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Relationship Between Red Cell Distribution Width and Serum C Reactive Protein Levels In Maintenance Hemodialysis Patients

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ABSTRACT

We aimed to investigate the relationship between RDW and serum CRP levels in maintenance hemodialysis patients.
We enrolled 112 eligible maintenance hemodialysis patients in this retrospective study. Two groups were identified according to red cell distribution width (RDW) values: patients with normal RDW (RDW < 14.5%) and patients with elevated RDW (RDW ≥ 14.5%). Spearman correlation analysis and linear regression analysis were used to investigate the relationship between the study parameters.
The only statistically significant difference between two groups was serum CRP levels (p= 0.007). Serum albumin levels had significant but weak inverse correlation with serum CRP levels (r= -0.257, p= 0.006). RDW values had significant but weak positive correlation with serum CRP levels (r= 0.289, p= 0.002). We did not found a significant correlation between hemoglobin levels and serum CRP levels and serum ferritin levels and serum CRP levels (p= 0.090 and p= 0.664, respectively). We made multivariate linear regression analysis and RDW was detected as the only independently associated factor for serum CRP levels (p= 0.028).
We found that there is a statistically significant positive correlation between CRP and RDW in maintenance hemodialysis patients. We also showed a significant relationship between RDW and serum CRP levels. We concluded that RDW can be used as an inflammatory marker for hemodialysis patients.

Key Words: Red cell distribution width, C-reactive protein, Inflammation, Hemodialysis

Introduction

Overall nearly 3 million people have been receiving renal replacement therapy (RRT) worldwide, of which greater than 2/3 receiving hemodialysis, although the number of patients needing RRT is much more higher (1). Mortality and morbidity rate in this population is several times higher than normal population (2). Chronic inflammatory state is the main mechanism accused for increased mortality and morbidity in hemodialysis patients. It is related to cardiovascular mortality, anemia, bone mineral disorder and malnutrition (3-5). There are several markers for detection of inflammation in hemodialysis patients. Serum C reactive protein (CRP) is a well known and mostly used inflammatory marker in worldwide due to availability and proven accuracy (6).

Red cell distribution width (RDW) is the measurement of the variability of erythrocyte size in circulation. It is a quantitative measure and automatically measured by complete blood cell counters by dividing RBC volume to mean corpuscular volume (MCV) and the result given as percentage (7). RDW, especially in combination with MCV, is traditionally used for the diagnosis of anemia. Elevated RDW values can also be seen in conditions which cause releasing of premature RBCs into circulation such as hemoglobinopathies and/or other hematological disorders (8). Recently, studies have shown that RDW was an important marker for mortality in general population (9) and it also strongly predicted the morbidity and mortality in heart failure populations (10). Also, there are several clinical conditions in which elevated RDW was associated with negative outcomes such as atrial fibrillation, acute pulmonary embolism, peripheral arterial disease, acute and chronic kidney disease (11-13). Although the relationships between RDW and adverse outcomes have been shown, the mechanisms that cause this relationship is not exactly determined. Apart from as a marker of ineffective erythropoiesis, there are various mechanisms that have been accused for this

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relationship such as endothelial dysfunction, inflammation, oxidative stress and malnutrition (14-16). As previously indicated, chronic inflammatory state in hemodialysis patients is generally known issue. Although, there are some studies that show significant relationship between elevated RDW values and morbidity and mortality in hemodialysis population, there are very limited number of studies which studied the relationship between RDW and inflammatory markers (17,18).

Therefore, our aim was to investigate the association between RDW and serum CRP levels in these patient population and to contribute the literature for using RDW as an inflammatory marker.

Materials and Methods

Study design: We designed this retrospective study to evaluate 133 conventional maintenance hemodialysis patients in our city between 01/07/2019 and 09/07/2019. Patients aged 18 years and older and patients who were on maintenance hemodialysis ≥3 months are our inclusion criteria. Patients with active infection, history of malignancy, history of immunosuppressive drug use, recent history of bleeding, recent history of blood and/or blood product transfusion, active inflammatory disease and patients who were unwilling to participate in the study were excluded. Overall, we excluded 9 patients due to active infection at the time of data collection, 4 patients due to history of malignancy, 3 patients due to history of immunosuppressive drug usage, 3 patients due to recent RBC transfusion and 2 patient was excluded due to active inflammatory disease at the time of data collection. At the end, 112 of 133 patients who were eligible for these criteria were enrolled to the study.

