doi: 10.4183/aeb.2018.514

RED CELL DISTRIBUTION WIDTH AND ACUTE COMPLICATIONS OF DIABETES

H. Atalay[1], B. Boyuk[2,*], M. Ates[2], S. Guzel[3], A. Celebi[2], I. Ekizoglu

[1]Gebze Government Hospital, Dept. of Internal Medicine, Izmit, [2]Gaziosmanpasa Taksim Education and Research Hospital, Dept. of Internal Medicine, Istanbul, [3]"Namik Kemal" University, Dept. of Biochemistry, Tekirdag, Turkey

Abstract

Context. Red cell distribution width (RDW) has been associated with type 2 diabetes (T2DM), however data in relation to diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar non-ketotic acidosis (HONK) remains unclear.

Objective. The aim of this study was to evaluate the association between RDW, MCV, and RDW/MVC values and acute complications in T2DM.

Patients and Methods. RDW was measured in 90 T2DM patients (30 DKA, 30 HONK and 30 T2DM without acute complications). Clinical variables were analyzed by One –Way ANOVA, Kruskal-Wallis and Pearson analysis with SPSS software. Diagnostic screening tests and ROC curve analysis determined the cut-off point of MCV,RDW and RDW/MCV values.

Results. DKA patients had higher levels of plasma glucose (524.20±201.43mg/dL, p<0.001), HbA1c (10.73±2.29%, p<0.001), osmotic pressure (310.32 mosm/L, p<0.001), RDW (14.61±1.75g/L, p<0.01), and the RDW/MCV ratio (0.17±0.04%, p<0.01), compared to HONK patients. RDW/MCV cut-off value was 0.15 with 90% sensitivity 50% specifity these values for only MCV were 76.67%-70%, for only RDW were 76.67%-63.33% respectively. The area under curve values for the ability to reflect DKA for RDW and the RDW/MCV ratio were 0.708 and 0.766, respectively (p<0.001).

Conclusions. RDW and RDW/MCV ratio were found associated with DKA and valuable in predicting DKA. However these parameters were not valuable in predicting HONK.

Key words: rdw, diabetic ketoacidosis, HONK.

INTRODUCTION

Red blood cell distribution width (RDW) is a valuable measure of variations of red blood cell volume, which is estimated in the evaluation and differentiation of anemia (1). An increase in RDW is related to an impairment of erythropoiesis, which reflects chronic inflammation and oxidative stress, both of which are cornerstones in the pathogenesis of type 2 diabetes mellitus (T2DM) (2). Recent studies showed that RDW was a strong independent predictor of prognosis in heart failure and coronary artery disease (3-4). However, there are few data on the relationship between RDW and diabetes. A population-based study by Veeranna V. *et al*. in 2012 demonstrated that RDW significantly predicted glycated hemoglobin (HbA1c) in healthy patients with no diabetes (5). Another study in 2014 by Engström G. *et al*. showed RDW was significantly and positively associated with HbA1c, an increase in HbA1c of 0.10% corresponded to a 1 SD increase in RDW. However, by contrast, the same study suggested that low RDW was also associated with a significantly higher waist circumference, and glucose, insulin, and triglyceride concentrations in patients with T2DM (6). Subsequent studies, albeit few in number, have tried to investigate the chronic macrovascular and microvascular complications of diabetes mellitus and RDW. These studies suggested that RDW may be an important clinical marker of vascular complications in T2DM (7-8). A recent study demonstrated that RDW and the RDW/mean corpuscular volume (MCV) ratio were significantly correlated with diabetic ketoacidosis (DKA) in a patient with type 1 diabetes (9). To the best of our knowledge, there are no studies on the association between red blood cell indices with both DKA and hyperosmolar non-ketotic acidosis (HONK) in patients with T2DM.

Our aim was to compare RDW and RDW/MCV in three groups of patients with diabetes. The primary outcome of this study was to determine whether RDW was a predictive marker in patients with DKA. The secondary outcome was to establish whether red blood cell indices were as valuable in HONK as they are in DKA.

