 70.11	0.016
WBC count	7.17 ± 2.26	6.96 ± 1.64	0.686	6.91 ± 1.79	0.347

WBC: white blood cell, MCV: mean corpuscular volume, RDW: red cell distribution width, MPV: mean platelet volume. Measuring units and reference ranges: WBC count: (4-11) 10^9/µl, platelet count: (140-440) 10^9/µl, MPV: 7-13 fl, RDW: 11-14%, MCV: 76- 96 fl.

Table VII: r and p values of the correlations between WBC count and other CBC indices

	r	p-value
RDW	0.118	0.059
MCV	0.036	0.562
MPV	0.038	0.542
Platelet Count	0.16	0.01

WBC: white blood cell, MCV: mean corpuscular volume, RDW: red cell distribution width, MPV: mean platelet volume. Measuring units and reference range s: WBC count: (4-11) 10^9/µl, platelet count: (140-440) 10^9/µl, MPV: 7-13 fl, RDW: 11-14%, MCV: 76- 96 fl.

Discussion:

In the present study, higher RDW in diabetic patients than healthy controls (p = 0.008) indicates the presence of anisocytosis which is related to impairment of erythropoeisis and degradation of erythrocytes by fragmentation or agglutination[29-32]. This occurs in presence of chronic inflammation and increased level of oxidative stress[33].

Hyperglycemia has several effects on RBCs, besides formation of glycated hemoglobin[34], it leads to reduced deformability and changes in mechanical properties of RBCs[35,36], increased adhesion[37] and increased osmotic fragility[38] leading to changes in erythrocyte structure and hemodynamic characteristics[39].

Hyperglycemia reduces RBC life span leading to high variability of the RBC volumes[40,41]. Charles has mentioned reduced average lifespan of RBCs in diabetic patients[42]. This was also demonstrated by Emilia who showed that an extracellular oxidative milieu can be responsible for erythrocyte caspase-3 activation in type 2 diabetes. Activated caspase-3 impairs the maintenance of erythrocyte shape and function, thus contributing to the shortened life span of RBCs[43].

The original studies of Charles[42] showed a modest but consistent increase in erythrocyte half-life after the establishment of tight glycemic control compared with the same patients studied in poor control. In our study, there was a significant difference in RDW, being significantly higher in patients with HBA1c > 7% indicating shorter life span with anisocytosis in uncontrolled diabetes. This suggests that tighter glycemic control might offer a hematologic benefit to diabetic patients undergoing chemotherapy or having a chronic transfusion or erythropoietin requirement.

Our report of higher RDW in diabetics is in contrast to a report by Lutfullah et al[44] who did not find a difference in RDW among diabetics and non diabetics (p=0.53). Moreover, he did not find a significant difference in RDW in patients with HbA1c <7% or > 7%. He also did not find a significant difference in RDW when diabetes duration was longer or shorter than 10 years. In our study we did not observe a correlation between RDW and duration of diabetes (p= 0.107).

Similar to our study, Amparo mentioned a significant strong correlation between RDW and BMI[45]. Obesity is associated with a low-grade inflammatory process in the white adipose tissue[41,46,47]. Some studies elicited the strong association between RDW and markers of chronic subclinical inflammation, so its positive association with obesity is reasonable.

In agreement with our findings, Heba did not observe significant correlations between RDW and HbA1c, SBP, DBP, or duration of diabetes[48]. Contrary to our results, she did not find a significant correlation between RDW and BMI.

In Amparo's study[45], an inverse correlation was observed between RDW and triglycerides, but was gender dependent and was evident only in women ($p<0.05$). In another study in the general population of unselected out patients, Lippi found an inverse association with HDL in both genders and a direct association with hypertriglyceridaemia and Cholesterol/HDL ratio only in women[49]. No significant associations between RDW and lipids were noted in our study.

We did not find significant effects of insulin, metformin, sulfonylurea, pioglitazone or DPP4I on any of the studied hematological indices. To our knowledge there is no previous report about the effects of hypoglycemic agents on RDW or any of the other blood indices mentioned in our study.

