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Association of red cell distribution width with coronary plaque burden and sub-types in patients with type-2 diabetes mellitus

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ABSTRACT

Red cell distribution width (RDW) is an inflammatory marker that is associated with CAD presence and prognosis.We aimed to evaluate the relationship between RDW value, coronary atherosclerosis, coronary plaque burden and morphology in diabetic patients.147 DM patients who were evaluated with 128-slice dual-source coronary computed tomography angiography (CCTA) for suspected CAD were included in the study. The study population was divided into two groups [a CAD group (Group I) and non-CAD group (Group II)]. The plaque characteristics were analyzed on a per-segment. RDW values were obtained from the automated complete blood count.RDW values were found to be significantly higher among diabetic patients with CAD compared to those without CAD (14.6±1.4% vs 13.3±1.6%, p<0.001). In the correlation analysis, RDW value showed significant positive correlation with hs-CRP (r=0.523, p<0.001), total plaque burden (r=0.379, p<0.001), mixed plaques (r=0.253, p=0.018) and non calcified plaques (r=0.413, p<0.001). Also, multivariate logistic regression analysis revealed RDW as a significant and independent predictor of the presence of CAD in patients with DM .(OR=1.659, 95% CI:1.257-2.190; p<0.001).In our study we have determined that RDW value is an independent predictor among diabetic patients for the presence of CAD. Moreover, RDW values showed significant correlation with total plaque burden, and the number of non-calcified and mixed plaques.

1. Introduction

Diabetes mellitus (DM) is an important cardiovascular risk factor. Cardiovascular disease is responsible for 70-80% of mortality among diabetic patients, and 3 out of 4 deaths among them is cause by coronary artery disease (CAD) (Johnstone and Nesto, 2005; Özgen, 2004). ´National Cholesterol Education Program Adult Treatment Panel III´ (NCEP ATP III) has listed diabetes among cardiovascular risk factors as equivalent to CAD. (Expert Panel, 2001). DM is the strongest risk factor among unmodifiable risk factors for atherosclerosis. Key players in the pathogenesis of atherosclerotic diseases, chronic inflammation and oxidative stress levels are high in diabetic patients (King and Loeken, 2004; Wellen and Hotamisligil, 2005). High morbidity and mortality in DM patients due to CAD has prompted researchers to search for new markers that can predict and aid in the prognosis of CAD.

Red cell distribution width (RDW) is indication of variation in size of the circulating erythrocytes which is get from a standart automated complete blood count. Increased RDW is sign of the presence of anisocytosis, that is related to impaired erythropoiesis and erythrocyte degradation, reflecting chronic inflammation and a high level of oxidative stres (Evans and Jehle, 1991; Weiss and Goodnough, 2005; Ferrucci et al., 2005). Studies have shown that high RDW values are associated with unfavorable prognosis in acute myocardial infarction (Dabbah et al., 2010; Uyarel et al., 2011), heart failure (Felker et al., 2007, Al-Najjar et al., 2009), stable angina (Tonelli et al., 2008), peripheric artery disease (Ye et al., 2011), and stroke (Ani and Ovbiagele, 2009). It has also been reported that higher RDW values are associated with CAD presence, extent and complexity among patients with stable angina and ST-elevation myocardial infarction (STEMI) (Isık et al., 2012, Akın et al., 2013).

A study by Malandrino et al that evaluated the association of RDW and macro- and microvascular complications in diabetic patients demonstrated that higher RDW values were associated with cardiovascular disease (myocardial disease, heart failure, stroke) and nephropathy, and RDW was implicated as an important clinic marker for vascular complications (Malandrino et al., 2012).

The use of coronary computed tomography angiography (CCTA) is as a sensitive and specific tool not only for the demonstration of significant coronary stenosis, but also for detecting plaque morphology and plaque outward expansion (Achenbach et al., 2004; Leber et al., 2005; Miller et al., 2008). Plaque morphology and vulnerability evaluated by CCTA can provide additional information about possible future acute coronary events (Leber et al., 2003; Motoyama et al., 2009). Although the relationship between RDW and cardiovascular diseases is well documented, there are no data concerning the relationship between RDW and CCTA findings in diabetic patients. Therefore, we have aimed to evaluate the association between RDW values and coronary atherosclerosis, coronary plaque burden and plaque morphology.