*Correspondence to: Banu Boyuk MD, GOP Taksim Education and Research Hospital, Internal Medicine, Karayolları mah. no:112, Istanbul, 34343, Turkey, E-mail: banuilk@gmail.com

MATERIALS AND METHODS

Study population

The present study was performed at Gaziosmanpasa Taksim Education and Research Hospital's inpatient department of internal medicine between 2010 and 2014. A total of 90 patients with T2DM with and without complications (DKA and HONK) were divided into three groups; those with DKA (DKA group, n=30), those with HONK (HONK group, n=30), and those with no acute complications (controls, n=30). The patients with DKA had plasma glucose >250 mg/dL, ketonuria, and an arterial pH value <7.30. HONK was defined as plasma glucose >600 mg/dL, osmolality >320 mosm/L, none or low levels of ketonuria, and pH >7.30. The presence of diabetes was based on a previous diagnosis of T2DM or a random plasma glucose level of 200 mg/dL or higher, together with classic features of DM, such as polyuria, polydipsia, polyphagia, and weight loss, or a fasting blood glucose level of >126 mg/dL or a HbA1C level of 6.5% or higher (10). The exclusion criteria were the presence of systemic diseases; neoplastic, inflammatory, and infectious diseases; liver disease, heart failure, hematologic disease; or receiving steroid treatment. The study protocol was approved by the ethics committee of Gaziosmanpasa Taksim Research and Education Hospital, Istanbul.

Measurements

Hypertension was defined as antihypertensive drug use or systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg. Blood samples were obtained after overnight fasting in the control group. Blood samples were taken at the time of admission to emergency in the DKA and HONK groups. Leukocytes, hemoglobin, MCV, RDW, and platelets concentrations were analyzed in fresh blood. Complete blood count levels were measured using an automatic hematology analyzer (Beckman Coulter, Brea, CA, USA). Reference values of RDW were 10-16%. The RDW to MCV ratio was calculated using the following formula: RDW/MCV x 100%. Serum cholesterol, triglyceride, and high-density lipoprotein cholesterol (HDL-C) were measured using enzymatic colorimetric methods with commercially available kits (COBAS 311, Roche Diagnostics GmbH, Mannheim, Germany), and low-density lipoprotein cholesterol C (LDL-C) was calculated in accordance with the Friedewald formula. Serum glucose levels were determined enzymatically using the hexokinase method (Roche Diagnostics GmbH, Mannheim, Germany). Blood HbA1c was determined using a COBAS 311 analyzer using particle-enhanced immunoturbidimetric assay (Roche Diagnostics, Mannheim, Germany). The final results are expressed as percentage HbA1c of the total hemoglobin in accordance with the protocol of the Diabetes Control and Complications Trial/National Glycohemoglobin Standardization Program (DCCT/NGSP). A particle-enhanced immunoturbidimetric assay was performed using a Behring Nephelometer BN-100 (Behring Diagnostic, Frankfurt, Germany) to measure C-reactive protein (CRP). The sensitivity of the test was 0.1 mg/L. The erythrocyte sedimentation rate (ESR) was determined using the Westergren method using an established normal range of 0-20 mm/1 hr. Ketonuria was measured using a Dirui urine analyzer (Dirui H-100 Urine Analyzer, Changchun, China). Blood gas analysis was performed using a Roche cobas b 221 blood gas analyzer with an electrode ion-selective membrane (Roche diagnostics).

Statistical analyses

Number Cruncher Statistical System (NCSS) 2007 and Power Analysis and Sample Size (PASS) 2008 Statistical Software (Utah, USA) programs were used for the statistical analysis. Descriptive statistical methods (mean, standard deviation, frequency, ratio, minimum, maximum) were used to evaluate the study data. Student's t-test was used for normally distributed quantitative parameters. The Mann-Whitney U test was used for quantitative parameters that were not normally distributed. The one-way ANOVA test was used to compare means of samples and Tukey's honestly significant difference test was used for the determination of significant differences between groups. For optimum cut-off values of RDW, MCV and RDW/MVC ratio, receiver operating characteristic (ROC) curve analysis and diagnostic determination tests were used. Values of $p<0.05$, $p<0.01$, and $p<0.001$ were accepted as statistically significant.

