CHAPTER 7

ERYTHROCYTES, LEUKOCYTES, PLATELETS IN OBESITY AND METABOLIC SYNDROME

Mustafa Metin DONMA[1]
Orkide DONMA[2]

INTRODUCTION

Obesity is a health threatening clinical problem, because it has a great potential to cause severe chronic diseases. Associated low-grade inflammatory state leads the researchers to be focused on the studies examining the diagnostic efficacy of immunologic parameters on obesity, and metabolic syndrome (MetS). (1, 2)

Hematologic parameters obtained from a complete blood cell count (CBC) analysis give diagnostic information about the type and nature of anemia as well as other hematologic diseases. Members of CBC analysis, and particularly the indexes as well as some ratios may be useful from an inflammatory point of view. (3, 4)

Red blood cells (RBCs, erythrocytes), white blood cells (WBCs, leukocytes) and platelets (PLTs, thrombocytes) are hematological parameters. Indices related to these parameters are also components of CBC analysis. They are recently being introduced as the indicators of proinflammatory states. They may be used as the early and late indicators of gaining weight and are reported as the associates of MetS. (5,6)

Inflammation contributes to pathogenesis of many diseases including obesity, which in turn may lead to MetS. Within the scope of the complicated network of inflammation, elements of CBC analysis should also be considered. Obesity and MetS are not generally taken into account when evaluating a patient's CBC. However, some RBC, WBC and/or PLT-related indices have recently been introduced as inflammatory markers during the evaluation of obesity and MetS states. (6-11)

There are relatively few studies concerning some WBC subpopulations, RBC indices, PLT indices and CBC-based inflammatory markers performed on children, adolescents and adults with obesity and MetS. (5, 6, 12-14)

[1] Prof. Dr., Tekirdag Namik Kemal University, Medical Faculty, mdonma@nku.edu.tr
[2] Prof. Dr., Istanbul University-Cerrahpasa, Medical Faculty, odonma@gmail.com

The studies performed on pediatric population are particularly important, because childhood obesity may be a preparatory stage for severe chronic diseases during the adulthood period of the child. There are many studies examining the differences between obese (OB) and normal body mass index (N-BMI) states. However, it is also important to discriminate OB cases from morbid obese (MO) and MO cases from those with MetS. (15-18)

The childhood obesity is a multisystem disease. Since it may be complicated by severe health problems, this disease requires the attention of health professionals. Obesity is one of the cardiovascular (CV) risks. In pediatric age group, obesity may lead to hypertension, dyslipidemia, chronic inflammation, increasing tendency to blood coagulation, endothelial dysfunction and hyperinsulinemia, all of which may be considered as important risk factors for cardiovascular diseases (CVDs) as in the case of adults. (17)

Subclinical inflammation is a central component of cardiometabolic disease risk in obese subjects. White blood cells may be associated with early derangements in metabolism and preclinical signs of cardiac damage and may be effective tools during the evaluation of obese children. (19)

Hematological parameters and indices are greatly affected by gender. Due to the possibility of causing significant differences, gender must be considered while the clinical parameters are evaluated. There is not sufficient information related to differences caused by obesity. Gender differences may cause alterations in inflammatory markers and affect the associations between some physiological events and particularly WBCs and their subsets. (20-22)

The aim of this chapter is to evaluate hematological inflammatory parameters in obesity and MetS. Alterations between genders in terms of WBCs and their subpopulations, RBCs, PLTs and their indices among adult as well as pediatric populations with obesity and MetS will also be considered.

ERYTHROCYTES AND INDICES

The relationship between adiposity and hematological profiles related to RBCs and the indices was investigated in adults. Relatively low number of studies were performed also in children and adolescents. Controversial results were reported. Positive correlations between waist circumference and RBCs as well as hemoglobin (HGB) were detected, while HGB was negatively correlated to the sum of skinfold. Hemoglobin concentrations did not change with MetS parameters. However, in another study performed on MO children with MetS, HGB values were found to be higher in boys than in girls. (5, 9, 13,14, 23-25)

Hematocrit (HTC) is an important hemorheological parameter that provides the estimate of RBC proportion in a volume of blood. This measurement depends on the number as well as the size of RBCs. Both HTC and obesity are strongly correlated with CVDs. Hematocrit and mean corpuscular hemoglobin concentration (MCHC) play very important roles in the evaluation of CVDs and anemia. (6, 26)

Some studies were introduced to explore the association of HTC as well as MCHC and obesity in pediatric populations. Significantly lower MCHC values in overweight (OW) children were found than those detected for N-BMI cases. Decrease in MO children was even much greater. (13, 27, 28)

