ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

DOI: 10.5336/ophthal.2016-50943

The Correlation Between Red Cell Distribution Width and Diabetic Retinopathy in Patients with Type 2 Diabetes Mellitus

Tip 2 Diabetes Mellituslu Hastalarda Eritrosit Dağılım Genişliği ve Diyabetik Retinopati Arasındaki İlişki

Bengi Ece KURTUL,[a]
Besime İNAL,[b]
Pınar ALTIAYLIK ÖZER,[a]
Emrah Utku KABATAŞ[a]

Clinics of
[a]Ophthalmology,
[b]Family Medicine,
Dr. Sami Ulus Maternity and Children's Health and Diseases Training and Research Hospital, Ankara

Geliş Tarihi/*Received:* 18.02.2016
Kabul Tarihi/*Accepted:* 08.05.2016

Yazışma Adresi/*Correspondence:*
Bengi Ece KURTUL
Dr. Sami Ulus Maternity and Children's Health and Diseases Training and Research Hospital,
Clinic of Ophthalmology, Ankara, TÜRKİYE/TURKEY
becekurtul@yahoo.com

ABSTRACT Objective: Diabetic retinopathy (DR) is a serious complication of type 2 diabetes mellitus (DM), and is the leading cause of blindness among adults. Inflammation and oxidative stress play an important role in DR pathogenesis. Red cell distribution width (RDW) is a reliable inflammatory and oxidative stress marker in various cardiovascular diseases, but there is a little data regarding its usefulness in ocular diseases. Thus, we aimed to investigate the correlation between RDW and DR in this study. **Material and Methods:** A total of 180 patients with type 2 DM were enrolled in this study. Patients were divided into 2 groups. A hundred-forty nine patients (82.77%) had no DR and, thirty one patients (17.22%) had DR. Complete blood cell parameters including RDW and biochemical tests including hemoglobin A1c were noted at the time of first ophthalmic examination. **Results:** RDW values were higher in DR (+) group than DR (-) group (14.92±1.71% vs. 13.81±1.00%, respectively, p<0.001). In multivariate analysis, RDW remained an independent predictor of DR (Odds ratio [OR] 1.691, 95% confidence interval (1.036-2.763), p=0.036) together with duration of DM (OR 1.199, p<0.001) and hemoglobin A1c (OR 2.366, p=0.006). **Conclusion:** Elevated RDW levels were significantly associated with DR in patients with type 2 DM.

Keywords: Diabetic retinopathy; erythrocyte indices; inflammation; oxidative stress

ÖZET Amaç: Diyabetik retinopati (DR), Tip 2 diabetes mellitus (DM) hastalığının ciddi bir komplikasyonu ve erişkinlerde körlüğün en önde gelen sebebidir. İnflamasyon ve oksidatif stres DR patogenezinde önemli bir rol oynar. Kırmızı hücre dağılım genişliği [Red cell distribution width (RDW)] pek çok kalp ve damar hastalığında güvenilir bir inflamasyon ve oksidatif stres belirtecidir, ancak göz hastalıklarında kullanımının yararı konusunda mevcut bilgi azdır. Bu nedenle çalışmamızda, RDW ile DR arasındaki ilişkiyi araştırmayı amaçladık. **Gereç ve Yöntemler:** Çalışmaya Tip 2 DM tanılı 180 hasta dahil edildi. Hastalar 2 gruba ayrıldı. Hastaların 149'unda DR tespit edilmedi (%82,77), 31 hastada DR mevcuttu (%17,22). RDW dahil olmak üzere tam kan sayımı parametreleri ve hemoglobin A1c ölçümünü içeren kan biyokimya testlerinin ilk muayenedeki değerleri kayıt edildi. **Bulgular:** DR mevcut hastalarda RDW değerleri, DR olmayanlara göre daha yüksek idi (%14,92±1,71, %13,81±1,00, p<0,001). Multivaryant analizinde; DM süresi (Odds oranı-OR; 1,199, p<0,001) ve hemoglobin A1c düzeyi ile birlikte (OR: 2,366, p=0,006), RDW değeri DR için bağımsız bir etken olarak bulundu (OR: 1,691, %95 güven aralığı (1,036-2,763), p=0,036). **Sonuç:** Yüksek RDW değerleri, Tip 2 DM hastalarında DR varlığı ile anlamlı olarak ilişkilidir.