2. Material and method

Study population

This retrospective analysis was performed in a subset of 681 patients, who were admitted to our Cardiology departmant for cardiovascular evaluation between January 2010 and March 2015 and in whom CCTA was performed for suspicion of CAD after clinical assessment. Among these patients, 147 diabetic patients were included in this study. The indications for CCTA were atypical chest pain with an intermediate risk for CAD, inconclusive stress test result, suspected coronary anomalies and exclusion of CAD among patients undergoing noncoronary cardiac surgery. After an assessment of the CCTA images, the study population was divided into two groups [a CAD group (Group I) and non-CAD group (Group II)] on the basis of the presence of coronary atherosclerosis. Missing demographic, clinical and medication information about the patients was completed from patient files.

Patients with history of documented CAD, percutaneous coronary intervention, acute coronary syndrome (ACS), heart failure, coronary bypass surgery, renal disease, hepatic dysfunction, myeloproliferative disease, malignancy, anemia, pregnancy, active or chronic inflammatory or autoimmune diseases were excluded from the study.

Diabetes mellitus was defined as fasting plasma glucose levels >126 mg/dl or hemoglobin A1c (HbA1c) >6.5%, or current treatment with insulin or oral hypoglycemic agents. Hypertension (HT) was defined as systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg, or treatment with antihypertensive drugs. Anemia was defined as a hemoglobin level <12.0 gr/dl in women and <13.0 gr/dl in men, based on the World Health Organization definition (World Health Organ., 1968)

Laboratory measurements

Venous blood samples were obtained by the venipuncture of the large antecubital veins of the patients. Blood values that were determined at the time of cardiovascular evaluation (before CCTA) were recorded from medical reports. RDW, hemoglobin, platelet values and white blood cell count were obtained from the automated CBC using a Sysmex XE-2100 Automated Hematology Blood Analyzer System (Sysmex, Kobe, Japan). Biochemical parameters were measured in Cobas 8000 Modular Analyzer (Roche Diagnostics, Indianapolis, USA) using commercially available assay kits. High sensitive C-reactive protein (hs-CRP) was quantitatively measured by BN II System Nephelometer (Global Siemens Healthcare, Erlangen, Germany) by immunonephelometric method from patients' serum and the results were reported in mg/L.

Coronary computed tomography angiography: image acquisition

All the scans were obtained using 128-slice dual source computed tomography system. (Somatom Definition AS; Siemens Healthcare, Forchheim, Germany). Patients with an initial heart rate of ≥65 beats/min were taken β blocker therapy according to the local protocols. Every participant received 0.4 mg of sublingual nitroglycerin 1 minute prior to contrast administration for coronary arteries dilatation. The coronary angiographic scan was obtained with injection of 70-80 ml nonionic contrast medium (350 mg I/ml iomeprol; Bracco Omnipaque, Milano, Italy) at flow rate of 5 mL/s followed by 50 mL of saline solution and contrast administration was controlled with bolus tracking. The acquisition parameters were 2x64x0.6 mm detector collimation, resulting in 2x128x0.6 mm sections by means of the z-axis flying focal spot technique, 280 ms gantry rotation time, 75 ms temporal resolution, 100 to 120 kV tube voltage depending on body mass index (no greater than 30 kg/m2 BMI 100 kV; greater than 30 kg/m2 BMI 120 Kv), 330 mAs per rotation tube current and 0.2-0.47 pitch adapted to the heart rate. ECG-gated helical mode scan was performed with the full radiation dose window set at 68-78% of the R-R interval in patients with heart rates ≤70 bpm or 200-400 ms after the R peak in patients with heart rate of >70 bpm. The minimum tube current with 4% of the full radiation dose (MinDose; Siemens Healthcare, Forchheim, Germany) was applied to the remainder of the R-R interval to minimise radiation dose. Images were reconstructed with a slice thickness of 0.6 mm, a reconstruction increment of 0.4 mm and using a soft-tissue convolution kernel (B26f).

Coronary computed tomography angiography: image analysis

All scans were performed independently by two experienced radiologists who were blinded to the clinical information using a 3D workstation (Syngo; Siemens Healthcare, Erlangen, Germany) After making independent evaluations, a consensus interpretation was concluded at to obtain a final CCTA diagnosis. Each identified lesion was examined using maximum intensity projection and multiplanar reconstruction techniques on short axis and along multiple longitudinal axis. The radiologists analyzed the plaque characteristics on a per-segment basis according to the modified American Heart Association classification (Austen et al., 1975). Plaques were defined as structures >1 mm2 within and/or adjacent to the vessel lumen, which could be clearly distinguished from the lumen and surrounding pericardial tissue. Coronary plaques were classified as non calcified, calcified and mixed according to their morphology.