Obese patients displayed increased HTC percentages. Elevated HTC levels may be positively associated with CV risk factors and combined evaluation of HTC values and CV risk factors may enable early diagnosis of CVDs. Within the normal range, somewhat higher levels of HTC were associated with an increased risk of developing heart failure. Statistically higher levels were observed in MO children than those with N-BMI. (28-31)

These findings may point out the onset of inflammatory processes in obese individuals from early life as the indicators of cardio-metabolic factors.(28)

Red blood cell distribution width (RDW), a measure of the variation in the size of circulating RBCs, is available in the standard CBC analysis. It serves as a quantitative measure of an isocytosis. (32)

This index is related to both anemia and inflammatory status. This parameter is closely associated with iron deficiency. High levels indicate iron deficiency status. Lower HGB, lower mean corpuscular volume (MCV), lower MCHC, higher RDW are associated with higher prevalence of microcytic anemia. (33)

Its relation with inflammatory processes has also been declared. As obesity is related to increased inflammatory pattern, RDW was also analyzed within this context. Besides its traditional use in the differential diagnosis of anemias, RDW values reflect abnormalities in erythropoiesis and RBC metabolism related to aging, sex, ethnicity, inflammation, and oxidative stress. Thus, higher RDW values are common findings in several acute clinical conditions and chronic diseases. (33-38)

Red blood cell distribution width is also associated with mortality and adverse outcome in selected populations with CVDs and inflammation. Since higher RDW is related to erythrocyte deformability and delayed RBC clearance, it has been shown to predict CV mortality and morbidity. Increasing evidence suggests a prognostic role of higher RDW levels in many CVDs. In a similar manner, higher RDW levels in patients with acute heart failure suggest that this parameter,

which is the most important mortality predictor, is independently associated with systemic inflammation in these patients. (27, 35, 39-44)

Red blood cell distribution width may be a biomarker reflecting multiple physiological impairments related to atherosclerosis and coronary artery disease (CAD). High RDW is a strong prognostic factor in patients with CVDs and associated with increased incidence of fatal coronary events. The patients with heart failure exhibiting higher RDW levels may have poorer prognosis than those with lower RDW and are associated with increased risk of mortality. (45-47)

This easy and quick measurable index can predict early-stage renal function damage and may be used as an early marker of CV risk in rheumatoid arthritis. (27,48)

Association of RDW with MetS was also reported. The strong correlation of RDW and chronic inflammation suggests that this parameter may be defined as a chronic disease prognostic marker. (36,49)

This standard, clinically relevant hematological variable may also be related to the underlying pathophysiological changes associated with obesity and Type 2 diabetes (T2D). (28, 50)

Higher RDW was found in OW children and OB adolescents than N-BMI group. This index can be considered as a surrogate marker of inflammation and, consequently, CV risk in OB individuals. (28, 51)

In a study performed on adults, RDW was higher while MCHC was lower in MO patients than the cases with N-BMI. In another study, increased RDW along with decreased MCHC were prominent during the early phases of obesity. (28, 38)

The relationship between obesity and erythrocyte indices still needs further investigation, however, elevated RDW, elevated HTC and reduced MCHC in obese children may be of significance to link obesity and CVDs. (28)

Concerning the pathophysiology of these relationships, some reports have suggested that inflammation affects the hepatic production of the iron regulatory peptide hormone hepcidin. Increased hepcidin expression leads to obesity-related inhibition of iron absorption. This may cause abnormal iron absorption, thereby affecting RDW. (34, 52)

LEUKOCYTES AND SUBSETS

The components of CBC analysis including WBCs may exhibit alterations in many diseases including obesity and MetS. Aside from the consideration of WBC counts, lymphocytes (L), neutrophils (N) and eosinophils (EO) are the most com-

monly investigated subsets in this field. Gender differences were noted in thrombogenic profile associated to coronary obstruction. Gender differences have also drawn interest concerning various inflammatory markers. However, studies examining gender differences for hematological parameters as well as indices in obesity and MetS are relatively few. (10, 19, 21, 53-57)

So far, WBCs have been widely investigated in adults as well as pediatric populations.There are some relations between WBCs and MetS components. Increased WBC count is an independent risk factor for CVDs. Abdominal fat accumulation was associated with atherosclerosis and trombogenic profile during which, elevations in WBC count were detected. In a study, increased WBC, EO and segmented N counts were reported in adolescents with excess body fat. Inflammation and thrombogenesis were introduced as potential causes of CVDs in patients with MetS. (2, 58)

