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Research Article

The Relation between Red Cell Distribution Width and Hypertension, Dipper Pattern and End-Organ Damage Independent from Vitamin B12, Folic Acid and Ferritin Levels

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ABSTRACT

Background and Aim: Many studies have found association between Red Cell Distribution Width (RDW) values and hypertension, dipping pattern, and end-organ damage. RDW values are affected by blood vitamin B12, iron, and folic acid levels, parameters that were not assessed in the previous studies. The aim of our study was to evaluate the relation between RDW and hypertension, dipper pattern, and end-organ damage independently from vitamin B12, folic acid, and ferritin levels in newly diagnosed hypertensive patients.

Material and Methods: Hundred and sixty-three hypertensive patients with two different-time measured office blood pressure > 140/90 mmHg, and 85 normotensive subjects with office blood pressure < 140/90 mmHg were included in the study. Ambulatory blood pressure monitoring was performed in all participants. Twenty-two participants were excluded because of white-coat syndrome and 10 subjects due to masked-hypertension. Patients were classified into three subgroups according to ambulatory blood pressure measurements; non-dipper hypertensive (n = 88), dipper hypertensive (n = 53), and normotensive (n = 75). Left ventricular mass index, glomerular filtration rate, and microalbuminuria were measured to determine end-organ damage. RDW and serum levels of ferritin, vitamin B12 and folic acid were measured in all participants.

Results: When we evaluated all participants without taking the baseline values of vitamin B12, folic acid and ferritin into account, RDW was found higher in non-dipper hypertension group but the difference did not reach statistically significant level (p = 0.263). When participants with vitamin B12, ferritin and folic acid levels below normal levels were excluded, the mean RDW decreased but no statistically significant difference between the groups was detected (p = 0.187). RDW was positively correlated with LVMI, age and urine albumin in hypertensive patients (r = 0.476, p < 0.001; r = 0.342, p < 0.001; r = 0.212, p = 0.006, respectively); but not with GFR (r = -0.0015, p = 0.852).

Conclusion: In conclusion, in newly diagnosed hypertensive patients, although RDW levels were associated with LVMI and microalbuminuria, hypertensive patient group was not statistically different from normotensive group; and non-dipper hypertensive group was not statistically different from dipper hypertensive group. It was found that vitamin B12, folic acid and ferritin levels did not affect this correlation.

INTRODUCTION

Red Blood Cell Distribution Width (RDW) is a numerical measure of the variability of the size of circulating erythrocytes. It is routinely reported as component of complete blood count used in differential diagnosis of anaemia. Increased RDW have been found to be associated with inflammation and increased levels of neurohormonal mediators [1,2]. The arterial blood pressure shows a diurnal rhythm that is higher daytime than at night [3,4]. Non-dipper hypertension is defined as decrease less than 10% in blood pressure at night [5]. Previous studies have shown that non-dipper hypertension is associated with adverse cardiovascular events, serious renal failure, and cerebrovascular diseases [6-8]. Although the causes of non-dipper hypertension have not been fully understood, it has been reported to be associated with volume expansion, increased sympathetic activation, and inflammatory status [9,10]. Most of the previous studies have shown that RDW values increase in hypertension, especially in non-dipper hypertension [11-13]. In another study, increased RDW values in systolodiastolic hypertensive patients were found to be associated with end-organ damage [14].

On the other hand, RDW values are known to be influenced by vitamin B12, iron and folic acid levels. Decreased blood vitamin B12, folic acid and iron levels may affect RDW first, before affecting haemoglobin levels. In the studies related to the RDW until now, those values have not been routinely evaluated and this has been stated as the limitation of the study. Our aim in this study was to investigate whether RDW is associated with hypertension, dipper pattern and end-organ damage independently from vitamin B12, folic acid and ferritin levels in newly diagnosed hypertensive patients.