Data collection: Age, gender, dialysis access, conventional hemodialysis type, length of time on hemodialysis (months), comorbidity scores of patients according to Charlson Comorbidity Index (CCI) body mass index (BMI), Kt/v index, medications, hemoglobin, RDW, serum levels of albumin, C reactive protein (CRP), ferritin, intact parathyroid hormone (iPTH) and lipid profiles were assessed for all patients. Blood samples were taken from patients within 15 minutes before the first midweek dialysis of the month. Hemoglobin and RDW were measured as part of complete blood cell count (Sysmex XN 2000 was used). Beckman Coulter AU 2700 spectrophotometry was used for albumin measurement, immunonepholometric method (NFL BN-2) was used for CRP measurement, ferritin immunoassay (ADVIA Centaur XPT immunoassay, Siemens) was used for measurement of ferritin levels, a chemiluminescence method (ADVIA centaur XPT immunoassay, Siemens) was used for measurement of iPTH levels and enzymatic color test was used for lipid parameters. According to our laboratory parameters, RDW value ≥14.5% were evaluated as elevated RDW value so we divided patients into two groups according to RDW values as patients with normal RDW and patients with high RDW.

Statistical analysis: We presented the results of categorical variables as numbers and percentages and the results of continuous variables as mean ± standard deviation. SPSS 19 for Windows was used for data analysis (IBM Corp. Released 2010. IBM Statistics for Windows, Version 19.0.) The chi-square test was used for analyzing categorical variables and the independent samples t test was used for analyzing continuous variables. The correlation between variables was identified by using Spearman's rho correlation analysis (for variables that were not normally distributed). Results were given as correlation coefficient (r) and p values. We used linear regression analysis for defining independent variables associated with serum CRP levels. Age and gender were included in the model as biological adjustment factors. Any variable with a result of $p<0.25$ in univariate analysis was included in the linear regression analysis (19). A statistically significant p value was considered as <0.05

Results

112 conventional maintenance hemodialysis patients were included to our study according to the eligibility criteria. The main age of the patients was 61.91± 12.91 and 57.1% of the patients were male. We divided patients into two groups according to RDW value. Patients with normal RDW values (RDW <14.5%) and patients with elevated RDW values (RDW ≥14.5). The mean RDW values in both groups were 13.69±0.53 and 16.09±1.59 respectively.

CRP levels was the only statistically significant difference between two groups ($p = 0.007$). We did not find a significant difference between groups in terms of hemoglobin and ferritin levels ($p = 0.702$ and $p = 0.283$). Demographic, clinical and laboratory parameters of the groups and comparison between them was given in table 1.

Table 1. Demographics and clinical and laboratory parameters of the patients with normal RDW values and patients with elevated RDW values

	Patients with normal RDW (n=32)	Patients with elevated RDW (n=80)	p
Age (years)	59.03±15.39	63.06±11.68	0.188
Gender			0.596
Male	17 (53.1%)	47 (58.7%)	
Female	15 (46.9%)	33 (41.3%)	
Dialysis access			0,345
Fistul or graft	26 (81.2%)	61 (76.3%)	
Catheter	6 (18.8%)	19(23.7%)	
Conventional maintenance hemodialysis (4 hours per session)			0,587
Thrice-weekly	31 (96,1%)	78 (97.5%)	
Twice-weekly	1(3,9%)	2 (2,5%)	
Dialysis vintage (months)	63.09±62.55	59.24±52.64	0,759
Comorbidity index	7.06±3,42	7.45±2.79	0,572
Body mass index (kg/m2)	24.61±5.63	26.11±4.92	0,208
Kt/v index	1.58±0.29	1.60±0.31	0.806
Hemoglobin (g/dl)	11.15±11.31	11.26±1.40	0.702
Albumin (g/dl)	3.85±0.34	3.82±0.36	0.636
Crp (mg/l)	7.42±6.66	11.81±9.53	0.007
Ferritin (ng/ml)	457.56±300.86	395.29±189.45	0.283
iPTH (pg/ml)	455.23±408.26	386.65±376.32	0,415
LDL-C (mg/dl)	80.64±30.08	89.02±35.44	0.212
HDL-C (mg/dl)	38.88±8.59	38.83±11.30	0.980
Triglyceride (mg/dl)	166.31±97.95	207.41±153.04	0,162
Medications			
ESA	27(84.4 %)	61 (76.3%)	0.319
Vitamin D analogs	23(71.8 %)	59(73.7%)	0,714
Antihypertensive	22 (68.7 %)	57(71.2%)	0,329
ESA dose (units/week)	3312.21±2583.29	3177.21±2921.01	0.811
Iron dose (mg/week)	75.00±80.32	89.74±131.51	0,475