Anahtar Kelimeler: Diyabetik retinopati; eritrosit indeksleri; inflamasyon; oksidatif stres

Diabetic retinopathy (DR) is a sight threatening, microvascular complication of diabetes that affects the retinal vasculature.[1,2] The overall prevalence of DR in diabetic patients is about 34% worldwide and it is the leading cause of blindness among adults.[3] It is characterized by

microaneurysms, hemorrhages, exudates, intraretinal microvascular abnormalities, abnormalities in the venous caliber and neovascularization which are the signs of both retinal ischemia and increased vascular permeability. This progresses from mild nonproliferative disease, to moderate or severe nonproliferative retinopathy, and finally proliferative disease.[4] Pathophysiologic mechanisms of DR have not been fully elucidated yet, but increased inflammatory response and oxidative stress are widely accepted to play a key role in development of DR.[3,4] Noninvasive markers of DR development may help to identify high risk patients in the setting of type 2 diabetes mellitus (DM).

Red cell distribution width (RDW), a measure of heterogeneity in the size of circulating erythrocytes, is regarded to be inflammatory and oxidative stress marker in many diseases as hypertension, heart failure, coronary artery diseases, and stroke.[5,6] RDW is being known as a global marker of chronic inflammation and oxidative stress both of which are telltale signs of type 2 diabetics.[7] Elevated RDW indicates the presence of anisocytosis, which is related to impaired erythropoiesis and erythrocyte degradation, reflecting chronic inflammation and high levels of oxidative stress.[2,7] Oxidative stress directly damages erythrocytes and leads to shortened erythrocyte survival, resulting in elevated RDW.[7] The role of RDW in various cardiovascular diseases has been reported but there is little data on the relationship between RDW and diabetes-related ocular complications.[5]

Hence, in this study based on the role of inflammation and oxidative stress in damage and pathogenesis of DR, we aimed to evaluate whether there is a correlation between RDW and DR in the setting of type 2 DM.

MATERIAL AND METHODS

The study was undertaken at Dr. Sami Ulus Training and Research Hospital, Ophthalmology Department, from June 2014 through 2015 November and was designed as a retrospective clinical study. A total of 180 patients with type 2 DM were examined. Patients were divided into 2 groups as with and without DR. A hundred- forty nine patients (82.77%) who had no DR and 31 patients (17.22%) who had DR were determined at the time of first routine ophthalmologic examination in our out-patient polyclinic. Diabetes were diagnosed and classified according to the World Health Organization criteria in the family medicine department of our hospital. The demographic data, initial ophthalmic examination in our out-patient clinic such as visual acuity, slit lamp examination of anterior and posterior segment, intraocular pressure were evaluated. The presence of DR was assessed by fundus examination from biomicroscopy through dilated pupils in slit lamp examination. Retinopathy was classified as absent or presents (either nonproliferative or proliferative type). DR was described according to American Academy of Ophthalmology (AAO) and was based on the type in worse eye.[8]

The patients with; type 1 DM; or other diabetes types, such as gestational diabetes, hematologic disorders, iron, vitamin B12 and folat deficiency, acute or chronic infection, inflammatory ocular and systemic diseases, any ocular medication, chronic obstructive pulmonary disease, chronic liver disease, end-stage renal failure, current steroid therapy and/or history of steroid use 3 month before the admission and a history of cancer and/or treatment with radiation or chemotherapy were excluded from the study.