MATERIALS AND METHODS

A total of 248 people, aged between 35 and 87 years who applied to the outpatient clinic, were included in the study. Of these, 163 were patients who had Office Blood Pressure (OBP) higher than 140/90 mmHg measured at least twice at different times, and the rest 85 were subjects with OBP lower than 140/90 mmHg. All participants had a 24h Holterblood pressure monitoring. Upon 24h Holter blood pressure monitoring, among patients with high OBP, 22 were found to have white-coat hypertension and 10 of those with normal OBP had masked hypertension; and were excluded from the study. Patients' medical history, physical examination findings, and anthropometric measurements were recorded by an experienced cardiologist.

Hypertension was defined as OBP higher than 140/90 [15]. Normal blood pressure was defined as normal OBP and normal daytime ambulatory blood pressure without current use of any antihypertensive medication [16]. Dipper hypertension was defined as reduction of nocturnal blood pressure measured by ambulatory blood pressure monitoring in either daytime systolic blood pressure or diastolic blood pressure of more than 10%. Non-dipper hypertension, on the other hand, was defined as the reduction less than 10% [5]. Patients were classified into three groups according to ambulatory blood pressure and OBP values: Non-dipper hypertension (n = 88), dipper hypertension (n = 53) and normal blood pressure (n = 75), respectively.

Diabetes was defined based on the American Diabetes Association Guideline criteria that was fasting blood glucose ≥ 126 mg/dL (7 mmol/L) or postprandial blood glucose ≥ 200 mg/L(11.1 mmol/L) or current use of anti-diabetic drugs [17]. Body Mass Index (BMI) was calculated by dividing body weight in kg by the square of the body height in meters. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [18].

Urinary albumin was expressed in milligrams per gram (mg/g). Albuminuria was defined as the ratio of albumin/creatinine > 30 mg/g and was classified into two groups: Microalbuminuria if the ratio of albumin/creatinine was 30-299 mg/g and macroalbuminuria if it was ≥ 300 mg/g.

Echocardiographic evaluations were performed using a Phillips EPIQ 7G echocardiograph (USA) and S5-1 probe by a cardiologist.

Left Ventricular Mass (LVM) was calculated in grams by M-mode echocardiography as described by Deverux et al. [19]. Left Ventricular Mass Index (LVMI) was calculated by dividing left ventricular mass by body surface area (g/m^2).

Exclusion criteria of the study were; moderate-to-severe cardiac valve disease upon echocardiography, heart failure with an ejection fraction < 50%, ≥ grade 2 diastolic dysfunction, and eGFR ≤ 60mL/min/1.73 m^2. Patients with coronary artery disease, stroke, chronic liver disease, thromboembolic diseases, haematological diseases, malignancy and chronic obstructive pulmonary disease were also excluded. The ethics committee approved the study protocol and the informed consent that was obtained from all patients.

Ambulatory blood pressure monitoring

Ambulatory Blood Pressure Monitoring (ABPM) was performed for 24h using an ambulatory blood pressure monitor (Mobil Graph NG, New Generation 24h ABPM Classic, Germany). The monitor was programmed for blood pressure measurements from 08:00 to 23:45 for every 15 minutes, and from 00:00 to 07:30 for every 30 minutes. Daytime and nocturnal blood pressures were defined from 07:30 to 00:00 and from 00:00 to 07:30, respectively. Mean 24h systolic and diastolic blood pressures were automatically measured by 24 h monitoring.

Blood sampling

RDW was measured in blood samples collected in EDTA tubes by an automated haematology analysis system (Mindray BC5800). Normal RDW values in our laboratory ranged from 11-14%. Standard laboratory parameters such as total leukocyte count, neutrophil count, haematocrit, glucose, creatinine, lipid profile, etc. were determined by standard methods.

Ferritin (13-150 ng/mL) (REF 04491785), vitamin B12 (197-771 pg/mL) (REF 07212771) and folic acid (3.8-16 ng/mL) (REF 07559992) was measured by190 cobas analyser (Roche Diagnostics GmbH, Germany).