Eosinophils are found in blood circulation in extremely low levels. Endothelial cells lining cardiac cavities are mainly the same as those lining blood vessels. Therefore, mechanisms account for damages and dysfunctions detected in these cells are similar. Eosinophils damage endothelial cells and activate coagulation pathway. These cells directly affect various factors participating in coagulation and increase tendency to thrombus formation in hypereosinophilia. Cytotoxic and procoagulant features of eosinophils cause cardiovascular complications in most of the hypereosinophilic patients. These patients also develop venous thrombosis. (59)

Endothelial cell damage and thrombosis may progress faster in eosinophilic inflammation areas. Cardiovascular complications mediated by eosinophils are major determinants of hypereosinophilia associated morbidity and mortality. In these patients, thrombosis may develop relatively early. Eosinophils may contribute to thrombus development in acute coronary syndrome and thrombus pathogenesis in myocardial infarction (MI). (59-61)

The evaluation of hematological parameters from the gender point of view in morbid obesity and MetS is under investigation. In adults with MetS, EO counts in men were reported statistically higher than those in women. Gender differences in terms of CBCs as well as their indices were also considered in children with MetS. Significantly elevated EO values were found in boys compared to those in girls for MO children with MetS. Elevated EO associated with the development of CVDs observed in boys was introduced as an early indicator of cardiometabolic complications, which may be met in the future years in this gender. (2, 25, 57)

Obese adolescents exhibit higher WBC counts than adolescents with N-BMI.

This is the indicator of a chronic proinflammatory stage in OB children. A positive correlation between this parameter and adiposity and a negative correlation with cardiorespiratory health were reported in male children. (62)

Increased WBC count as well as N and L percentages were observed in adult male patients with MetS. These parameters were in accordance with the number of MetS components. Increased WBC count confined to male gender during obesity and MetS may be related to the vascular protective effects of estrogens. In general, morbidity and mortality caused by CVDs are much higher in males than in females. This may be due to estrogens playing protective roles in women against atherosclerosis by decreasing inflammatory cell adhesion. In some studies, significant correlations were found between CVDs and N as well as EO counts. (2, 63, 64)

These findings have pointed out the importance of gender to be considered in clinical studies. Male and female children may exhibit different WBC trafficking profiles during inflammatory states as in the case of morbid obesity. (57)

Gender exhibits significant effects on alterations in N percentages. In the late stages of obesity, female children had higher circulating N than male children as the indicator of more depressed immune system. Heart disease is generally thought of as a "man's disease", however, recent data informs that around the same number of men and women lose their lives due to heart diseases each year. Women with diabetes exhibit much higher CVDs mortality when compared with diabetic men. Women suffered from heart crisis have been detected to exhibit higher mortality than men of the same age. Based upon the recent reports, CVDs affect not only men but also affect women. Since the disease differs in its presentation, progression or in its clinical consequences in different genders, disease is less undrestandable in women than in men. Therefore, diagnosis or treatment options may be insufficient. This may be more risky particularly in low – and middle-income countries compared to that in developed countries due to less access to effective health care services. Within this context, women represented 49.7 % of deaths from CVDs in 2013 based on the 2016 year statistics. (65-68)

In a study, which reports no significant difference between the genders in terms of *hs*CRP concentrations, differences in N percentages as well as N-to-L ratios becomes more valuable. In this study, the importance of the association between gender and N recruitment was emphasized. (58)

In a study, elevated N percentages were observed in MO female children. Data, which are being recorded against female gender in recent years, can be evaluated as the extrapolation of this finding detected in childhood period. Women are

associated with much less physical activity, higher total cholesterol, triglycerides, low density lipoprotein cholesterol concentrations than men. Smoking rates have already been equalized in both genders. Due to all of these factors as well as several others the risk observed in both genders has already been balanced. This risk may increase among women in future years. Supporting findings were detected among pediatric population in this study. Increased risks related to CVDs were observed starting from the early periods of life. (58)

PLATELETS AND INDICES

Platelet count is an important hematologic parameter to predict MetS in children, adolescents and adults. This parameter has been introduced as a link between insulin resistance (IR) and MetS. Higher PLT count was associated with increased prevalence and risk of MetS in children and adolescents. Platelet count was associated with MetS with gender effects. Most of the MetS components were independent factors for increasing PLT count. The risk for MetS development was observed above 223 × 10(3)/μl in elderly women. In another study, PLT counts are higher in boys in comparison with girls. (25, 69-72)