The complete blood cell parameters, fasting blood glucose levels, glycosylated hemoglobin (hemoglobin A1c) levels, fasting serum lipids, serum creatinine, body mass index scores, duration of DM were determined at the time of the first ophthalmic examination. The other systemic disorders were also reported including hypertension and coronary artery disease.

The serum RDW values were evaluated by *ABX Pentra DF120/USA* biochemical analyzer. Body mass index scores were calculated as weight in kilograms divided by height in meters squared (kg/m^2).

This submission has received Institutional Review Board/Ethics Committee approval. Described research adhered to the tenets of the Declaration of Helsinki.

STATISTICAL ANALYSIS

All analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows (version 18.0, SPSS, Chicago, IL). Quantitative variables were expressed as mean value ± standard deviation for continuous variables or percentages for categorical variables/string variables. Comparison of continuous values between two groups was performed by means of independent samples t-test. Categorical variables were compared by x^2 test. The receiver operating characteristic (ROC) curve analysis was performed in order to determine the best cut-off values for RDW, hemoglobin A1c and duration of DM to predict DR and the sensitivity and specificity at that point were obtained. Univariate and multivariate logistic regression analysis were used to identify the independently associated predictors of DR. All significant variables in univariate analysis were entered to multivariate analysis. Two-tailed p value <0.05 was considered statistically significant.

RESULTS

Of 180 patients, 31 patients (17.22%) had DR. Oral agent use was higher in without DR and, insulin use was significantly higher in with DR. The demographic and clinical findings of study patients were shown in Table 1. Duration of DM was longer in DR (+) group. The rate of oral agent use was higher in DR (-) group, while the prevalence of insulin usage was higher in DR (+) group (p<0.001 for both). Age and prevalence of history of coronary artery disease were higher in DR (+) group, but this difference was not statistically significant (p=0.066 and p= 0.056, respectively). The RDW levels were 13.81±1.00% in DR (-) group and, 14.92±1.71% in DR (+) group. The RDW values were significantly higher in DR (+) group than DR (-) group (p<0.001) (Figure 1). The comparisons of laboratory measurements between groups were shown in Table 2. Fasting serum glucose, serum creatinine, hemoglobin A1c levels and neutrophil to lymphocyte ratio (NLR) values were also significantly higher in DR (+) group. In multivariate analysis, RDW remained an independent predictor of DR (Odds ratio [OR] 1.691, 95% confidence interval [CI] (1.036-2.763), p=0.036) together with duration of DM (OR 1.199, 95% CI (1.083-1.327), p<0.001) and hemoglobin A1c (OR 2.366, 95% CI (1.286-4.354), p=0.006) (Table 3). The area under the ROC curve for RDW was 0.717, and a RDW of 14.15 or higher predicted DR with a sensitivity of 65% and specificity of 65% (Figure 2). In addition, the area under the ROC curves for hemoglobin A1c and duration of DM were 0.776 and 0.857, respectively (cut off value for hemoglobin A1c was 7.55% and for duration of DM was 9.5 year) (Figure 3).

TABLE 1: The demographic and clinical findings of subjects included in the study

	Diabetic retinopathy		
Parameter	**No (n=149)**	**Yes (n=31)**	**p**
Age (year)	60.82±7.57	63.68±8.91	0.066
Women	94 (63.08%)	23 (74.19%)	0.238
Duration of diabetes (year)	7.14±5.65	17.0±7.09	<0.001
Type of therapies			
Oral agent use	143 (95.97%)	15 (48.38%)	<0.001
Insulin use	23 (15.43%)	22 (70.96%)	<0.001
Oral agent and insulin use	18 (12.08%)	6 (19.35%)	0.278
Body mass index score (kg/m^2)	31.35±5.20	32.00±6.3	0.833
Presence of hypertension	112 (75.16%)	26 (83.87%)	0.297
History of coronary artery disease	9 (6.04%)	5 (16.12%)	0.056