Statistical analyses

Statistical analyses were performed using the SPSS software version 17 (Statistical Package for Social Sciences for Windows, released in 2008; SPSS Inc., Chicago, USA). The variables were evaluated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov) to determine whether they were normally distributed. Descriptive analyses were presented using means and Standard Deviations (SD) for normally distributed; and using medians and maximum-minimum for the non-normally distributed variables. Categorical variables were expressed as percentages. Groups were compared with one-way Analysis of Variance (ANOVA) for age, total cholesterol, Low Density Lipoprotein (LDL)-cholesterol, body mass index, haematocrit; and the Kruskal-Wallis test, and the Chi-Square test for others where appropriate. Comparisons of non-parametric values among groups were performed by the Kruskal Wallis test. Mann-Whitney U-test (for non-parametric variables) with Bonferroni adjustment was used for multiple comparisons between the groups. *P* value of less than 0.017 was considered to be significant upon Bonferroni adjustment. A Spearman correlation analysis was performed to determine the association of RDW with GFR, LVMI, age and urine albumin in the hypertensive groups. An overall 5% type-I error level was used to infer statistical significance.

RESULTS

We analysed our data in two steps. At the first step, all 216 participants were included in the analysis regardless of the baseline levels of vitamin B12, folic acid and ferritin (Table 1). Of these, 88 (40%) were non-dippers Hypertension (HT), 53 (24%) were dippers hypertension, and 75 (34%) were normotensive. The mean age was significantly higher in non-dipper (57.9 ± 12.1 years) and dipper hypertension groups (54.2 ± 9.9 years) than normotensive group (46.0 ± 8.5 years) ($p < 0.001$). Body mass index was lower in the control group (28.6 ± 6.3 kg/m^2) than non-dippers (30.3 ± 4.4 kg/m^2) and dippers (30.0 ± 4.6 kg/m^2) groups, but the difference was not statistically significant($p = 0.106$). Type 2 diabetes mellitus was more frequent among non-dippers and dippers than the normotensive group ($p < 0.001$). Fasting blood glucose levels were higher in non-dippers (120.7 ± 60.5 mg/dL) and in dippers (109 ± 24.1 mg/dL) than normotensives (96 ± 17.7 mg/dL) (p = 0.001). Office blood pressure levels were higher in the non-dippers and dippers than in the normotensive group ($p < 0.001$) (Table 1). Although RDW values were higher in the non-dippers group, there was not statistically significant difference between the groups ($p = 0.263$). Vitamin B12, ferritin and folic acid values were similar in all groups. Other laboratory clinical parameters and demographic characteristics were not different between the groups (Table 1).

At the second step, participants with levels of blood vitamin B12, folic acid and ferritin lower than normal range (197-771 pg/mL, 3.8-

Table 1: Characteristics of study population at baseline.