RESULTS

The clinical characteristics of the study subjects are shown in Table 1. A total of 90 participants were included in this study. The RDW and RDW/MCV values among the three groups were statistically significant ($p<0.01$, $p<0.001$). The DKA group had significantly higher RDW and RDW/MCV than the other groups. The MCV value was significantly

Table 1. Clinical and biochemical characteristics of patients with diabetes in the three groups

	Type 2 DM	HONK	DKA
Female/Male (n/n)	15/15	12/18	14/16
Age (years)	54.57±9.24	65.80±14.11	50.53±12.62***
Duration of diabetes (years)	4 (2-8)	11.5 (1-20)	8 (2.75-15.25)
Systolic pressure (mm Hg)	125.40±15.02	117.33±27.16	120.17±23.87
Diastolic pressure (mm Hg)	73.67±11.06	73.00±16.22	74.33±11.94
Blood glucose (mg/dL)	180.70±63.77	739.90±260.17	524.20±201.43***
HbA1c	8.54±2.46	11.82±2.67	10.73±2.29***
Total cholesterol (mg/dL)	211.20±45.70	182.24±64.07	168.48±54.64**
Triglyceride (mg/dL)	167.13±67.77	163.28±79.72	196.03±160.29
Low-density lipoprotein (mg/dL)	127.80±37.86	111.68±56.01	90.69±37.06**
High-density lipoprotein (mg/dL)	49.90±10.65	37.96±16.94	38.62±15.71**
C-reactive protein (mg/L)	3.66 (3.36-6.02)	27.8 (11.45-48.5)	8.9 (3.36-29)***
Erythrocyte sedimentation rate (mm/hr)	20 (14.5-34.5)	65 (43.5-85.5)	24 (12-43)***
White blood cell ($\times 10^3/\mu L$)	7070.00±2320.10	12116.67±4598.96	11841.33±5732.32***
Red blood cell ($\times 10^{12}/L$)	4.59±0.54	4.17±0.81	4.72±0.73*
Hemoglobin (g/L)	13.76±1.56	12.00±2.14	13.18±1.75***
Mean corpuscular volume (fL)	91.83±4.52	89.00±5.62	86.24±8.21**
Red cell distribution width %	13.14±1.88	13.92±1.43	14.61±1.75**
Mean corpuscular hemoglobin (pg)	30.12±1.44	28.72±2.30	28.19±3.00**
Mean corpuscular hemoglobin concentration (g/dL)	32.79±0.92	32.53±0.90	32.63±1.43**
RDW/MCV (%)	0.14±0.02	0.16±0.02	0.17±0.04**
Arterial pH	7.41 (7.36-7.41)	7.35 (7.3-7.41)	7.3 (7.21-7.3)***
Serum HCO_3 (mmol/L)	24 (23-25)	19.4 (14.55-22.48)	12 (7.13-15)***
Osmolality (mosm/L)	297.88 (293.25-301.11)	332.71 (322.53-341.98)	310.32*** (298.23-322.86)
Ketonuria	0	0 (0-1.25)	100 (35-150)***

One-Way ANOVA; mean±sd †Kruskal-Wallis test; median (Q1-Q3) ††Pearson Chi-square test.
Statistical significance: *p<0.05, **p<0.01, ***p<0.001. Abbreviations; DM: diabetes mellitus, HONK: hyperosmolar non-ketotic acidosis, DKA: diabetic keto-acidosis.

Table 2. MCV, RDW ve RDW/MCV ratio analysis in DKA patients

	Cut-off point	Sensitivity	Specificity	Positive predictive value	Negative predictive value
MCV	***≤90***	***76.67***	***70.00***	***71.88***	***75.00***
RDW	***≥13.50***	***76.67***	***63.33***	***67.65***	***73.08***
RDW/MCV	***≥0.15***	***90.00***	***50.00***	***64.29***	***83.33***

Abbreviations; MCV: mean corpuscular volume, RDW: red cell distribution width, RDW/MCV: red cell distribution width and mean corpuscular volume ratio, DKA: diabetic keto-acidosis.

lower in the DKA group compared with the control group (p<0.01). Patients with DKA and HONK had statistically significantly lower MCH and MCHC values than the controls (p<0.01, p<0.001).

