

Association Between Red Cell Distribution Width (RDW) and HbA1c in Non-Anemic Patients with Type 2 Diabetes Mellitus

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Abstract

Aim: Diabetes mellitus (DM) is a complex disease characterized by chronic hyperglycemia that leads to complications affecting the kidneys, eyes, peripheral nerves, and micro- and macrovascular systems. Monitoring glycemic control is crucial for the prevention of these complications. Hemoglobin A1c (HbA1c) has long been used as the gold standard indicator of glycemic control. In recent years, red cell distribution width (RDW), one of the hematological parameters, has been associated with cardiovascular diseases, chronic kidney disease, and diabetes-related complications. The aim of this study was to evaluate the relationship between red cell distribution width (RDW) and HbA1c, as well as micro- and macrovascular complications, in patients with type 2 diabetes mellitus. In addition, the potential utility of RDW as a marker of microvascular complication risk was investigated. **Materials and Methods:** This retrospective study included 310 patients with type 2 diabetes mellitus and 328 healthy controls. Medical records of non-anemic patients were reviewed. Data regarding RDW, hemoglobin, and creatinine were collected. Microvascular complications were also assessed: retinopathy by ophthalmologic examination, nephropathy by 24-hour or spot urine analysis, and neuropathy by electromyography. **Results:** RDW levels were significantly higher in the diabetic group (13.92 ± 1.22) compared with the control group (12.77 ± 1.54) ($p < 0.001$). A significant positive correlation was observed between RDW levels and microalbuminuria in 24-hour urine samples ($r = 0.291$, $p < 0.001$). An RDW cut-off value of 13.47% predicted nephropathy with 73% sensitivity and 61% specificity (AUC = 0.689, $p < 0.001$). **Conclusion:** RDW was found to be associated with HbA1c in patients with type 2 diabetes mellitus. Among microvascular complications, only diabetic nephropathy was significantly associated with RDW levels.

Keywords: RDW, diabetes, HbA1c, microvascular complications, retinopathy, nephropathy, neuropathy

1. Introduction

Type 2 diabetes mellitus (DM) is a chronic metabolic disease characterized by insulin resistance and beta-cell dysfunction. Microvascular complications—nephropathy, retinopathy, and neuropathy—and macrovascular complications—coronary artery disease,

stroke, and peripheral arterial disease—are the main outcomes of diabetes that increase morbidity and mortality¹.

Red cell distribution width (RDW) is a parameter routinely measured in the complete blood count and reflects the heterogeneity in the size of circulating erythrocytes. Traditionally used in the differential diagnosis of anemia, RDW has recently been reported to be associated with cardiovascular diseases and diabetic complications^{2–4}. Previous studies have shown that, in addition to its classical role, RDW increases in conditions characterized by subclinical inflammation and enhanced oxidative stress. Inflammation leads to the release of inflammatory cytokines such as tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), and interleukin-6 (IL-6), which suppress erythropoietin activity, impair hemoglobin synthesis, promote the release of immature erythrocytes into the circulation, and consequently increase RDW levels^{5,6}.

In a cohort study, RDW was reported to have a stronger predictive value for cardiovascular mortality than high-sensitivity C-reactive protein (hs-CRP), an important marker of chronic inflammation⁷. Another study demonstrated that elevated RDW levels were independently associated with microalbuminuria, an independent predictor of cardiovascular events⁸. Although the exact mechanism remains unclear, RDW has recently been proposed as an indicator of chronic inflammation, oxidative stress, and cardiovascular disease⁹.

2. Materials and Methods

This study was conducted between 2014 and 2015 and included diabetic patients who presented to the Dokuz Eylül University Endocrinology Outpatient Clinic, along with a non-diabetic control group. In this retrospective analysis, a total of 638 individuals were evaluated, including 310 patients with type 2 diabetes mellitus and 328 non-diabetic controls.

2.1. Inclusion Criteria

Non-anemic individuals aged 18–65 years, with or without type 2 diabetes mellitus, were included. The diagnosis of type 2 diabetes mellitus was established according to the American Diabetes Association (ADA) criteria.