Elevations in PLT count are important, because PLTs are the major parameter contributing hypercoagulation. In adults, after bariatric surgery, significant decreases in PLT count mediated by weight loss were observed. (12)

Platelet count and some related indices gained significant importance. Platelet indices may have prognostic and predictive value in numerous conditions. These indices are markers of platelet activation. Platelet activation and aggregation play roles in the pathophysiology of CVDs. (58, 73-77)

The association of IR with some hematological parameters including PLTs was reported. Insulin resistance accompany various metabolic disorders such as obesity, MetS, T2D and leads to endothelial and PLT dysfunctions, which may be involved in vascular complications and may be associated with PLT reactivity, which is associated with elevated PLT count. (71, 78-86)

The most frequently evaluated parameters are mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT) and platelet larger cell ratio (P-LCR). The values of platelet indices were increased or decreased in patients suffering from T2D, obesity, MI, cancer or acute surgical conditions. (77, 87)

Mean platelet volume, the most commonly investigated platelet parameter, signifies the average size of platelets in the blood. Increased PLT activity is observed in patients with MetS and these patients are more liable to CVDs. In a study, in which higher MPV was reported in MetS patients compared to normal

individuals, a correlation between this parameter and waist circumference were noted among the adults with abdominal obesity. (88)

Mean platelet volume is a marker of PLT activation. It is an inflammatory marker. In some studies, children with MetS had higher levels of PLT and lower levels of MPV. Platelet count was positively whereas MPV was negatively associated with the risk of developing MetS. Mean platelet volume was found to be negatively correlated with PLT count. In T2D, MPV was found higher. It was reported that as MPV level is becoming lower, the PLT aggregation function becomes weaker. Therefore, more PLTs are produced to support metabolism. Platelet lifespan appears to be shorter in individuals with IR. This increases PLT count. (13, 71, 72, 78,82-86, 89, 90)

Platelet distribution width (PDW) is a marker of PLT anisocytosis, which describes the size distribution of PLT. Negative correlations were obtained between PLT and MPV as well as PLT and PDW in MO children. (87)

Mean platelet volume and PDW levels showing platelet activation increase significantly in the presence of MetS in patients with mild psoriasis vulgaris, a common inflammatory skin disease. (91)

Platelet count, PDW, and MPV levels were significantly higher in patients with MetS compared to healthy individuals. (92)

Plateletcrit (PCT) measures total PLT mass as a percentage of volume occupied in the blood. It was suggested as a useful marker for the determination of increased thrombotic state and inflammatory response in morbid obesity. Both PLT and PCT were associated with body fat. Since PCT is mainly influenced by PLT, these associations suggest that PLT quantity is more closely related to body fat mass and fat distribution. (93, 94)

In a study, which was designed to find the missing link between IR and platelet activation, PLT and PCT were pointed out to be related to IR during morbid obesity. (87)

CONCLUSION

Upon evaluation of the CBC analysis parameters including RBC, WBC, PLT counts and the associated indices in both adults and children, interesting increasing or decreasing trends were noted caused by varying degrees of obesity and the presence of MetS components.

Several CBC analysis parameters are subjected to variations in such diseases. These alterations gain even more importance during childhood period of life. Great variations were confirmed depending on different age intervals of the

individuals. In a similar manner, the influence of the above disease states upon the magnitutes of the concentrations confined to these hematologic parameters should also be taken into consideration. It may be suggested that reference intervals of CBC constituents may be revised based upon the view that obese individuals should have their own normal values. Obese patients may have an altered hematology and should be handled accordingly.

The differences based upon gender observed in HGB, MCHC concentrations, WBC count, N, L, EO percentages, and PLT count emphasize the need for the establishment of different reference intervals confined to males as well as females