Serum glucose, osmolality, and HbA1C levels were significantly higher among patients with DKA and HONK compared with control patients, as expected (p<0.001). Patients with DKA and HONK had significantly lower levels of HCO_3 than the controls (p<0.001). Ketonuria was significantly higher in the DKA group than in the other groups (p<0.001). The lipid variables (total cholesterol, LDL, and HDL) were lower in the DKA and HONK groups than in the control group (p<0.01). Patients with DKA and HONK had significantly higher WBCs, CRP, and ESH than the controls (p<0.001).

There were statistically significant differences between MCV, RDW, and RDW/MCV values in the controls and patients with DKA. ROC analysis and diagnostic screening tests were used to determine the cut-off point for MCV, RDW, and RDW/MCV values (Table 2). Patients who had RDW/MCV levels higher than 0.15 were reaching study group levels with a sensitivity of 90%, specificity of 50%, a positive predictive value of 64.29%, and a negative predictive value of 83.33%.The area under the ROC and standard deviation were 71.8% and 0.061%, respectively (Table 3). RDW/MCV was the best predictor, followed by MCV and RDW (Fig. 1).

Table 3. MCV, RDW ve RDW/MCV Area Under Curve

	Area Under theCurve				
	Area	Std. Error(a)	p	95% CI	
				Upper	Lower
MCV	0.758	0.064	0.001**	0.634	0.883
RDW	0.708	0.067	0.006**	0.576	0.840
RDW/MCV	0.766	0.061	0.001**	0.646	0.886

Abbreviations; MCV: mean corpuscular volume, RDW: red cell distribution width, RDW/MCV: red cell distribution width and mean corpuscular volume ratio, DKA: diabetic keto-acidosis.

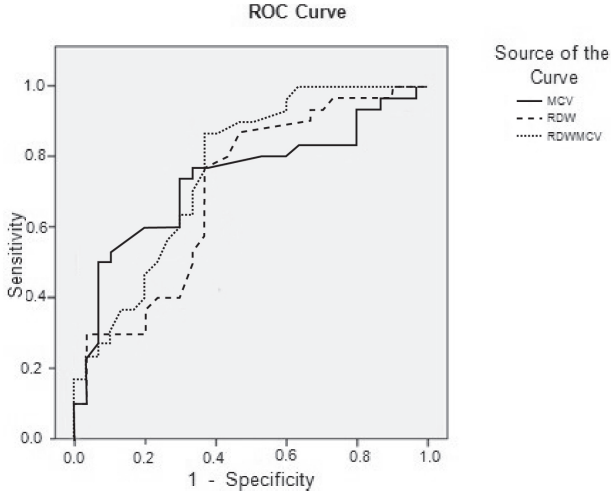

Figure 1. MCV, RDW and RDV/MCV ratio analysis on RocCurve.
Abbreviations; MCV: mean corpuscular volume, RDW: red cell distribution width, RDW/MCV: red cell distribution width and mean corpuscular volume ratio, DKA: diabetic keto-acidosis.

DISCUSSION

In the literature, there are limited data about the association between acute complications in type 2 diabetes and erythrocyte indices. The latest investigations encouraged us to study whether these indices were associated with DKA and HONK in patients with T2DM.

In our study RDW and the RDW/MCV ratio were found significantly higher in patients with DKA than in the control and HONK groups. Moreover, discriminative analysis revealed that the RDW/MCV ratio, RDW and MCV have quite low prognostic values. Between these erythrocyte indices, RDW/MCV ratio has the best negative prognostic value for DKA. The only study in the literature about the relationship between erythrocyte indices and DKA was conducted by Liu DS *et al*. who reported that RDW/MCW ratio values higher than 45.40% had 75.0% sensitivity and 99.9% specificity for predicting DKA (9). In the same study, the sensitivity and specificity values for MCV were 23.1% and 91.7%, and for RDW they were 53.8% and 87.5%, respectively. In our study, the sensitivity and specificity for a cut-off of 0.15 for RDW/MCV was 90% and 50%, for MCV they were 76.67% and 70%, and for RDW 76.67% and 63.33%, respectively. Various results in literature demonstrate us the need of further data to use erythrocyte indices to predict DKA in clinical practice. To our best knowledge, we are the first to investigate the predictability of erythrocyte indices for HONK. However, we suggest that the RDW/MCV ratio, and RDW or MCV alone do not predict HONK.