2.2. Exclusion Criteria

Patients with type 1 diabetes mellitus or other specific types of diabetes, individuals younger than 18 years or older than 65 years, males with hemoglobin levels <14 g/dL and females with hemoglobin levels <12 g/dL were excluded. In addition, patients with malignancy, severe renal failure, severe hepatic failure, and pregnant women were excluded.

2.3. Data Collection

The following data were collected from medical records: age, sex, hemoglobin (Hgb), red cell distribution width (RDW), hemoglobin A1c (HbA1c), serum creatinine, urinalysis, spot urine or 24-hour urine microalbumin levels, electromyography (EMG) findings, fundoscopic examination results, and history of cardiovascular disease. Microvascular complications were defined as follows: retinopathy was assessed by ophthalmologic examination, nephropathy by 24-hour or spot urine analysis, and neuropathy by electromyography.

2.4. Statistical Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software, version 18.0 (SPSS Inc., USA). The distribution of continuous variables was assessed using the Kolmogorov–Smirnov test, which confirmed normal distribution. Independent samples t-test was used to compare demographic and laboratory variables between groups. Pearson's correlation analysis was used to evaluate

associations between variables. Results were expressed as mean $\pm$ standard deviation, and a p-value < 0.05 was considered statistically significant.

Table 1. Demographic and laboratory characteristics of the study groups

Variable	Control (n = 328)	Type 2 Diabetes (n = 310)	p value
Age, years	53.49 $\pm$ 8.10	53.67 $\pm$ 8.24	0.777
Sex, Female/Male	177 / 151	165 / 145	0.874
BMI, kg/m ²	30.98 $\pm$ 6.58	31.20 $\pm$ 6.55	0.666
Cardiovascular disease, yes/no	43 / 285	57 / 253	0.067
Hypertension, yes/no	162 / 166	154 / 156	0.942
Hyperlipidemia, yes/no	83 / 245	101 / 209	0.043*
Retinopathy, yes/no	–	36 / 274	–
Nephropathy, yes/no	–	70 / 240	–
Neuropathy, yes/no	–	52 / 258	–
Fasting glucose, mg/dL	90.80 $\pm$ 5.45	157.07 $\pm$ 64.74	$<0.001^*$
Creatinine, mg/dL	0.78 $\pm$ 0.19	0.79 $\pm$ 0.19	0.524
Urea, mg/dL	14.43 $\pm$ 5.35	14.75 $\pm$ 5.42	0.463
ALT, U/L	28.74 $\pm$ 31.07	28.85 $\pm$ 31.87	0.963
HbA1c, %	5.31 $\pm$ 0.19	8.04 $\pm$ 2.35	$<0.001^*$
Total cholesterol, mg/dL	195.88 $\pm$ 44.06	202.59 $\pm$ 39.43	0.043*
HDL cholesterol, mg/dL	50.30 $\pm$ 11.12	46.97 $\pm$ 11.50	$<0.001^*$
LDL cholesterol, mg/dL	121.31 $\pm$ 41.40	124.88 $\pm$ 33.19	0.229
Triglycerides, mg/dL	141.04 $\pm$ 87.56	189.05 $\pm$ 103.28	$<0.001^*$
Hemoglobin, g/dL	13.94 $\pm$ 1.21	13.94 $\pm$ 1.20	0.937
MCV, fL	85.15 $\pm$ 8.40	85.67 $\pm$ 7.49	0.411
RBC, $\times 10^6/\mu\text{L}$	4.82 $\pm$ 0.45	4.81 $\pm$ 0.46	0.884
Hematocrit, %	41.66 $\pm$ 3.41	41.69 $\pm$ 3.39	0.920
Platelets, $\times 10^3/\mu\text{L}$	252.99 $\pm$ 64.11	254.66 $\pm$ 63.64	0.740
WBC, $\times 10^3/\mu\text{L}$	7.91 $\pm$ 1.91	7.89 $\pm$ 1.93	0.894
hs-CRP, mg/L	2.54 $\pm$ 1.72	3.00 $\pm$ 1.70	$<0.001^*$
RDW, %	12.77 $\pm$ 1.54	13.92 $\pm$ 1.22	$<0.001^*$

Data are presented as mean $\pm$ standard deviation or number. Statistically significant ($p < 0.05$).