REFERENCES

1. Ebron K, Andersen CJ, Aguilar D, et al. A larger body mass index is associated with increased atherogenic dyslipidemia, insulin resistance, and low-grade inflammation in individuals with metabolic syndrome. Metab Syndr Relat Disord. 2015;13:458-464.
2. Kim JA, Choi YS, Hong JI, et al. Association of metabolic syndrome with white blood cell subtype and red blood cells. Endocrine J. 2006;53: 133-139.
3. Donma O, Donma MM. The potential involvement of platelet indices in insulin resistance in morbid obese children. Int J Med Health Sci. 2020;14:85-88.
4. Donma MM, Donma O. The evaluation of complete blood cell count-based inflammatory markers in pediatric obesity and metabolic syndrome. Int J Med Health Sci. 2020;14:89-92.
5. Mansourian M, Kazemi I, Kelishadi R. Pediatric metabolic syndrome and cell blood counts: bivariate Bayesian modeling. J Trop Pediatr. 2014;60:61-67.
6. Vuong J, Qiu Y, La M, et al. Reference intervals of complete blood count constituents are highly correlated to waist circumference: Should obese patients have their own "normal" values? Am J Hematol. 2014;89: 671-677.
7. Donma M, Karasu E, Ozdilek B, et al. CD4(+), CD25(+), FOXP3 (+) T regulatory cell levels in obese, asthmatic, asthmatic obese, and healthy children. Inflammation. 2015;38:1473-1478.
8. Donma O, Donma M, Nalbantoglu B, et al. The importance of erythrocyte parameters in obese children. Int J Med Health Biomed Bioeng Pharmaceu Eng. 2015;9:361–364.
9. Ferreira LCCN, da Silva HJG, Lins TA, et al. Relationship between lipid and hematological profiles with adiposity on obese adolescents. Rev Bras Hematol Hemoter. 2013;35:163-166.
10. Furuncuoğlu Y, Tulgar S, Dogan AN, et al. How obesity affects the neutrophil/lymphocyte and platelet/lymphocyte ratio, systemic immune-inflammatory index and platelet indices: a retrospective study. Eur Rev Med Pharmacol Sci. 2016;20:1300-1306.
11. Zhao L, Cheng J, Chen Y, et al. Serum alanine aminotransferase/aspartate aminotransferase ratio is one of the best markers of insulin resistance in the Chinese population. Nutr Metab (Lond.). 2017;14:64.
12. Raoux L, Moszkowicz D, Vychnevskaia K, et al. Effect of bariatric surgery-induced weight loss on platelet count and mean platelet volume: a 12-month follow-up study. Obes Surg. 2017;27:387-393.
13. Aypak C, Turedi O, Bircan MA, et al. Could mean platelet volume among complete blood count parameters be a surrogate marker of metabolic syndrome in pre-pubertal children? Platelets. 2014;25:393-398.
14. Kelishadi R, Hashemipour M, Ashtijou P, et al. Association of cell blood counts and cardiometabolic risk factors among young obese children. Saudi Med J. 2010;31:406-412.
15. Donma MM, Ekmekci OB, Ekmekci H, et al. Evaluation of the markers affecting obesity in children. Med One. 2018;2: e180004.