Recent studies suggested that RDW predicted cardiovascular diseases, in addition to anemia (11-13). Although the exact mechanism of the association between red blood cell indices and cardiovascular disease remains unclear, studies hypothesized about the effect of systemic factors on erythrocyte homeostasis, especially inflammation and oxidative stress (14). Based on previous investigations, we suggest that similar mechanisms play a role in the relationship between RDW and DM.

From past to present, several markers have been used to account for the inflammatory processes in diabetes. Interleukin (IL)-6, CRP, and their association with diabetes have already been investigated (15,16). Tumor necrosis factor (TNF)-α is known to have a role in insulin resistance (17). Orosomucoid and sialic acid (18), and IKK-beta, which are central coordinators of inflammatory responses (19), were recently found to be associated with insulin resistance. The results of the National Health And Nutrition Examination Survey, 2012, showed that high levels of both CRP and RDW were associated with low cardiorespiratory fitness, which suggests a link between inflammation and RDW values (20).

Inflammation may increase RDW levels both by impairing iron metabolism and inhibiting the production or response to erythropoietin, or by shortening red blood cell survival (21). On the other hand, inflammatory markers such as TNF-α and IL-6 may affect erythropoiesis via direct suppression of erythroid precursors or promotion of apoptosis of precursor cells. Oxidative stress may reduce erythrocyte

survival, which results in anisocytosis due to an increase of circulating premature erythrocytes (20). Similarly, Juan Acosta *et al*. showed that glycation increased the sensitivity of red blood cells to membrane attack complex (MAC)-mediated lysis in patients with diabetes and suggested that previously unexplained hematologic abnormalities seen in diabetes could be complement-mediated as a consequence of glycation-inactivation of CD59 (22).

DKA and HONK are acute complications of T2DM, and both are associated with metabolic acidosis, systemic inflammation, and oxidative stress (23). Our study revealed that the DKA and HONK groups had significantly higher CRP, ESR, and WBC levels than the control group, which indicated an inflammatory state in these patient groups. However, higher RDW values in the DKA group rather than in the HONK group support the data of Shao-gang M *et al*. who reported that RDW might have an important role in the pathogenesis of DKA (24). Although both of these conditions are acute complications of diabetes, the main distinctions are ketosis and low insulin levels due to islet cell damage, which are seen in patients with DKA (23). Both ketosis and lack of insulin may explain the lower RDW values of patients with HONK by comparison with patients with DKA; further investigations are merited on this topic.

DKA is one of the indicators of poor metabolic control in diabetes mellitus. There is no statistically demonstrated correlation between HbA1C and RDW values in our DKA group, however high values of RDW suggest that hematimetric indices namely RDW/MCV ratio point out poor metabolic control.

Although high LDL is a risk factor for cardiovascular diseases and diabetes, there are conflicting data about the association between RDW and lipid profile. Kucera M *et al*. suggested that MPV and RDW reflect a pro-atherogenic lipid profile demonstrating a strong correlation of RDW with AIP (25). Similarly, in a large population-based study, RDW values were positively associated with AIP and hypertriglyceridemia in women, which suggests the relationship between high RDW values with unfavourable lipid profile in women (26). In contrast, in 2015, 1111 healthy subjects were studied and it was suggested that RDW was associated with inflammatory markers and hematimetric indices, but not with plasma lipid levels in a healthy population (27). We found significantly low LDL values in the DKA group. HDL levels were significantly higher in the control group than in the DKA and HONK groups ($p=0.012$; $p=0.015$), which supports the study of Lippi *et al*. In our study, triglyceride values were not statistically different between groups.