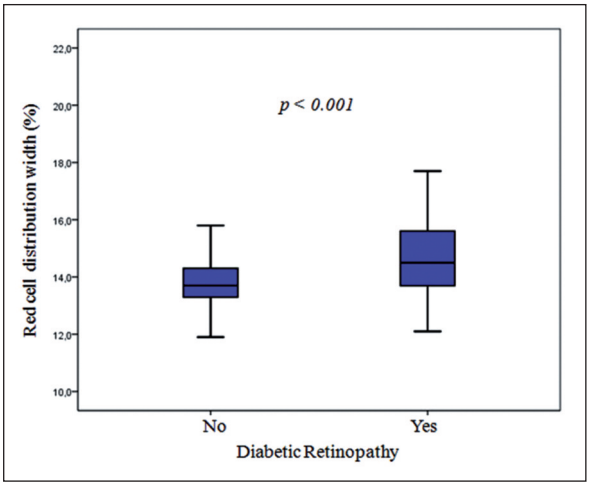

FIGURE 1: Comparison of red cell distribution width levels between the groups.

DISCUSSION

In our study, we have demonstrated a significant association between DR and RDW in patients with type 2 DM as well as duration of DM and hemoglobin A1c.

TABLE 2: Comparison of laboratory parameters of the study population.

	Diabetic retinopathy		
Parameter	**No (n=149)**	**Yes (n=31)**	**p**
Red cell distribution width (%)	13.81±1.00	14.92±1.71	<0.001
Hemoglobin (g/dL)	14.04±1.26	13.64±1.03	0.143
White blood cell count (10^3/μL)	7.28±1.98	7.51±2.09	0.572
Neutrophil count (10^3/μL)	4.15±1.54	4.68±1.61	0.096
Lymphocyte count (10^3/μL)	2.31±0.75	2.09±0.65	0.134
Neutrophil to lymphocyte ratio	1.94±0.90	2.38±0.96	0.016
Mean platelet volume (fL)	8.78±0.88	8.83±0.76	0.753
Fasting serum glucose (mg/dL)	154.76±51.76	177.97±60.13	0.029
Hemoglobin A1c (%)	7.17±1.55	9.05±2.16	<0.001
Serum creatinine (mg/dL)	0.80±0.17	0.92±0.29	0.004
High-density lipoprotein cholesterol (mg/dL)	42.80±10.06	45.87±11.79	0.148
Low-densitiy lipoprotein cholesterol (mg/dL)	121.58±32.44	121.61±50.02	0.997
Total cholesterol (mg/dL)	196.94±37.40	190.90±46.74	0.449
Triglyceride (mg/dL)	172.32±104.78	150.93±71.70	0.303

TABLE 3: Factors predicting diabetic retinopathy on logistic regression analysis.

	Univariate Analysis		Multivariate Analysis	
Variable	**Odds Ratio, 95% CI**	**p**	**Odds Ratio, 95% CI**	**p**
Duration of diabetes	1.238 (1.143-1.341)	<0.001	1.199 (1.083-1.327)	**<0.001**
Hemoglobin A1c	1.677 (1.319-2.131)	<0.001	2.366 (1.286-4.354)	**0.006**
Fasting serum glucose	1.007 (1.001-1.014)	0.033	1.020 (0.958-1.022)	0.080
Serum creatinine	11.704 (1.941-70.579)	0.007	1.652 (0.067-40.553)	0.759
RDW	2.020 (1.423-2.869)	<0.001	1.691 (1.036-2.763)	**0.036**
NLR	1.558 (1.071-2.266)	0.021	1.290 (0.347-1.733)	0.535

CI: Confidence interval; RDW: Red cell distribution width; NLR: Neutrophil to lymphocyte ratio.