Plaques without any calcification were defined as non calcified plaques, plaques with more than 50% of the plaque area occupied by calcified tissue (density ≥130 HU in native scans) were defined as calcified and plaques with less than 50% calcified tissue were defined as mixed type (Leber et al., 2006). All plaque components were assessed on a per-segment basis. The number of any plaques (total plaque burden), as well as plaques with different features was calculated per patient. Additionaly, as an indicator of vulnerable plaques, the ratio between non calcified plaques and total plaque burden was calculated. Inter-observer agreement for the detection of any plaque/patient and plaque/segment were excellent (Cohen's κ=0.94 and 0.82, respectively).

Statistical analysis

Statistical evaluation was performed using SPSS 15.0 (Statistical package for the social sciences, Chicago, IL, USA). Categorical variables were presented as frequencies and percentages and were compared with the $\chi 2$ test. Continuous variables were expressed as means and SD. The normal distribution of continuous variables was tested with Kolmogorov-Smirnov test. Differences in continuous variables between groups were examined using the nonparametric Mann-Whitney U test. Correlation analysis was performed using Spearman's coefficient of correlation. Multivariate logistic regression analysis was also performed and the model included potential confounders (age, body mass index [BMI], serum creatinine, low density lipoprotein cholesterol [LDL-C], high density lipoprotein cholesterol [HDL-C], HbA1c, hypertension, RDW, high sensitive C-reactive protein [hs-CRP]) for CAD. $p< 0.05$ was considered statistically significant.

3. Results

Baseline clinical characteristics

Eighty eight diabetic patients with CAD (Group I, 43 males; mean age 56.7±9.1) and 59 diabetic patients without CAD (Group II, 24 males; mean age 52.5±9.2) were included in the study. Demographic, clinical and laboratory parameters of the patients are presented in Table 1. No significant difference was detected between the groups regarding BMI, hypertension, smoking, white blood cell count, hemoglobin, platelet count, serum glucose, serum creatinine, HbA1c, triglyceride, total cholesterol, LDL-C values and medications ($p>0.05$). In the CAD group, hs-CRP values were significantly higher ($p=0.004$) while HDL-C levels were significantly lower ($p=0.019$) compared to the non-CAD group. RDW values were also significantly higher in the CAD group (14.6±1.4% vs 13.3±1.6%, $p<0.001$) (Figure 1). Number of plaques were detected as 4.81±2.1 in the CAD group. Among the 424 plaques evaluated for plaque subtypes, calcified type was the most frequent (n=187, 44.2%), followed by mixed type (n=124, 29.2%) and non-calcified type (n=113, 26.6%). Non-calcified/Total plaque burden ratio was 0.37±0.42 in the CAD group. (Table 1)

Association of RDW levels with clinical characteristics, laboratory findings and coronary plaque burden and sub-types

In the correlation analysis, RDW showed significant positive correlation with HbA1c ($r=0.212$, $p=0.047$), hs-CRP ($r=0.523$, $p<0.001$) (Figure 2), total plaque burden ($r=0.379$, $p<0.001$), number of mixed plaques ($r=0.253$, $p=0.018$), and non calcified plaques ($r=0.413$, $p<0.001$) (Figure 3) in the CAD group (Table 2). In addition, RDW was also positively correlated with non-calcified plaque/total plaque burden ratio ($r=0.307$, $p=0.004$) (Figure 4).

Association of RDW levels with the presence of coronary artery disease.

Simple logistic regression analysis revealed that age (OR=1.051, %95 CI:1.012-1.092; p=0.010), serum creatinine (OR=5.306, %95 CI:1.099-25.611; p=0.038), HDL-C (OR=0.954, %95 CI:0.924-0.985; p=0.004), RDW (OR=1.851, %95 CI:1.420-2.413; p<0.001) and hs-CRP (OR=1.535, %95 CI:1.207-1.952; p<0.001) showed an association with the presence of CAD in all patients. These variables were entered into a backward stepwise multivariate logistic regression model. Multivariate logistic regression analysis demonstrated that HDL-C, RDW and hs-CRP levels were significant and independent predictors for the predicting the presence of CAD in patients with DM (OR=0.953, %95 CI:0.921-0.988; p=0.008, OR=1.659, %95 CI: 1.257-2.190; p<0.001, OR=1.380, %95 CI:1.058-1.800; p=0.018 respectively) (Table 3).