Variables	Non-dippers (N = 88)	Dippers (N = 53)	Normotensives (N = 75)	*P*-value
Age, years	57.9 ± 12.1	54.2 ± 9.9	46.0 ± ,8.5	< 0.001
BMI, kg/m²	30.3 ± 4.4	30.0 ± 4.6	28.6 ± ,6.3	0.106
Gender (male),	28 (31.8)	22 (41.5)	36 (48)	0.105
Diabetes mellitus	22 (25)	15 (28.3)	3 (4)	< 0.001
Haematocrit,%	41.5 ± 4.4	42.4 ± 4.7	43.2 ± 6.7	0.127
Leukocyte, x 10/mm³	7.91 ± 2.72	7.9 ± 2.0	7.6 ± 1.9	0.703
Neutrophil, x 10³/mm³	5.2 ± 2.37	4.4 ± 1.46	4.4 ± 1.42	0.335
Glucose, mg/dL	120.7 ± 60.5	109 ± 24.1	96.5 ± 17.7	0.001
Creatinine, mg/dL	0.79 ± 0.24	0.80 ± 0.19	0.74 ± 0.14	0.133
RDW, %	13.8 ± 1.94	13.4 ± 1.55	13.4 ± 1.52	0.263
Total-cholesterol ,mg/dL	208.3 ± 43.2	209.5 ± 37.2	200.0 ± 48.4	0.375
LDL-cholesterol, mg/dL	129.7 ± 38.1	117.7 ± 31.9	120.8 ± 40.3	0.208
HDL-cholesterol, mg/dL	53.1 ± 14.9	53.9 ± 16.0	52.6 ± 14.5	0.884
Triglycerides, mg/dL	147.4 ± 64.8	142.5 ± 80.7	163.3 ± 114.1	0.355
Office SBP, mmHg	163.1 ± 19.0	166.7 ± 14.0	118.1 ± 20.7	< 0.001
Office DBP, mmHg	91.8 ± 13.0	93.5 ± 11.5	75.5 ± 10.0	< 0.001
Vitamin B12, pg/mL	368.2 ± 223.5	363.6 ± 174.9	344.5 ± 150.2	0.712
Ferritin, ng/mL	64.3 ± 52.1	71.5 ± 69.6	64.7 ± 73.3	0.791
Folate, ng/mL	9.1/ ± 3.6	9.5 ± 4.2	8.7 ± 2.9	0.461
eGFR, ml/sec/1.73m²	92.6 ± 21.7	93.0 ± 17.7	106.0 ± 17.5	< 0.001
Urine albumin, mg/g	34.7 ± 48.8	29.7 ± 40.5	12.8 ± 15.7	< 0.001

Data are expressed as the mean ± SD or n (%) of patients. BMI: Body Mass Index; RDW: Redcell Distribution Width; LDL: Low Density Lipoprotein; HDL: High Density Lipoprotein; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; eGFR: estimated Glomerular Filtration Rate.

16ng/mL, 13-150ng/mL, respectively) were excluded (20 participants from the non-dipper group, 7 from the dipper group, and 22 from the normotensive group) (Table 2). When evaluated among these 167 subjects, mean age, BMI, diabetes mellitus frequency, fasting blood glucose and office blood pressure values were found higher in the non-dipper and dipper groups similar to the first step (Table 2). Other laboratory, clinical and demographic characteristics were not significantly different between groups (Table 2). There was no change in RDW in dippers with the exclusion of the above described subjects, a decrease was determined from 13.8 ± 8 % to 13.5 ± 1.74 % and from 13.4 ± 1.52 % to 13.1 ± 1.1% in non-dippers and normotensives, respectively, though there was no statistically significant difference (p = 0.187) (Table 2). LVMI and albuminuria levels were higher, and eGFR levels were lower in hypertensive groups than normotensives, in both steps (Table 1, Table 2). These parameters were similar in dipper and non-dipper hypertensive groups (Table 1, Table 2).

As presented in table 3, RDW was positively correlated with LVMI, age, and urine albumin (r = 0.476, p < 0.001; r = 0.342, p < 0.001; r = 0212, p = 0.006, respectively). There was no significant correlation between RDW and eGFR(r = -0.015, p = 0.852).

Table 2: Characteristics of study patients with normal vitamin B12, folic acid and ferritin levels (20 from nondippers, 7 from dippers, 22 from normotensives were excluded from the analysis).