16. Donma MM, Erselcan SD, Yilmaz A, et al. The evaluation of new generation inflammatory markers in children with morbid obesity and metabolic syndrome. Nam Kem Med J. 2020;8:479-488.
17. Xu S, Xue Y. Pediatric obesity: Causes, symptoms, prevention and treatment. Exp Ther Med. 2016;11:15-20.
18. Magnussen CG, Koskinen J, Chen W, et al. Pediatric metabolic syndrome predicts adulthood metabolic syndrome, subclinical atherosclerosis, and type 2 diabetes mellitus but is no better than body mass index alone: the Bogalusa Heart Study and the Cardiovascular Risk in Young Finns Study. Circulation. 2010;122:1604-1611.
19. Di Bonito P, Pacifico L, Chiesa C, et al. White blood cell count may identify abnormal cadiometabolic phenotype and preclinical organ damage in overweight/obese children. Nutr Metab Cardiovasc Dis. 2016; 26:502-509.
20. Obayashi K, Saeki K, Kurumatani N. Gender differences in theassociation between objective sleep quality and leukocyte count: The HEIJE-KYO cohort. Physiol Behav. 2016;164:19-24.
21. Casimir JAG, Mulier S, Hanssens L, et al. Gender differences in inflammatory markers in children. Shock. 2010;33:258-262.
22. Casimir JAG, Mulier S, Hanssens L, et al. Chronic inflammatory diseases in children are more severe in girls. Shock. 2010;34:23-26.
23. Donma MM, Donma O. Links between inflammation and insulin resistance in children with morbid obesity and metabolic syndrome. Int J Med Health Sci. 2019;13:219-222.
24. Adediran A, Uche E, Akinbami A, et al. Hemoglobin and ferritin concentrations in subjects with metabolic syndrome. Nutr Metab Insights. 2015;8:15-19.
25. Donma O, Donma MM. Eosinophils and platelets: Players of the game in morbid obese boys with metabolic syndrome. Int J Med Health Sci. 2017;11:257-260.
26. Zhao J, Lin L, Lu XZ et al. Noninvasive detection of hematocrit and the mean corpuscular hemoglobin concentration levels by Vis-NIR spectroscopy. Guang Pu Xue Yu Guang Pu Fen Xi. 2014;34:652-655.
27. Rodriguez-Carrio J, Alperi-Lopez M, Lopez P, et al. Red cell distribution width is associated with cardiovascular risk and disease parameters in rheumatoid arthritis. Rheumatology (Oxford). 2015;54(4):641-646.
28. Donma O, Donma MM, Nalbantoglu B, et al. The importance of erythrocyte parameters in obese children. Int J Med Health Sci. 2015;9:361-364.
29. Sola E, Vaya A, Simo M, et al. Fibrinogen, plasma viscosity and blood viscosity in obesity. Relationship with insulin resistance. Clin Hemorheol Microcirc. 2007;37:309-318.
30. Jin YZ, Zheng DH, Duan ZY, et al. Relationship between hematocrit level and cardiovascular risk factors in a community-based population. J Clin Lab Anal. 2015;29:289-293.
31. Coglianese EE, Qureshi MM, Vasan RS, et al. Usefulness of the blood hematocrit level to predict development of heart failure in a community. Am J Cardiol. 2012;109:241–245.
32. Caporal FA, Comar SR. Evaluation of RDW-CV, RDW-SD, and MATH-1SD for the detection of erythrocyte anisocytosis observed by optical microscopy. J Bras Patol Med Lab. 2013;49:324-331.
33. McSorley ST, Tham A, Steele CW, et al. Quantitative data on red cell measures of iron status and their relation to the magnitude of the systemic inflammatory response and survival in patients with colorectal cancer. Eur J Surg Oncol. 2019;45:1205-1211.
34. Thavaraputta S, Dennis JA, Ball S, et al. Relation of hematologic inflammatory markers and obesity in otherwise healthy participants in the National Health and Nutrition Examination Survey, 2011-2016. Proc (Bayl Univ Med Cent). 2021;34:17-21.
35. Targoński R, Sadowski J, Starek-Stelmaszczyk M, et al. Prognostic significance of red cell distribution width and its relation to increased pulmonary pressure and inflammation in acute heart failure. Cardiol J. 2020;27:394-403.
36. Zurauskaite G, Meier M, Voegeli A, et al. Biological pathways underlying the association of red cell distribution width and adverse clinical outcome: Results of a prospective cohort study.

PLoS One. 2018;13:e0191280.
37. Hoffmann JJ, Nabbe KC, van den Broek NM. Effect of age and gender on reference intervals of red blood cell distribution width (RDW) and mean red cell volume (MCV). Clin Chem Lab Med. 2015;53:2015-2019.
38. Vayá A, Alis R, Hernandez-Mijares A, et al. Red blood cell distribution width is not related with inflammatory parameters in morbidly obese patients. Clin Biochem. 2014;47:464–466.
39. Skjelbakken T, Lappegård J, Ellingsen TS, et al. Red cell distribution width is associated with incident myocardial infarction in a general population: The Tromsø Study. J Am Heart Assoc. 2014;3:e001109.
40. Vaya A, Alis R, Suescun M, et al. Association of erythrocyte deformability with red blood cell distribution width in metabolic diseases and thalassemia trait. Clin Hemorheol Microcirc. 2015;61:407-415.
41. Patel HH, Patel HR, Higgins JM. Modulation of red blood cell population dynamics is a fundamental homeostatic response to disease. Am J Hematol. 2015;90:422-428.
42. Arbel Y, Weitzman D, Raz R, et al. Red blood cell distribution width and the risk of cardiovascular morbidity and all-cause mortality. A population-based study. Thromb Haemost. 2014;111:300-307.
43. Valenti AC, Vitolo M, Imberti JF, et al. Red cell distribution width: a routinely available biomarker with important clinical implications in patients with atrial fibrillation. Curr Pharm Des. 2021.
44. Li N, Zhou H, Tang Q. Red blood cell distribution width: a novel predictive indicator for cardiovascular and cerebrovascular diseases. Dis Markers. 2017;2017:7089493.
45. Su C, Liao LZ, Song Y, et al. The role of red blood cell distribution width in mortality and cardiovascular risk among patients with coronary artery diseases: a systematic review and metaanalysis. J Thorac Dis. 2014;6:1429-1440.
46. Borné Y, Smith JG, Melander O, et al. Red cell distribution width in relation to incidence of coronary events and case fatality rates: a population-based cohort study. Heart. 2014;100:1119-1124.
47. Huang YL, Hu ZD, Liu SJ, et al. Prognostic value of red blood cell distribution width for patients with heart failure: a systematic review and meta-analysis of cohort studies. PLoS One. 2014;9:e104861.
48. Li ZZ, Chena L, Yuan H, et al. Relationship between red blood cell distribution width and early-stage renal function damage in patients with essential hypertension. J Hypertens. 2014;32:2450–2456.
49. Farah R, Khamisy-Farah R. Significance of MPV, RDW with the presence and severity of metabolic syndrome. Exp Clin Endocrinol Diabetes. 2015;123:567–570.
50. Hanley AJ, Retnakaran R, Qi Y, et al. Association of hematological parameters with insulin resistance and beta-cell dysfunction in nondiabetic subjects. J Clin Endocrinol Metab. 2009;94:3824-3832.
51. Fujita B, Strodthoff D, Fritzenwanger M, et al. Altered red blood cell distribution width in overweight adolescents and its association with markers of inflammation. Pediatr Obes. 2013;8:385–391.
52. Wei S, Zhang W, Wang C, et al. Increased hepcidin expression in adipose tissue as a primary cause of obesity-related inhibition of iron absorption. J Biol Regul Homeost Agents. 2019;33:1135-1141.
53. Murphy AJ, Tall AR. Disordered haematopoiesis and atherothrombosis. Eur Heart J. 2016;37:1113-1121.
54. Kahraman NK, Kahraman C, Kocak FE, et al. Predictive value of neutrophil to lymphocyte ratio in the severity of non-alcoholic fatty liver disease among type 2 diabetes patients. Acta Gastroenterol Belg. 2016;79:295-300.
55. Su BY, Tian CF, Gao BL, et al. Correlation of the leukocyte count with traditional and non-traditional components of metabolic syndrome. Postgrad Med. 2016;128:805 – 809.