DR is one of the most important causes of blindness. Monitoring of DM is very important in order to prevent retinal complications with other types of problems (renal, sensitive). The pathogenesis of DR is complex and several vascular, inflammatory, and neuronal mechanisms are involved. Inflammation mediates structural and molecular alterations associated with DR.[9,10] The underlying mechanisms of this disease include inflammatory changes and remodeling processes of the extracellular-matrix (ECM) leading to pericyte and vascular endothelial cell damage that affects the retinal circulation. In turn, this causes hypoxia leading to release of vascular endothelial growth factor (VEGF) to induce the angiogenesis process.[3]

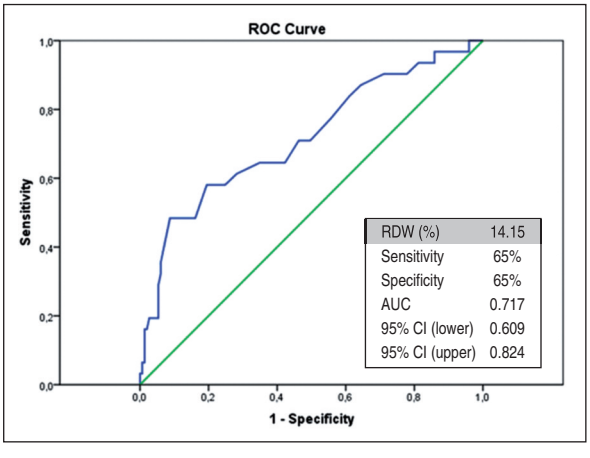

FIGURE 2: The receiver operating characteristic curve analysis for red cell distribution width (RDW) levels in predicting of diabetic retinopathy. Area under curve (AUC) = 0.735 (0.680-0.791).

(See color figure at http://www.turkiyeklinikleri.com/journal/oftalmoloji-dergisi/1300-0365/)

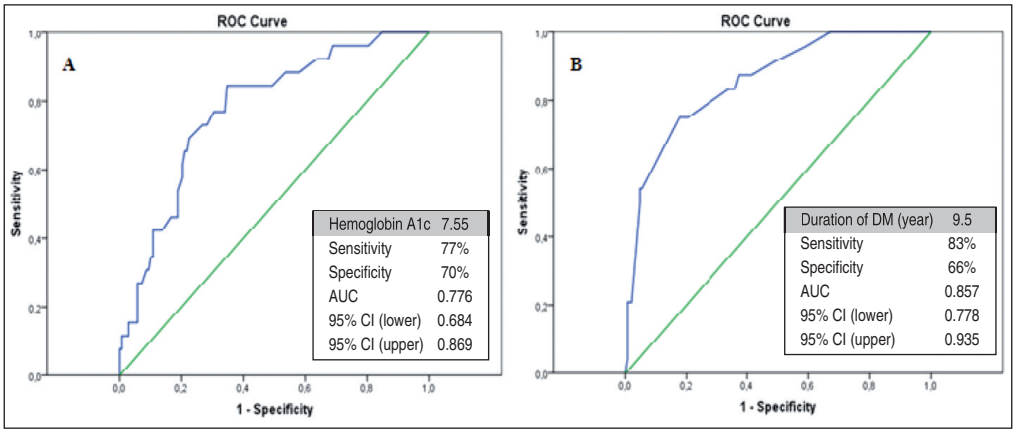

FIGURE 3: A) The receiver operating characteristic curve analysis for hemoglobin A1c levels in predicting of diabetic retinopathy. Area under curve (AUC) = 0.776 (0.684-0.869). **B)** The receiver operating characteristic curve analysis for duration of diabetes mellitus (DM) in predicting of diabetic retinopathy. AUC= 0.857 (0.778-0.935).