RDW: Red cell distribution width, CRP: C reactive protein, iPTH: Intact parathyroid hormone, LDL-C: Low density lipoprotein cholesterol, HDL-C: High density lipoprotein cholesterol, ESA: Erythropoiesis stimulating agent. Results are presented as Mean± standard deviation for continuous variables and n (%) for categorical variables

We made correlation analysis between study parameters. Serum albumin levels had significant but weak inverse correlation with serum CRP levels (r= -0.257, p= 0.006). RDW values had significant but weak positive correlation with serum CRP levels (r= 0.289, p= 0.002). We did not found a significant correlation between hemoglobin levels and serum CRP levels and serum ferritin levels and serum CRP levels (p= 0.090 and p= 0.664, respectively). We show scatter plot graphics of correlations in figure 1.

We also analyzed the independent factors associated with serum CRP levels by using multiple linear regression analysis. RDW was detected as the only independently associated factor for serum CRP levels (p= 0.028). In table 2, we give linear regression analysis results.

Discussion

The present study was conducted in hemodialysis population in which chronic inflammatory state is

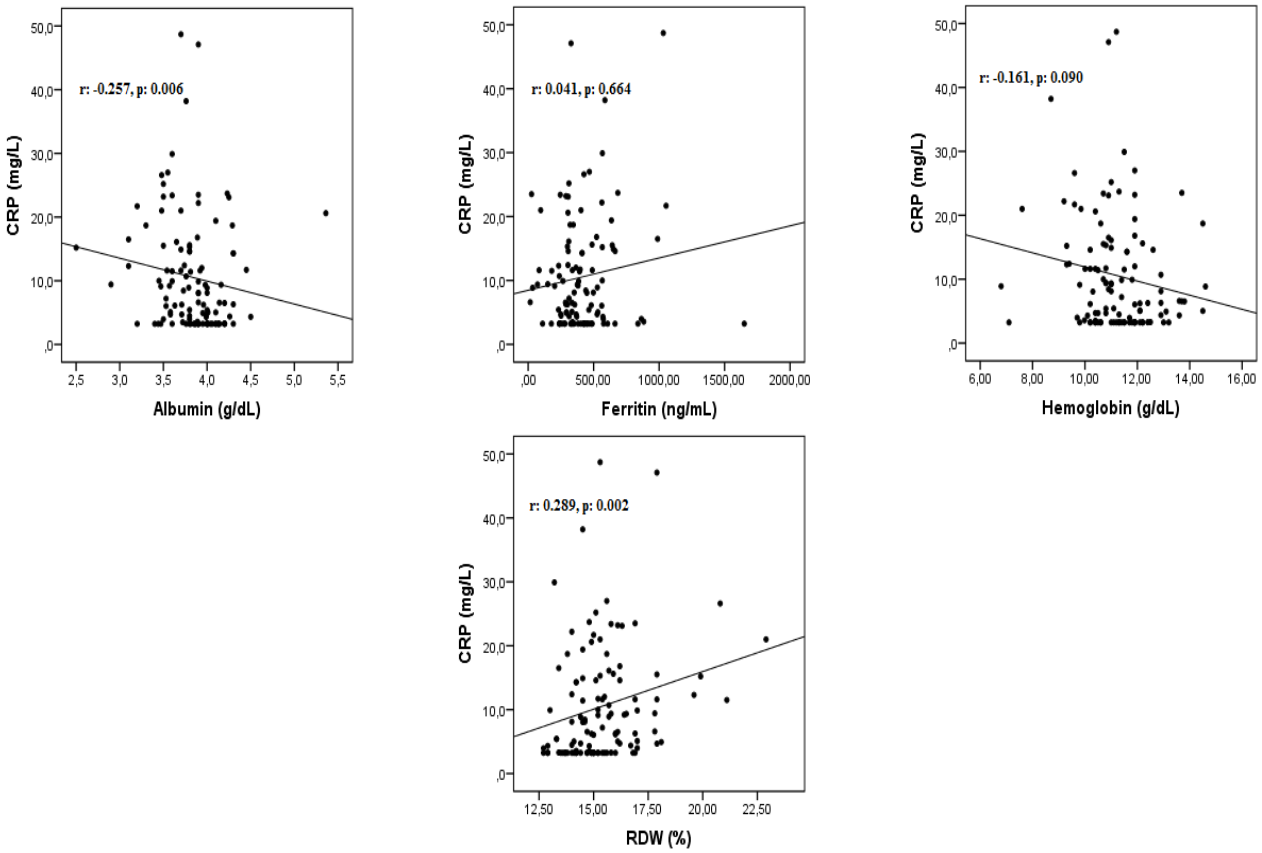

Fig. 1. Scatter plot graphs of correlation analysis a) between albumin and CRP b) between ferritin and CRP c) between hemoglobin and CRP d) between RDW and CRP. **CRP:** C reactive protein, **RDW:** Red cell distribution width

commonly seen and one of the leading factors responsible for increased morbidity and mortality. Recent studies show that chronic inflammation in hemodialysis patients may cause progressive atherosclerosis and malnutrition by several pathogenic mechanisms (20). CRP is currently best validated inflammatory marker and its efficacy has been shown in many studies (6,21). It has been shown that hemodialysis patients have increased level of serum CRP levels (22,23). In our study we also found that 60% of our patients have elevated levels of CRP in consistent with the literature. In recent years, an increasing number of studies have been made which show association of RDW with adverse outcomes in several disease (24-26). Although the exact mechanism is not known, inflammation is thought to be one of the leading causes. Despite all this knowledge, the relationship between inflammation and RDW in hemodialysis patients in which inflammation is so widespread has been studied in very few studies.