56. Vacas M, Saez Y, Sagastagoitia JD, et al. Gender differences in thrombogenic profile associated to coronary obstruction angiographically evaluated. Open Atheros Thrombos J. 2011;4:11-15.
57. Donma MM, Donma O. Neutrophil-to-lymphocyte ratio: A predictor of cardiometabolic complications in morbid obese girls. Int J Med Health Sci. 2017;11:261-264.
58. Oliveira TM, de Faria FR, de Faria ER, et al. Nutritional status, metabolic changes and white blood cells in adolescents. Rev Paul Pediatr. 2014;32:351-359.
59. Roufosse FL. Eosinophils: How they contribute to endothelial damage and dysfunction. Presse Med. 2013;42:503-507.
60. Sakai K, Inoue S, Matsuyama T, et al. Eosinophils may be involved in thrombus growth in acute coronary syndrome. Int Heart J. 2009;50: 267-277.
61. Finn AV. Eosinophils: an overlooked player in acute myocardial infarction. Editorial. Coron Artery Dis. 2015;26:99-100.
62. Tenório TR, Farah BQ, Ritti-Dias RM, et al. Relation between leukocyte count, adiposity and cardiorespiratory fitness in pubertal adolescents. Einstein (Sao Paulo). 2014;12:420-424.
63. Mendelsohn ME, Karas RH. Molecular and cellular basis of cardiovascular gender differences. Science. 2005;308:1583-1587.
64. Prentice RL, Szatrowski TP, Fujikura T, et al. Leukocyte counts and coronary heart disease in Japanese cohort. Am J Epidemiol. 1982;116: 496-509.
65. Centers for Disease Control and Prevention (CDC). Women and Heart Disease Fact Sheet. Available at: https://www.cdc.gov/dhdsp/data_statistics/fact_sheets/fs_women_heart.htm. Accessed on June 16,2016.
66. World Heart Federation. Women and CVD. Available at:http:// www.world-heart-federation.org/what-we-do/awareness/womenand-CVD. Accessed on October 1, 2016.
67. World Health Organization (WHO). Cardiovascular Diseases (CVDs).Available at: http://www.who.int/mediacenter/factsheets/fs317.Accessed on September 2016.
68. American Heart Association. Statistical Fact Sheet 2016 Update. Women & Cardiovascular Diseases. Available at: www.heart.org/idc/groups/heart-public. Accessed on 2016.
69. Lim HJ, Seo MS, Shim JY, et al. The association between platelet count and metabolic syndrome in children and adolescents. Platelets. 2015;26:758-763.
70. Chen YL, Hung YJ, He CT, et al. Platelet count can predict metabolic syndrome in older women. Platelets. 2015;26:31-37.
71. Zhao F, Yan Z, Meng Z, et al. Relationship between mean platelet volume and metabolic syndrome in Chinese patients. Sci Rep. 2018;8: Art. No. 14574.
72. Park BJ, Shim JY, Lee HR, et al. The relationship of platelet count, mean platelet volume with metabolic syndrome according to the criteria of the American Association of Clinical Endocrinologists: a focus on gender differences. Platelets. 2012;23:45-50.
73. Walinjkar RS, Khadse S, Kumar S, et al. Platelet indices as a predictor of microvascular complications in type 2 diabetes. Indian J Endocrinol Metab. 2019;23:206-210.
74. Rajagopal RL, Arunachalam S, Abdullah SM, et al. Can mean platelet volume and platelet distribution width be used as predictor markers for impending diabetic vascular complications? J Clin Diagn Res. 2018;12:EC01-EC05.
75. Samocha-Bonet D, Justo D, Rogowski O, et al. Platelet counts and platelet activation markers in obese subjects. Mediators Inflamm. 2008; 2008:834153.
76. Santilli F, Vazzana N, Liani R, et al. Platelet activation in obesity and metabolic syndrome. Obes Rev. 2012;13:27-42.
77. Pogorzelska K, Krętowska A, Krawczuk-Rybak M, et al. Characteristics of platelet indices and their prognostic significance in selected medical condition – a systematic review. Adv Med Sci. 2020;65: 310-315.
78. Kim JA, Montagnani M, Koh K, et al. Reciprocal relationships between insulin resistance and endothelial dysfunction: Molecular and pathophysiological mechanisms. Circulation. 2006;113:1888-1904.
79. Khan SH, Khan AN, Chaudhry N, et al. Comparison of various steady state surrogate insulin