DR is more among Mexico-Americans than non-Hispanic whites. Sociodemographic factors such as age, medical treatment, education, and gender of the patient are not considered to be risk factors.[11] DR development depends on different factors including time affected by diabetes, blood pressure, blood glucose, hemoglobin A1c and lipid levels and, efficacy of multidisciplinary therapeutic interventions.[9,12] In addition to above mentioned findings, in this study, we have detected independent association between elevated RDW levels and DR together with hemoglobin A1c and duration of DM. The prevalence of DR increases with duration of diabetes, and more than 60% of those with type 2 DM have some form of DR after 20 years.[13] However, up to 25% of patients newly diagnosed with type 2 DM may have retinopathy, at the time of diagnosis.[1] In our study 17.22% of patients had DR and cut off value for duration of DM was 9.5 year. Individuals with hemoglobin A1c levels <6.5% generally develop little or no DR.[14] In our study cut off value for hemoglobin A1c was 7.55.

RDW was shown to be significantly associated with diabetic nephropathy in a type 2 diabetic population with advanced proliferative retinopathy.[9] In another study, RDW may be treated as effective predictive index in the evaluation of diabetes nephropathy or diabetes-associated complications.[15] Malandrino et al. have shown that RDW may be an important clinical marker of vascular complications in diabetes and one that is independent of traditional risk factors and disease duration.[16] An interesting study has been made by Chung et al. and they have mentioned reducing lipid peroxidation stress of erythrocyte membrane by alpha-tocopherol nicotinate plays an important role in improving blood rheological properties in type 2 diabetic patients with retinopathy.[17] Red blood cell deformability index is impaired in diabetics with retinopathy, especially in those with severe vascular complications, and that this abnormal rheological behavior of erythrocytes can be found even in the early stages of diabetic microangiopathy.[18]

Numerous inflammation factors have shown as having an effect on the development and progression of DR. Raised levels of inflammatory and proliferative factors such as VEGF, interleukins may demonstrate a significant role of activation of vascular proliferation and local inflammation in the pathogenesis of PDR.[19] The relationship between NLR as another inflammation marker and DR had shown.[20] Platelet-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, NLR and mean platelet volume are novel potential markers of inflammatory responses. They are significantly increased in the setting of DR.[21] In our study, NLR value was significantly higher in DR (+) group, but it was not significant according to multivariate analysis results.

Our study had several limitations. First, the study was a single center study. Second, we assessed a relatively small number of subjects. Third, we could not investigate other inflammatory markers such as high sensitivity C reactive protein and interleukin-6 of patients which would support predictive value of RDW.

In conclusion, based on the role of inflammation and oxidative stress in damage and pathogenesis of DR; we thought that, elevated RDW levels may be an indicator of an increased inflammatory activity in patients with DR and as a simple and a reliable prognostic biomarker, and RDW levels should be evaluated in DR. Duration of DM and hemoglobin A1c also remain as key factors for the progression of DR. Further investigations and controlled studies carried on larger groups are needed to investigate the possible role of serum RDW levels in DR patients.

Çıkar Çatışması

Yazarlar herhangi bir çıkar çatışması veya finansal destek bildirmemiştir.

Authorship Contributions

Study conception and design: *Bengi Ece Kurtul, Besime İnal, Pınar Altıaylık Özer, Emrah Utku Kabataş,* ***Acquisition of data:*** *Bengi Ece Kurtul, Besime İnal,* ***Analysis and interpretation of data:*** *Bengi Ece Kurtul, Besime İnal,* ***Drafting of manuscript:*** *Bengi Ece Kurtul.*