Tekce et al. studied the association between RDW and inflammatory, nutritional and volume markers in hemodialysis patients without anemia and they found a significant association between RDW and these markers [18]. In a retrospective observational study by Vashistha T. et al. they found that increased RDW levels are associated with higher mortality risk and weak correlation between CRP and RDW (17). Yonemoto S. et al. showed higher RDW was independently associated with worse renal outcome in non dialysis dependent chronic kidney disease population and in the same study, a weak positive correlation between RDW and CRP was also shown (27). In a study examining the prognostic value of RDW in maintenance hemodialysis patients, they found higher RDW was common and significantly related with poor outcomes (28). In our study, we also found a significant difference between two groups in terms of CRP levels. In accordance with above studies, we showed a weak positive correlation between CRP levels and RDW. Our regression analysis showed that the only significantly associated variable with serum CRP levels was RDW. This result is consistent with the general idea that the inflammation was one of the major underlying mechanism responsible for the elevated RDW levels. We found also that this relationship between CRP and RDW levels was independent of hemoglobin and ferritin levels.

There are several limitations of our study. A casual relationship between serum CRP levels and RDW values was not established due to cross-sectional nature of this study. Relatively small sample size of our study is one of the limitations of our study. Another limitation of the study is that CRP is the only studied inflammatory marker although it is most widely used and validated inflammatory marker.

Table 2. Univariate and multivariate linear regression analysis results of factors associated with serum CRP levels

	Univariate			Multivariate		
	β±SE	95% CI	p	β±SE	95% CI	p
Age (years)	0.078±0.066	-0.053 to 0.209	0.241	-0.261±0.070	-0.114 to 0.164	0.725
Gender (female)	-0.299±1.726	-3.720 to 3.123	0.863	-0.080±1.746	-3.541 to 3.382	0.964
Albumin (g/dl)	-3.601±2.404	-8.365 to 1.164	0.137	-1.074±2.666	-6.360 to 4.211	0.688
Ferritin (ng/mL)	0.005±0.004	-0.002 to 0.012	0.181	0.006±0.004	-0.002 to 0.014	0.156
Hemoglobin (g/dL)	-1.105±0.618	-2.330 to 0.121	0.077	-0.590±0.694	-1.966 to 0.786	0.397
RDW (%) (fL)	1.176±0.477	0.231 to 2.122	0.015	1.156±0.520	0.125 to 2.187	0.028

RDW: Red cell distribution width

In conclusion, we found that there is a statistically significant positive correlation between CRP and RDW in maintenance hemodialysis patients. We also showed a significant relationship between RDW and serum CRP levels. This study is important for contributing to current literature which has very few limited number of studies in such an important population. We believe that our study can lead to more comprehensive prospective studies to clarify the RDW and inflammation relationship and the role of RDW as an inflammatory marker.

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