3. Results

In this retrospective study, a total of 638 individuals were evaluated, including 310 patients with type 2 diabetes mellitus and 328 non-diabetic controls. The mean age of the study population was 53.57 ± 8.16 years. The demographic and laboratory characteristics of individuals with and without type 2 diabetes mellitus are presented comparatively in Table 1.

No statistically significant differences were observed between the two groups in terms of age, sex, or body mass index (BMI) ($p > 0.05$). Similarly, platelet count, hemoglobin, hematocrit, red blood cell count, mean corpuscular volume, alanine aminotransferase, urea, and creatinine levels did not differ significantly between groups ($p > 0.05$).

In contrast, serum RDW levels were significantly higher in the type 2 diabetic group compared with the control group ($13.92 \pm 1.22\%$ vs. $12.77 \pm 1.54\%$; $p < 0.001$). The RDW

cut-off value for detecting diabetic nephropathy was determined to be 13.47%, with a sensitivity of 73% and specificity of 61% based on receiver operating characteristic (ROC) curve analysis ($AUC = 0.689$, $p < 0.001$).

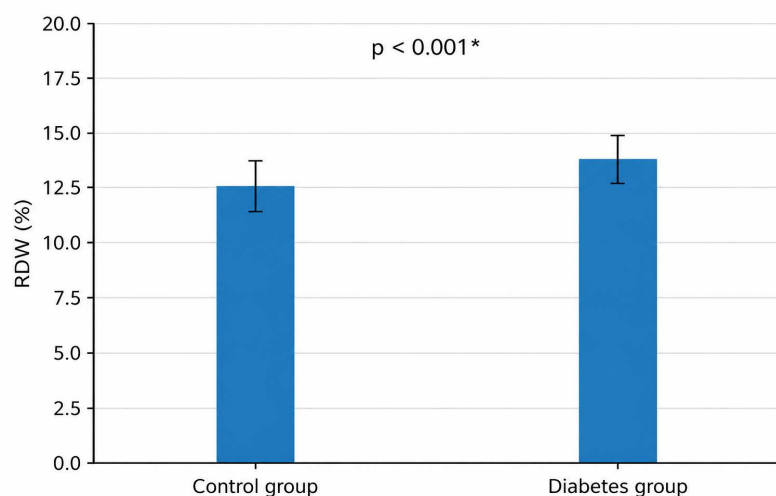


Figure 1. Comparison of RDW levels between diabetic and control groups using the independent samples t-test.

Serum total cholesterol and triglyceride levels were significantly higher, whereas HDL cholesterol levels were significantly lower in patients with type 2 diabetes mellitus. As expected, fasting plasma glucose and HbA1c levels were also significantly higher in the diabetic group.

Among patients with type 2 diabetes mellitus, neuropathy was detected in 52 patients, retinopathy in 36 patients, nephropathy in 70 patients, and cardiovascular disease in 57 patients. Hypertension was present in 162 individuals in the control group and in 154 individuals in the diabetic group.