resistance indices in diagnosing metabolic syndrome. Diabetol Metab Syndr. 2019;11:44.
80. Ferreira D, Severo M, Araujo J, et al. Association between insulin resistance and haematological parameters: A cohort study from adolescence to adulthood. Diabetes Metab Res Rev. 2019;35:e 3194.
81. Park JM, Lee JW, Shim JY, et al. Relationship between platelet count and insulin resistance in Korean adolescents: A nationwide population-based study. Metab Syndr Relat Disord. 2018;16:470-476.
82. Freeman AM, Soman-Faulkner K, Pennings N. Insulin resistance. NCBI Bookshelf, StatPearls Publishing LLC Jan. 2019.
83. Tagi VM. Insulin resistance in children. Front Endocrinol (Lausanne). 2019;10:342.
84. Kaur R, Kaur M, Singh J, Endothelial dysfunction and platelet hyperactivity in type 2 diabetes mellitus: molecular insights and therapeutic strategies. Cardiovasc Diabetol. 2018;17:121.
85. Marques P, Collado A, Martinez – Hervas S, et al. Systemic inflammationin metabolic syndrome. J Clin Med. 2019;8:708.
86. Grandl G, Wolfrum C. Hemostasis, endothelial stress, inflammation and the metabolic syndrome. Semin Immunopathol. 2018;40:215-224.
87. Donma O, Donma MM. The potential involvement of platelet indices in insulin resistance in morbid obese children. Int J Med Health Sci. 2020;14:85-88.
88. Furman-Niedziejko A, Rostoff P, Rychlak R, et al. Relationship between abdominal obesity, platelet blood count and mean platelet volume in patients with metabolic syndrome. Folia Med Cracov. 2014;54:55-64.
89. Erdoğan S, Dursun F, Kırmızıbekmez H, et al. Evaluation of erythrocyte and thrombocyte parameters in pediatric patients with diabetes mellitus. J Clin Anal Med. 2017;8:98-101.
90. Ozsu E, Yazicioglu B. Relationship between obesity and platelet indices in children. Cukurova Med J. 2018;43(1):30-35.
91. Korkmaz S. Mean platelet volume and platelet distribution width levels in patients with mild psoriasis vulgaris with metabolic syndrome. Postepy Dermatol Alergol. 2018;35:367-371.
92. Abdel-Moneim A, Mahmoud B, Sultan EA, et al. Relationship of leukocytes, platelet indices and adipocytokines in metabolic syndrome patients. Diabetes Metab Syndr. 2019;13:874-880.
93. Erdal E, İnanir M. Platelet-to-lymphocyte ratio (PLR) and plateletcrit (PCT) in young patients with morbid obesity. Rev Assoc Med Bras (1992). 2019;65:1182-1187.
94. Han S, Gan D, Wang G, et al. Associations of platelet indices with body fat mass and fat distribution. Obesity (Silver Spring). 2018;26:1637-1643.