REFERENCES

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2011;34(Suppl 1):62-9.
2. Dada OA, Uche E, Akinbami A, Odesanya M, John-Olabode S, Adediran A, et al. The relationship between red blood cell distribution width and blood pressure in patients with type 2 diabetes mellitus in Lagos, Nigeria. J Blood Med 2014;19(5):185-9.
3. Ortiz G, Salica JP, Chuluyan EH, Gallo JE. Diabetic retinopathy: could the alpha-1 antityrpsin be a therapeutic option? Biol Res 2014;47:58.
4. Yau JW, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, et al. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care 2012;35(3):556-64.
5. Ozcan F, Turak O, Durak A, Işleyen A, Uçar F, Giniş Z, et al. Red cell distribution width and inflammation in patients with non-dipper hypertension. Blood Press 2013;22(2):80-5.
6. Jimenez-Baez MV, Marquez-Gonzalez H, Barcenas-Contreras R, Morales Montoya C, Espinosa-Garcia LF. Early diagnosis of diabetic retinopathy in primary care. Colomb Med (Cali) 2015;46(1):14-8.
7. Tsuboi S, Miyauchi K, Kasai T, Ogita M, Dohi T, Miyazaki T, et al. Impact of red blood cell distribution width on long-term mortality in diabetic patients after percutaneous coronary intervention. Circ J 2013;77(2):456-61.
8. Colosia AD, Palencia R, Khan S. Prevalence of hypertension and obesity in patients with type 2 diabetes mellitus in observational studies: a systematic literature review. Diabetes Metab Syndr Obes 2013;17(6):327-38.
9. Magri CJ, Fava S. Red blood cell distribution width and diabetes-associated complications. Diabetes Metab Syndr 2014;8(1):13-7.
10. Semeraro F, Cancarini A, dell'Omo R, Rezzola S, Romano MR, Costagliola C. Diabetic retinopathy: vascular and inflammatory disease. J Diabetes Res 2015;2015:582060.
11. Crosby-Nwaobi R, Chatziralli I, Sergentanis T, Dew T, Forbes A, Sivaprasad S. Cross talk between lipid metabolism and inflammatory markers in patients with diabetic retinopathy. J Diabetes Res 2015;2015:191382.
12. Fornal M, Wizner B, Cwynar M, Krȯlczyk J, Kwater A, Korbut RA, et al. Association of red blood cell distribution width, inflammation markers and morphological as well as rheological erythrocyte parameters with target organ damage in hypertension. Clin Hemorheol Microcirc 2014;56(4):325-35.
13. Semba RD, Patel KV, Ferrucci L, Sun K, Roy CN, Guralnik JM, et al. Serum antioxidants and inflammation predict red cell distribution width in older women: the Women's Health and Aging Study I. Clin Nutr 2010;29(5):600-4.
14. Frank RN. Diabetic retinopathy and systemic factors. Middle East Afr J Ophthalmol 2015; 22(2):151-6.
15. Zhang M, Zhang Y, Li C, He L. Association between red blood cell distribution and renal function in patients with untreated type 2 diabetes mellitus. Ren Fail 2015;37(4):659-63.
16. Malandrino N, Wu WC, Taveira TH, Whitlatch HB, Smith RJ. Association between red blood cell distribution width and macrovascular and microvascular complications in diabetes. Diabetologia 2012;55(1):226-35.
17. Chung TW, Yu JJ, Liu DZ. Reducing lipid peroxidation stress of erythrocyte membrane by alpha-tocopherol nicotinate plays an important role in improving blood rheological properties in type 2 diabetic patients with retinopathy. Diabet Med 1998;15(5):380-5.
18. Chernykh VV, Varvarinsky EV, Smirnov EV, Chernykh DV, Trunov AN. Proliferative and inflammatory factors in the vitreous of patients with proliferative diabetic retinopathy. Indian J Ophthalmol 2015;63(1):33-6.
19. Ulu SM, Dogan M, Ahsen A, Altug A, Demir K, Acartürk G, et al. Neutrophil-to-lymphocyte ratio as a quick and reliable predictive marker to diagnose the severity of diabetic retinopathy. Diabetes Technol Ther 2013;15(11):942-7.
20. Diamantopoulos EJ, Raptis SA, Moulopoulos SD. Red blood cell deformability index in diabetic retinopathy. Horm Metab Res 1987;19(11):569-73.
21. Yue S, Zhang J, Wu J, Teng W, Liu L, Chen L. Use of the monocyte-to-lymphocyte ratio to predict diabetic retinopathy. Int J Environ Res Public Health 2015;12(8):10009-19.