In the present study, absence of a significant difference in MPV between diabetics and non-diabetics is in consonance with results obtained by Dada et al in Nigerian diabetics (p=0.593)[50]. On the contrary, several other authors stated a significantly higher MPV in patients with diabetes such as Hekimsoy[20], Demietunc[51], Papanas[52], and Thomas[53]. This also agrees with the findings seen in studies conducted by Zuberi[21] and Jindal[54]. One explanation for the higher MPV in diabetics is that a significant number of these studies was done in diabetic patients post myocardial infarction. This leads to

quicker consumption of smaller platelets that are compensated for by production of younger platelets with larger MPV[55, 56]. Our study was done while the patients were stable with no recent insult.

Absence of a significant correlation between MPV and FPG or HbA1c in our study is consistent with reports by Sharpe[57], and Unubol[58]. Similarly, Ezgi[59] found no association between MPV and FPG, HbA1c, patient age, duration of diabetes, or blood pressure. This is also in agreement with our report and other reports (60, 61). Similar to Thomas we did not find a significant difference in MPV in patients with HbA1c≤7% or >7% and no association with the BMI was found[53]. Peterson, in his study, found no difference in mean platelet survival in uncontrolled diabetics and diabetics with good control[42]. Their reports and ours suggest that other factors rather than hyperglycemia may account for the thrombotic potential of diabetics with time. If vascular damage was only due to increased number of large and reactive platelets, then the rate of damage would have been constant for the duration of disease and independent of diabetic control. This clearly shows that platelet reactivity alone cannot explain the progression of vascular complications in DM since there are other vascular risk factors that may be influenced by the degree of control of diabetes[20,62]. This was supported by the non significant statistical correlation between MPV and duration of diabetes. A direct relation between platelet dysfunction and the development of diabetic complications has yet to be firmly established[20, 22].

Platelet hyper-reactivity and increased baseline activation in patients with diabetes is multifactorial and can not be attributed only to hyperglycemia. It is associated with biochemical factors such as hyperglycemia and hyperlipidemia, insulin resistance, an inflammatory and oxidant state and also with increased expression of glycoprotein receptors and growth factors[63- 66].

On the other hand, positive correlations were demonstrated by Shah[67], Dada[50], Giuseppe[68] and Demirtunc[51] among the diabetics between MPV and FPG and duration of diabetes. They suggested that achieving good glycemic control may limit platelet activation and delay the onset and progression of vascular complications.

Giuseppe[68] demonstrated that MPV is not related to platelet aggregation, the extent of coronary artery disease and carotid intimal medial thickness. Accordingly, he concluded that MPV cannot be considered as a marker of platelet reactivity or a risk factor for coronary artery disease. This necessitates further work up to confirm if MPV can be used as an indicator of platelet function.

Similar to Giuseppe[68], we found an inverse relation between MPV and platelet count. However, in contrast to his report, we did not find a significant association of MPV with age, triglycerides or statin use. Table (4)

Increases in MPV are often associated with decreases in platelet count[69, 70] perhaps as a result of small platelets being consumed in order to maintain a constant platelet functional mass[71]. Also in consistence with our study, a negative linear relationship between MPV and the number of platelets (p=0.006) was observed in Dada's report [50].

Absence of a significant effect of antiplatelets in the form of ASA (aspirin) and clopidogrel on MPV is in agreement with a report by Colkesen[72]. In his study, aspirin treated patients did not show a significant difference in MPV (p=0.9). Shechter et al mentioned individual variability of platelet response to clopidogrel which affects the clinical outcome[73]. In one study, clopidogrel reduced MPV in patients with stable angina after two months of treatment [74]. In another study by Shah, he stated that, when standardized, MPV is a reproducible marker of platelet size and not affected by low-dose aspirin and that MPV is modestly associated with some, but not all, markers of platelet activity[75]. Absence of an effect of aspirin on MPV and the extent of platelet aggregation was mentioned by Giuseppe[76]. Both studies suggest that larger MPV does not imply higher platelet reactivity and may not be considered to monitor platelet reactivity and the efficacy of antiplatelet therapies.

The antiplatelet effects of perindopril and other ACE inhibitors appear to be small. In Gupta's study, perindopril treatment did not affect platelet indices[77]. Other studies of the ACE inhibitor quinapril[78] and the angiotensin

receptor blocker losartan[79,80] similarly have shown little effect on MPV. This is quitely in consistence with our findings as ACE inhibitors and ARBs did not show a significant effect on MPV (p=0.291, 0.106 respectively).