Naturally, this work has some limitations. First, our results may not be appropriate for generalization because of its single-center nature and the small sample size. Thus, this study should serve as a pilot. Second, investigations of inflammation markers other than CRP such as IL-2 and TNF-α may help to clarify the pathogenesis of the relationship between red blood cell indices and inflammation. Third, we could not evaluate the body mass index of the patients, the history of smoking and the history of metformin usage, due to retrospective design of the study (28, 29). These factors could have affected the RDW values.

Despite the limitations of our study, RDW and the RDW/MCV ratio were studied in both HONK and DKA patient groups for the first time in the literature. Furthermore, previous research was conducted on patients with chronic diabetes and their chronic complications. In contrast, our study focused on critically ill patients, which strengthens our results.

In conclusion, we observed that low RDW values were strongly associated with DKA but not with HONK. The results of the present study suggest that the RDW/MCV ratio alone reflects DKA markedly stronger than both RDW and MCV values.

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Evans TC, Jehle D. The Red Blood Cell Distribution Width. J Emerg Med 1991; 9 (1):71–74.
2. Dada OA, Uche E, Akinbami A, Odesanya M, John-Olabode S, Adediran A, Oshinaike O, Ogbera AO, Okunoye O, Arogundade O, Aile K, Ekwere T. 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;5:185-189.
3. Osadnik T, Strzelczyk J, Hawranek M, Lekston A, Wasilewski J, Kurek A, Gutowski AR, Wilczek K, Dyrbuś K, Gierlotka M, Wiczkowski A, Gąsior M, Szafranek A, Poloński L. Red Cell Distribution Width is Associated with Long-term Prognosis in Patients with Stable Coronary Artery Disease. BMC Cardiovasc Disord 2013;13:113.
4. Li W, Li X, Wang M, Ge X, Li F, Huang B, Peng J, Li G, Lu L, Yu Z, Ma J, Xu L, Jin M, Si H, Wan R. Association Between Red Cell Distribution Width and The Risk of Heart Events in Patients with Coronary Artery Disease. Exp Ther Med 2015;9(4):1508-1514.
5. Veeranna V, Zalawadiya SK, Panaich SS, Ramesh K, Afonso L. The Association of Red Cell Distribution Width with Glycated Hemoglobin Among Healthy Adults without Diabetes Mellitus. Cardiology 2012;122(2):129-132.