Variables	Non-dippers (N = 68)	Dippers (N = 46)	Normotensives (N = 53)	P
Age, years	59.0 ± 12.4	55.8 ± 9.7	46.9 ± 9.2	< 0.001
BMI, kg/ m²	30.4 ± 4.2	29.5 ± 4.9	28.1 ± 3.7	0.016
Gender(male)	25 (36.8)	20 (43.5)	28 (52.8)	0.210
Diabetes mellitus	17 (25)	14 (30.4)	3 (5.7)	0.004
Haematocrit, %	41.9 ± 3.8	42.8 ± 4.6	44.4 ± 6.6	0.034
Leukocyte, x 10/mm³	7.9 ± 3.8	7.8 ± 2.0	7.6 ± 1.9	0.767
Neutrophil, x 10³/mm³	4.81 ± 2.6	4.3 ± 1.46	4.2 ± 1.28	0.269
Glucose, mg/dL	123.7 ± 62.5	110 ± 26.1	98.1 ± 20.4	0.007
Creatinine, mg/dL	0.82 ± 0.24	0.82 ± 0.19	0.76 ± 0.15	0.195
RDW, %	13.5 ± 1.74	13.4 ± 1.4	13.1 ± 1.1	0.187
Total-cholesterol, mg/dL	210.3 ± 43.2	203.5 ± 37.2	205.0 ± 48.1	0.669
LDL-cholesterol, mg/dL	125.7 ± 38.5	125.5 ± 31.9	116.1 ± 39.7	0.250
HDL-cholesterol, mg/dL	52.7 ± 14.8	56.2 ± 16.2	51.8 ± 14.1	0.367
Triglycerides, mg/dL	144.4 ± 62.2	140.5 ± 86.7	167.3 ± 99.3	0.201
Office SBP, mmHg	163.6 ± 20.0	166.0 ± 15.0	119.1 ± 19.0	< 0.001
Office DBP, mmHg	90.5 ± 13.0	94.5 ± 12.1	76.5 ± 10.7	< 0.001
Vitamin B12 ,pg/mL	393.8 ± 244.6	383.4 ± 166.8	382.0 ± 139.0	0.780
Ferritin, ng/mL	73.5 ± 53.6	79.8 ± 71.0	76.0 ± 80.0	0.583
Folate, ng/mL	9.7 ± 3.4	9.8 ± 3.9	9.0 ± 3.0	0.409
eGFR, mL/sec/1.73m²	91.2 ± 23.2	92.2 ± 18.6	106.4 ± 14.2	< 0.001
Urine albumin, mg/g	49.2 ± 70.0	31.3 ± 42.1	13.8 ± 18.6	< 0.001
LVMI, g/m²	114.0 ± 24.0	115.5 ± 28.7	77.9 ± 22.6	< 0.001

Data are expressed as the mean ± or n (%) of patients. BMI: Body Mass Index; RDW: Redcell Distribution Width; LDL: Low-Density Lipoprotein; HDL: High Density Lipoprotein; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; eGFR: estimated Glomerular Filtration Rate; LVMI: Left Ventricular Mass Index.

Table 3: Correlations between selected covariates and red cell distribution width.

	r	*p*-value
eGFR, mL/sec/1.73m²	- 0.015	0.852
LVMI, g/m²	0.476	< 0.001
Age, years	0.342	< 0.001
Urine albumin, mg/g	0.212	0.006

eGFR: Estimated Glomerular Filtration Rate; LVMI: Left Ventricular Mass Index.

DISCUSSION

In this study, no statistically significant difference in RDW values was detected between the groups no matter subjects with low vitamin B12, folic acid and ferritin were included or not; although mean RDW values were slightly higher in non-dippers when all subjects were included and decreased after having excluded participants with vitamin B12, ferritin and folic acid values below normal range. Finally, significant association was found between increased RDW levels and LVMI, urine albumin and age in newly diagnosed hypertensive patients.

RDW is the measure of the variation in erythrocyte size and increased RDW values reflect more heterogeneous red cell distribution. Besides iron, vitamin B12 and folic acid deficiencies, inflammation and oxidative stress may also cause increased RDW values by impairing the iron metabolism, suppressing the erythropoietin production or shortening red blood cell life [20-24].

An association have been shown between increased RDW values and mortality in patients with coronary artery disease and heart failure [25,26]. Many community-based studies have also reported that higher RDW values were associated with increased risk of mortality in general population [27,28].