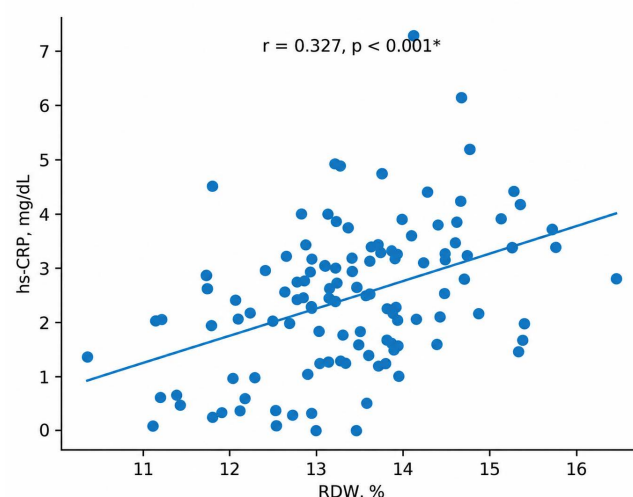


Figure 2. Pearson correlation analysis demonstrating the relationship between RDW levels and hs-CRP.

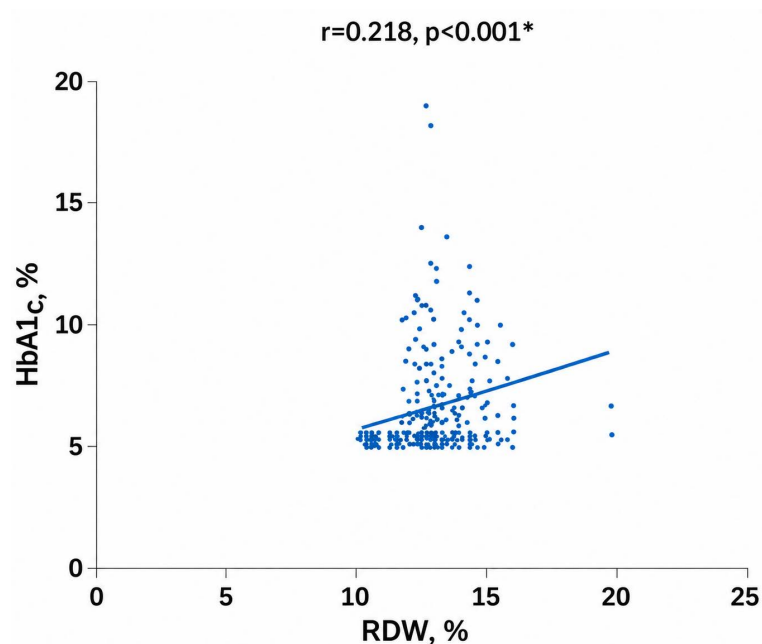


Figure 3. Pearson correlation analysis demonstrating the relationship between RDW levels and HbA1c.

3.1. Correlation Analysis

Serum RDW levels were significantly higher in the diabetic patient group. Pearson's correlation analysis revealed a statistically significant positive correlation between RDW levels and fasting plasma glucose ($r = 0.183, p < 0.001$). RDW levels were also positively correlated with HbA1c ($r = 0.218, p < 0.001$) and hs-CRP levels ($r = 0.327, p < 0.001$).

A statistically significant positive correlation was found between RDW levels and microalbuminuria in 24-hour urine samples ($r = 0.291, p < 0.001$). No statistically significant differences in RDW levels were observed between diabetic patients with and without neuropathy ($p = 0.264$), retinopathy ($p = 0.175$), cardiovascular disease ($p = 0.077$), or hypertension ($p = 0.667$).

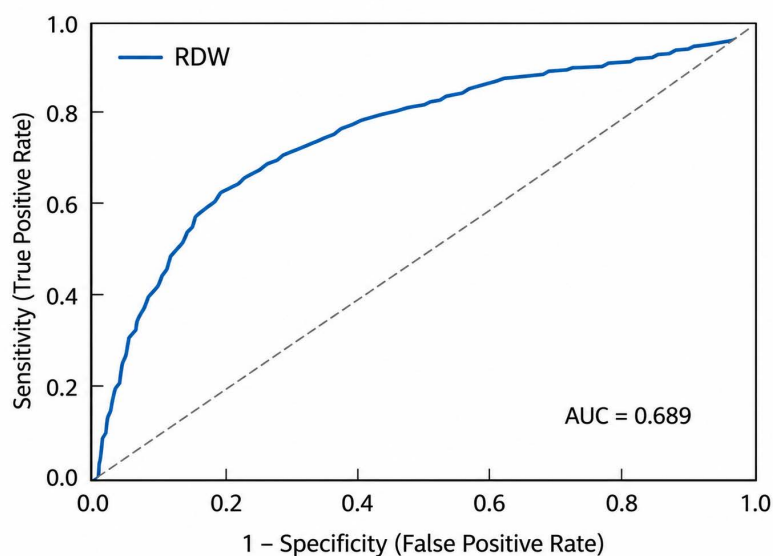


Figure 4: ROC curve of RDW for predicting diabetic nephropathy.