Analysis of the effects of antihypertensive medications in our study elicited that the use of indapamide may be preferable to the use of thiazides because it is associated with comparable RDW and MPV to the controls. On the other hand, the combination therapy of thiazides and ARBs may be preferable to the combination of indapamide and ACE inhibitors for the same reason. Table (4)

In our study, Platelet count inversely correlated with triglycerides and directly with HDL (p=0.015, 0.008). In another study, platelet count was correlating negatively with triglycerides in hypertriglyceridemia (r = -0.489, P < 0.05)[86]. This is in agreement with our study results (r = - 0.1, p= 0.015) which state that the higher the triglycerides, the lower the platelet count.

Both Iolanda and Papatheo[81,82] demonstrated a positive association between WBC count and platelet count. In our study WBC count was positively associated with RDW and platelet count (p= 0.01), although the association with RDW did not reach a statistical significance (p=0.059). No association was found between WBC count and MPV (p=0.542) or MCV (p= 0.562) although the relation between WBC count and MPV was reported by Iolanda[81]. The association of platelet count and RDW with WBC count may underline the role of both platelets and erythrocytes in inflammation.

No association was found between WBC count or platelet count and the FPG, BMI, or lipids in the study conducted by Papatheo [82]. This is in agreement with our report apart from the relation to lipids. Our study revealed a strong negative correlation between WBC count and LDL (r= -0.152, p= 0.008) and total cholesterol (r=-0.155, p=0.007). This seems a paradox which advocates further studies.

In the study conducted by Peter, subjects with higher WBC counts had longer disease duration, higher SBP, DBP, BMI, HbA1c, FPG, LDL cholesterol, TGs and lower HDL [26].

In consistence with Peter's findings, our study results demonstrated a positive correlation between WBC count and duration of diabetes (p= 0.049). However, the association between WBC count and T-ch and LDL was an inverse one. We did not find a significant association with any of the FPG, HbA1c, TG, SBP or DBP and WBC count.

Pre and postmenopausal women had higher RDW, platelet count (p<0.0001, 0.002 respectively) and smaller MCV (p=0.001) than men. Higher platelet count in women can not be explained by the different hormonal profiles or a compensatory mechanism associated with menstrual blood loss, because the difference was persistent regardless of women's age. We did not find a significant difference between pre and post menopausal women in any of the studied indices except for the MCV.

Lippi found higher RDW in non diabetic men than women[49]. Some researchers found no correlation and no statistically significant differences in MPV between both sexes[83, 84]. In another study, platelet count was lower in postmenopausal women compared to young menstruating women. However, MPV values were similar in both groups [85].

Achie, in agreement with our report, did not find a significant difference in RBC indices between pre and post menopausal healthy women[86]. The increase in MCV in menopausal women was elicited by Chalmers, although it was not statistically significant in our study population (p=0.061). Higher MCV indicates a probable risk for developing anaemia especially vitamin B12 and folate deficiency anemia[87].

Our results in pre and menopausal women whether in comparison to each other or to men can be explained by the fact that following menopause the cardioprotective effects of endogenous estrogen is lost[88,89]. Interestingly, sex difference, which normally vanishes after menopause, is rapidly lost in premenopausal T2DM patients, with cardiovascular disease reaching 2- to 5-fold higher rates than

in age matched non-diabetic women[90] and several-fold higher rates of death related to coronary artery disease, with event rates nearly identical to those observed in T2DM men[91]. Diabetes potentiates the effects of major atherosclerotic cardiovascular diseases than in the normal population in a percentage of the diabetic patients, most of them are females[92]. This can explain such differences found even in premenopausal women when compared with men.

Conclusion:

It can be concluded that RDW is higher in type 2 diabetic patients than healthy population. In diabetic patients the glycemic control does affect the RDW. Our study adds to the studies which considered RDW as a marker for subclinical inflammation because of its higher values in diabetics and its positive association with the BMI. The study in our population can be considered as an initial one that necessitates further studies to define the relation between RDW and different diabetic complications and its prognostic value. Further studies are also required to define specific values of the RDW to indicate specific risks.

This study also emphasizes the positive effects of some medications in diabetic patients such as indapamide and the combined therapy of thiazides and ARBs. These positive effects may be of importance in analysis of the beneficial effects of these medications on various morbidities and mortalities in diabetes.

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