In previous studies, RDW values were found higher in patients with hypertension than prehypertensive and healthy subjects [12]. Furthermore, in some of the studies conducted in hypertensive patients, RDW values have been associated with non-dipper patterns [11,13,29]. The relationship between hypertension, non-dipper pattern, and RDW has been associated with increased inflammation, oxidative stress, and sympathetic activity. In this study, although we found slightly higher levels of RDW in non-dipper hypertension group, the difference from dipper and normotensive groups did not reach to statistically significant levels. In the previously cited studies, vitamin B12, folic acid, and ferritin levels that affect RDW levels have not been examined. In our study, although mean RDW values of the groups decreased when the patients with values below normal were excluded from the study, there was still no significant difference between the groups.

The development of end-organ damage such as LVMI, microalbuminuria and reduced GFR in hypertensive patients is an important indication of cardiovascular risk. In some studies, RDW values have been shown to be an independent predictor of elevated LVMI, microalbuminuria and reduced eGFR [14,30]. The development of LVMI and microalbuminuria in hypertensive patients was also indicative of increased inflammation, and has been linked to increased inflammation and increased sympathetic system activity of the relation between end-organ damage and increased levels of RDW [31,32]. In our study, RDW values were found to be

associated with age, elevated LVMI and microalbuminuria after the exclusion of hypertensive participants with abnormal values of folic acid, vitamin B12 and ferritin.

Although there are studies showing a relationship between reduced GFR and increased RDW [33], we found no significant correlation between RDW and eGFR despite a negative relation was observed. This could be due to the high mean GFR values, and low number of enrolled patients. We know that eGFR value lower than 60mL/sec/1.73m² is more likely associated with increased inflammation and adverse cardiovascular events.

There may be several reasons why we could not find a relationship between non-dipper HT and RDW values, unlike most previous studies have presented. Firstly, we have diagnosed non-dipper hypertension according to the Holter results, for which the repeatability is low. In a Holter-diagnosed non-dipper person, the probability of making the same diagnosis by second Holter monitoring is not high. Secondly, the majority of previous studies found higher end-organ damage in the non-dipper hypertension group. However, in the current study, there was no statistical difference for end-organ damage between the hypertension groups. RDW, which is an environmental marker of adverse cardiovascular event development, increased inflammation, sympathetic system and oxidative stress, might not be found that high in the non-dipper hypertension group because of this reason.

There could be several reasons why end-organ damage was more frequent, and RDW values were higher, but not statistically significant, in the hypertensive group than the normotensive group without statistical difference. It could be that newly diagnosed hypertensive patients were included and patients with cardiovascular disease and eGFR < 60mL/sec/1.73m² were excluded. Because of this, the end-organ damage marker LVMI, decreased eGFR and microalbuminuria were not detected in the hypertensive group (Tables 1 and 2). As a result, this group may not reflect a hypertensive group with increased inflammation and cardiovascular load. As RDW values are associated with various diseases and reflect multiple physiological impairments, we could not find high levels of RDW in this hypertensive group with relatively low cardiovascular load.

Conclusion

In conclusion, although the RDW values were correlated with LVMI and microalbuminuria in newly diagnosed hypertensive patients, they were not higher in hypertensive patients than normotensive subjects. There was no association between RDW values and the dipping pattern. Vitamin B12, folic acid levels and ferritin values did not affect this association. Increased RDW only itself may not predict hypertension, but may be indicative of end-organ damage, which is a predictor of adverse cardiovascular event development.

Limitations

This was a non-randomized study and therefore it was subjected to selection bias. This study included newly diagnosed hypertensive patients as well as hypertensive patients without coronary artery disease, moderate-advanced heart valve disease, heart failure, and stroke. Furthermore, patients with white-coat syndrome and masked-hypertension syndromes were not included. Therefore, our findings should not be generalized to all hypertensive patients. Finally, the association between RDW values, and inflammatory and neurohumoral mediators were not investigated in this study.

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