To investigate the predictive value of RDW for CAD in patients with DM, a receiver operator characteristic (ROC) curve was generated for sensitivity and specificity using the respective areas under the curve (AUC). The analysis indicated that RDW values of more than 16.05% had a 94.9% sensitivity and a 86.4% specificity for predicting CAD in the DM patients (AUC=0.722; 95% confidence interval, 0.637–0.807; P<0.001) (Figure 5).

4. Discussion

In the present study, we determined higher RDW values in diabetic patients with CAD than non-CAD patients. Moreover, RDW was associated with plaque morphology, and significantly correlated with total plaque burden and number of mixed plaques, and non-calcified plaques in diabetic patients. Diabetes is an important risk factor for cardiovascular diseases. Approximately 60% of diabetic patients have cardiovascular disease. Overall rate of cardiovascular mortality is twice as high in these patients compared to non-diabetic patients. (Seshasai et al., 2011). Evaluation of cardiovascular risk and detection of CAD is very important in managing treatment. Accordingly, new biomarkers that can contribute to detection of CAD in its early stages is enthusiastically awaited by researchers.

Red blood cell distribution width is an indicator of the heterogeneity in the size of circulating erythrocytes. RDW can be measured as part of daily automated CBC. In recent years, studies have focused on RDW and its association with CAD and adverse cardiovascular outcomes. In a study by Dabbah et al. in acute coronary syndrome patients, high RDW values were associated with long-term adverse clinical outcomes (Dabbah et al., 2010). Tonelli et al reported an association between high RDW values with death and cardiovascular events in CAD patients under long-term follow-up (Tonelli et al., 2008). In another study, higher RDW values were revealed as an independent predictor for in-hospital and long-term cardiovascular mortality among STEMI patients undergoing primary

percutaneous coronary intervention (PCI) (Uyarel et al., 2011). In a long-term prospective follow-up study among non-ST elevation myocardial infarction patients, high RDW values were associated with cardiovascular mortality, hospitalization for heart failure and reinfarction (Gül et al., 2012). Additionally, high RDW values were associated with angiographically detected CAD presence and complexity (Isık et al., 2012). Another study in hypertensive patients has shown an independent and strong association of RDW with carotis intima media thickness which is accepted as an early phase of atherosclerosis (Wen et al., 2010).

In general, patients with DM have oxidative stress and high levels of chronic inflammation which play key roles in the progression of atherosclerosis diseases (King and Loeken, 2004; Wellen and Hotamisligil, 2005). Consequently, recent studies have been designed to establish the relationship between RDW levels and CAD in diabetic patients. In a study by Tsuboi et al. increased RDW was significantly associated with long-term all-cause mortality in diabetic patients with stable angina undergoing PCI (Tsuboi et al., 2013). In a metaanalysis presented by Patel et al. an association between RDW and all-cause mortality was shown in the subgroup of diabetic patients. (Patel et al., 2010). Malandrino et al. reported a relationship between RDW and micro- and macrovascular complications in diabetic populations in the United States with the Third National Health and Nutrition Examination Survey (NHANES III). In that study, higher RDW levels are related with increased adjusted odds of myocardial infarction, nephropathy, heart failure and stroke. Also, RDW was underlined as an important clinical marker for vascular complications (Malandrino et al., 2012). A study presented by Heba et al reported similar findings and showed that higher RDW values were associated with increased macrovascular complication (CAD, peripheral vascular disease, cerebrovascular disease) risk (Sherif et al., 2013). Similar to these studies, we have shown higher RDW values in diabetic patients with CAD compared to those without CAD. Furthermore, we demonstrated that high RDW values were an independent predictor for presence of CAD in diabetic patients. There are reports supporting that inflammation increases RDW by inhibiting erythropoietin-induced erythrocyte maturation and iron metabolism (Weiss and Goodnough, 2005; Patel et al., 2009). A study by Pascual-Figal et al. revealed that inflammatory cytokines increase erythrocyte heterogeneity by suppressing erythrocyte maturation and releasing juvenile erythrocytes into circulation (Pascual-Figal et al., 2009). Considering the role inflammation plays in the development of atherosclerosis (Libby et al., 2002; Hansson, 2005), an inflammatory process may be the underlying cause of high RDW values observed in the CAD group in our study. Accordingly, we have also detected higher levels of hs-CRP in the CAD group.