4. Discussion

In this study, RDW levels were shown to be significantly higher in patients with type 2 diabetes mellitus compared with the control group. In addition, positive correlations were observed between RDW levels and fasting plasma glucose, HbA1c, and hs-CRP levels. A significant association was found between elevated RDW levels and diabetic nephropathy, whereas no significant association was detected with retinopathy, neuropathy, or cardiovascular disease.

Previous studies have reported similar findings. Magri et al. demonstrated an association between RDW and diabetic nephropathy, while no significant relationship was observed with neuropathy or retinopathy¹⁰. Similarly, Malandrino et al., in a large-scale NHANES-based study, reported that RDW was associated with myocardial ischemia, stroke, and nephropathy, but not with retinopathy¹¹.

The role of RDW in diabetic complications is thought to be related to systemic inflammation and oxidative stress. Elevated RDW levels may reflect alterations in erythrocyte lifespan and morphology. Chronic inflammatory responses and oxidative stress observed in diabetic nephropathy may contribute to increased RDW levels. Consistent with this hypothesis, several studies have demonstrated a significant association between RDW and microalbuminuria, independent of hs-CRP.

Although no significant association was found between RDW and cardiovascular disease or hypertension in the present study, conflicting results have been reported in the literature. Possible explanations include limited sample size and methodological differences among studies. Therefore, larger prospective studies are warranted. One of the strengths of this study is the exclusion of patients with anemia, minimizing potential hematological effects on RDW. However, the retrospective and single-center design limits the generalizability of the findings.

5. Conclusion

The findings of this study suggest that RDW may be associated with glycemic control and diabetic nephropathy in patients with type 2 diabetes mellitus. Given that RDW is a routinely measured and cost-effective hematological parameter, it may have potential value as a complementary marker for identifying patients at increased risk of diabetic nephropathy. Nevertheless, several limitations should be considered when interpreting these findings. The retrospective design prevented the establishment of a causal relationship, and the single-center setting may limit the generalizability of the results. Although patients with anemia were excluded, iron, vitamin B12, and folate levels were not assessed; therefore, the potential effects of subclinical nutritional deficiencies on RDW could not be excluded. In addition, diabetes duration was not available, despite being an established risk factor for diabetic nephropathy, and thus could not be included as a potential confounder in the analyses. Large-scale, prospective, multicenter studies incorporating nutritional parameters and diabetes duration are needed to confirm these findings and clarify the clinical utility of RDW in assessing diabetic nephropathy risk.

Statement of Ethics: The study protocol was approved by the Ethics Committee of Dokuz Eylül University (Decision No. 792, dated November 24, 2014). Owing to the retrospective design of the study, which was based on the review of medical records, informed consent was not obtained. The study was conducted in accordance with the Declaration of Helsinki.

Use of Artificial Intelligence: No artificial intelligence-based tools or generative AI technologies were used in this study. The entire content of the manuscript was originally prepared, reviewed, and approved by both authors.

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Conflict of Interest: The authors declare that they have no conflict of interest.

Availability of Data and Materials: Due to institutional privacy policies, the datasets generated and/or analyzed during the current study are not publicly available, but they are available from the corresponding author upon reasonable request.

Author Contributions: Conception and design: DBT,FB. Analysis and interpretation of data: DBT,FB. Drafting the article: DBT, FB. Revising the article: DBT, FB. All authors read and approved the final manuscript.

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