6. Engström G, Smith JG, Persson M, Nilsson PM, Melander O, Hedblad B. Red Cell Distribution Width, Hemoglobin A1c and Incidence of Diabetes Mellitus. J Intern Med 2014 ;276(2):174-183.
7. 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):226-235.
8. Magri CJ, Fava S. Red Blood Cell Distribution Width and Diabetes-Associated Complications. Diabetes Metab Syndr 2014;8(1):13-17.
9. Liu DS, Jin Y, Ma SG, Bai F, Xu W. The Ratio of Red Cell Distribution Width to Mean Corpuscular Volume in Patients with Diabetic Ketoacidosis. Clin Lab 2013;59(9-10):1099-1104.
10. ADA Clinical Practice Recommendations. Diabetes care 2004;27(1):94-102.
11. Saygin M, Ozturk O, Ozguner MF, Akkaya A, Varol E. Hematological Parameters as Predictors of Cardiovascular Disease in Obstructive Sleep Apnea Syndrome Patients. Angiology 2016;67(5):461-470.
12. Uemura Y, Shibata R, Takemoto K, Uchikawa T, Koyasu M, Watanabe H, Mitsuda T, Miura A, Imai R, Watarai M, Murohara T. Elevation of Red Blood Cell Distribution Width During Hospitalization Predicts Mortality in Patients with Acute Decompensated heart failure J Cardiol. 2016;67(3):268-273.
13. Yoon HE, Kim SJ, Hwang HS, Chung S, Yang CW, Shin SJ. Progressive Rise in Red Blood Cell Distribution Width Predicts Mortality and Cardiovascular Events in End-Stage renal disease patients. PLoS One 2015;10(5):e0126272.
14. Patel KV, Ferrucci L, Ershler WB, Longo DL, Guralnik JM. Red Blood Cell Distribution Width and The Risk of Death in Middle-Aged and Older Adults. Arch Intern Med 2009;169(5):515–523.
15. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive Protein, Interleukin 6, and Risk of Developing Type 2 Diabetes Mellitus. JAMA 2001;286(3):327–334.
16. Barzilay JI, Abraham L, Heckbert SR, Cushman M, Kuller LH, Resnick HE, Tracy RP. The Relation of Markers of Inflammation to the Development of Glucose Disorders in the Elderly: the Cardiovascular Health Study. Diabetes 2001;50(10):2384–2389.
17. Hotamisligil GS, Spiegelman BM. Tumor Necrosis Factor Alpha: A Key Component of the Obesity-Diabetes Link. Diabetes 1994;43(11):1271–1278.
18. Schmidt MI, Duncan BB, Sharrett AR, Lindberg G, Savage PJ, Offenbacher S, Azambuja MI, Tracy RP, Heiss G. Markers of Inflammation and Prediction of Diabetes Mellitus in Adults (Atherosclerosis Risk in Communities Study): A Cohort study. Lancet 1999;353(9165):1649-1652.
19. Arkan MC, Hevener AL, Greten FR, Maeda S, Li ZW, Long JM, Wynshaw-Boris A, Poli G, Olefsky J, Karin M. IKK-beta Links Inflammation to Obesity-Induced Insulin Resistance. Nat. Med 2005;11(2):191–198.
20. Shikhar Agarwal. Red Cell Distribution Width, Inflammatory Markers and Cardiorespiratory Fitness: Results From the National Health and Nutrition Examination Survey. Indian Heart J 2012; 64(4): 380–387.
21. Weiss G, Goodnough LT. Anemia of Chronic Disease. N Engl J Med 2005;352(10):1011–1023.
22. Acosta J, Hettinga J, Flückiger R, Krumrei N, Goldfine A, Angarita L, Halperin J. Molecular Basis for A Link Between Complement and The Vascular Complications of Diabetes. Proc Natl Acad Sci U S A 2000;97(10):5450-5455.
23. Kitabchi AE, Umpierrez GE, Fisher JN, Murphy MB, Stentz FB. Thirty Years of Personal Experience in Hyperglycemic Crises: Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State. J Clin Endocrinol Metab 2008;93(5):1541-1552.
24. Ma SG, Jin Y, Hu W, Bai F, Xu W, Yu WN. Evaluation of Ischemia-Modified Albumin and C-reactive Protein in Type 2 Diabetics with and without Ketosis. Biomark Insights 2012;7:19-26.
25. Kucera M, Balaz D, Kruzliak P, Ciccocioppo R, Oravec S, Rodrigo L, Zulli A, Hirnerova E, Sabaka P, Komornikova A, Sabo J, Slezak P, Gaspar L. The Effects of Atorvastatin Treatment on The Mean Platelet Volume and Red Cell Distribution Width in Patients with Dyslipoproteinemia and Comparison with Plasma Atherogenicity Indicators-A Pilot Study. ClinBiochem 2015;48(9):557-561.
26. Lippi G, Sanchis-Gomar F, Danese E, Montagnana M. Association of Red Blood Cell Distribution Width with Plasma Lipids in A General Population of Unselected Outpatients. Kardiol Pol 2013;71(9):931-936.
27. Vayá A, Sarnago A, Fuster O, Alis R, Romagnoli M. Influence of Inflammatory and Lipidic Parameters on Red Blood Cell Distribution Width in A Healthy Population. Clin Hemorheol Microcirc 2015;59(4):379-385.
28. Hendrawati YD, Andrajati R, Supardi S, Ariyani A. The Risk of Cobalamin Deficiency Symptoms Related to Long-Term Metformin Use in T2Dm Patients. Acta Endocrinologica -Bucharest 2018; 14(1):49-54.
29. Li Q, Yang LZ. Hemoglobin Alc Level Higher Than 9.05% Causes A Significant Impairment of Erythrocyte Deformability in Diabetes Mellitus. Acta Endocrinologica-Bucharest 2018; 14(1):66-75.