Red blood cells have a huge antioxidant capacity and they are prone to oxidative damage, which decreases cell survival and induces the release of juvenile erythrocytes into circulation (Kiefer and Snyder, 2000). Oxidative stress plays a role in the pathogenesis of atherosclerosis by causing endothelial dysfunction and increasing expression of proinflammatory mediators (Dzau et al., 2006). İn our study, oxidative stress may be a contributing factor for the high RDW values in the CAD group. Studies by Kato et al (Kato et al., 2005) and Cole et al (Cole et al., 2000) have illustrated that neurohormonal system activation influences red blood cell maturation through direct stimulation of endothelial progenitor cells and upregulation of erythropoietin. Several studies demonstrated an essential part of renin-angiotensin system (RAS) in pathophysiology of heart and vascular system, including atherosclerotic disease (Pacurari et al., 2014; Wu et al., 2014). In our study, higher RDW values observed in the CAD group compared to the non-CAD group might be caused by increased neurohormonal activation. In conclusion, the increase in RDW values in our study might be the combined result of increased inflammation, oxidative stress and neurohormonal activation among CAD patients with diabetes.

Besides revealing the severity of coronary stenosis, coronary computed tomography angiography can provide additional information on vessel walls and plaque composition (Miller et al., 2008). Coronary plaque composition is an important factor of clinical progression and outcomes in CAD (Greenland et al., 2003). Plaques with lipid rich core and proinflammatory immun cells are more vulnerable to rupture and are often non calcified plaques with low attenuation of CCTA (Motoyama et al., 2007). In a study by Pundziute et al. (Pundziute et al., 2008) demonstrated that non-calcified and mixed plaques were more extensive in ACS patients compared to stable CAD patients. In another study by Russo et al. (Russo et al., 2010) on suspected CAD patients reported that patients with non-calcified and mixed plaques suffered cardiac events more frequently than patients with calcified plaques. CCTA studies that assessed plaque subtypes in diabetic patients revealed a higher ratio of calcified plaques among these patients (Pundziute et al., 2007; Pundziute et al., 2009). Similarly, we have detected a higher ratio of calcified plaques than non-calcified and mixed plaque distribution.

Some studies report an association between non-calcified and mixed plaques and inflammatory markers. Hausleiter et al. detected a higher CRP level in patients with non-calcified plaques compared to those with calcified plaques, and associated it with increased inflammatory activity (Hausleiter et al., 2006). Similar results were reported in a study conducted by Bamberg et al. on patients with low cardiovascular risk profile, and higher CRP levels were observed in patients with non-calcified plaques (Bamberg et al., 2012). In another presented study, thin-cap fibroatheromas (TCFA) that play a key role in plaque vulnerability were more extensive in ACS patients, and observed more frequently in mixed plaques (Pundziute et al., 2008). A post-mortem study that analysed the association of CRP levels and TCFA demonstrated that increased CRP is significantly correlated with the number of TCFAs and associated with plaque vulnerability (Burke et al., 2002). Research investigating the relationship between inflammation and RDW detected an association between increased RDW and hs-CRP along with various other inflammatory markers (Patel et al., 2009; Lippi et al., 2009). Accordingly, RDW showed a significant correlation with hs-CRP in our study. This finding seems to support the role of inflammation in increased RDW.

Furthermore, we have detected significant correlations between RDW values and total plaque burden, non-calcified plaque and mixed plaque, along with non-calcified/total plaque burden ratio. Our study is the first study to assess the

relationship between RDW and coronary plaque subtypes. In light of the aforementioned studies, we believe that the significant correlation between RDW and the number of non-calcified and mixed plaques might be associated with the increased inflammatory activity observed in these plaque subtypes.

Study Limitations

Our study had some limitations. First, this was a retrospective study with a relatively small number of patients. Second, RDW levels may affected in conditions of ineffective red blood cell production (such as folate, iron or B12 deficiency and hemoglobinopathies), erythropoietin levels, increased red cell destruction (such as hemolysis), and after blood transfusion. Only Hb levels were measured in this study, and other factors including iron, folate and vitamin B12 were not measured. Third, the study could have provided more accurate information if the relationship between RDW levels and plaque morphology had been evaluated with intravascular ultrasound.

5.Conclusion

We have detected that RDW is an independent predictor for CAD among diabetic patients. Moreover, RDW was significantly correlated with total plaque burden, and the number of non-calcified, and mixed plaques. RDW can be a potential and cheap marker in the evaluation of diabetic patients for CAD, and contribute to risk assessment for coronary events and identification of suitable treatment strategies in diabetic patients.

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