European Review for Medical and Pharmacological Sciences 2022; 26: 249-256

Bone mineral density and complete blood count ratios in children and adolescents with obesity

M.M. BALA[1], K.A. BALA[2]

[1]Department of Orthopedics and Traumatology, Health Sciences University, Trabzon Kanuni Training and Research Hospital, Trabzon, Turkey
[2]Department of Pediatric Endocrinology, Health Sciences University, Trabzon Kanuni Training and Research Hospital, Trabzon, Turkey

Abstract. – OBJECTIVE: Monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), monocyte-to-high-density lipoprotein ratio (MHR), and mean platelet volume (MPV) are considered novel inflammatory markers. In this study, we aimed to investigate the relationship between bone mineral density (BMD) Z score and blood cell composition in children and adolescents with obesity and to create a suitable index for the diagnosis of obesity-associated osteoporosis.

PATIENTS AND METHODS: We included 148 children, comprising 112 children with obesity (obese group) and 36 sex- and age-matched healthy children (normal weight) (control group). Patient details acquired from medical records were used to measure blood count levels; BMD, using dual-energy X-ray absorptiometry; and BMD Z-scores, using race and sex specific curves.

RESULTS: Mean BMD Z score in the obese and normal weight group was within the normal limits and significantly higher in the obese group. The BMD Z score showed a significant relationship with MLR and PLR. Patient BMD Z-scores were negatively correlated with MLR and PLR in the obese group and positively correlated in the control group. In addition, a positive correlation was found between BMD Z score and NLR in the control group.

CONCLUSIONS: Our study outcomes show that there may be a relationship between bone mass and inflammation expressed as PLR and MLR in obese children and adolescents. PLR and MLR, which are common indicators of morbidity and mortality in many chronic inflammatory diseases, may also be useful for evaluating bone status in children with obesity. However, further research on the subject is warranted.

Key Words:
Bone mineral density, MLR, PLR, Obesity, Childhood.

Introduction

Prevalence of obesity and its related comorbidities has increased worldwide[1,2]. Aside from being one of the important risk factors related to impairment of bone health, the rapid increase in body mass index (BMI) associated with obesity in the pediatric population consequently impairs bone health and causes bone fractures early in life[3,4].

Subclinical inflammation accompanying obesity causes cardiometabolic complications and development of insulin resistance[5]. Increasing serum levels of proinflammatory cytokines (IL-1, IL-6, and TNF-a) and acute phase proteins in obesity, especially abdominal obesity, are important mediators in bone resorption and osteoclast differentiation[6]. Increase in proinflammatory cytokines caused by chronic inflammation result in bone loss and resorption[7]. The rapid progression of osteoarthritis in the obese population is another example of chronic inflammation affecting bone health[8].

Platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) are not old markers for increased inflammatory response[9,10]. Particularly, NLR and PLR are predictors of the inflammatory responses of the vascular system[10]. In addition, PLR and NLR are associated with osteoporosis and decreased bone mineral density (BMD)[11,12]. Additionally, the relationship between PLR and NLR and osteoporosis remains unclear.

Bone immunology has shown that the immune system and inflammatory mediators play major roles in osteoporosis[13]. Increase in monocyte-to-lymphocyte ratio (MLR), an inflammatory marker[14], in proportion to inflammation is associated with osteoporosis and bone-derived diseases[15,16].

Mean platelet volume (MPV) is widely used to evaluate platelet activation and function. Furthermore, MPV is strongly associated with various

Corresponding Author: Mehmet Murat Bala, MD; e-mail: muratbala@hotmail.com

cardiovascular and inflammatory diseases[17]. Few studies[18] in adults have reported the relationship between MPV and osteoporosis.

MPV is a distinguishing feature for platelet count (PC) activation[19]. The MPV/PC ratio has been associated with ischemic cardiovascular disease mortality[20]. However, we did not find any study that investigated the relationship between the MPV/PC ratio and bone health in both adults and children.

The monocyte-to-high-density lipoprotein cholesterol ratio (HDL-C) (MHR), an indicator of inflammation, is a novel predictor of mortality and morbidity as well as a prognostic factor in many diseases[21]. There is a close relationship between HDL and bone physiology and pathology[22]. However, the results obtained from epidemiological studies conducted in humans are contradictory. Although a negative correlation between bone mass and HDL levels has been reported[23], other studies[24] have shown that as HDL increases, bone quality improves the risk of osteoporosis decreases.

Despite the increased fracture risk in obesity, there is an increase in BMD[25]. Therefore, it is difficult to predict osteoporosis in obese individuals. Hence, more readily available inflammation biomarkers associated with BMD and BMI should be used.

A hemogram is widely used to study the distribution of blood cells. We aimed to investigate the differences in the proportions of blood cells and the relationship between BMD Z score and blood cell composition in children with obesity as well as to establish an appropriate index for the adjunctive diagnosis of osteoporosis. To the best of our knowledge, no study has reported on the relationship between blood count ratios and BMD in a pediatric population with obesity. Therefore, we aimed to investigate the relationships between NLR, MLR, PLR, MPV, MPV/PC, MHR, and BMD to show the associations with inflammation and bone metabolism in children and adolescents with obesity.

Patients and Methods

Patients

We included 148 children and adolescents aged 6-18 years who visited our outpatient clinics between 2018 and 2020. Among these patients, those with a BMI above the 95th percentile were defined as obese (n = 112; obese group), and those below the 85th percentile as normal weight (n = 36; control group), according to Turkish national standards, according to age and sex[26].

Those with BMI percentiles of 85th-95th (overweight) were not included in this study. We excluded children with diseases that could adversely affect bone health, such as a fracture in the previous year; orthopedic surgery or a history of chronic glucocorticoid use; a history of kidney, gastrointestinal, or liver disease; and obesity caused by endocrine disease.

For anthropometric measurements, patients' body weights and heights were measured with a digital scale (Seca pediatric digital scale, Hammer Steindamm 3-25, 22089 Hamburg, Deutschland) and a Harpenden stadiometer (Holtain, Crosswell, Crymych, Pembs., SA41 3UF, UK), respectively. BMI measurement was calculated as weight (kg) divided by height squared (m^2). We calculated the weight, height, and BMI standard deviation scores with reference to the 2015 Turkey National Growth Tables[26]. Tanner and Marshall staging methods were used to evaluate the state of puberty in girls and boys, respectively[27].

Autohematology analyzer (Abbott, Cell-Dyn Ruby, IL, USA) was used for acquiring complete blood counts. Biochemical parameters were measured *via* photometric analysis (Abbott, c16000, IL, USA). Hormone parameters were measured using chemiluminescence immunoassay (Abbott, i2000sr, IL, USA). MLR, NLR, PLR, MHR, and MPV/PC were calculated using the following formulas: Monocyte count/lymphocyte count; neutrophil count/lymphocyte count; platelet count/lymphocyte count; monocyte count/high-density lipoprotein level and mean platelet volume/platelet count, respectively.

We acquired height, weight, BMI, blood count levels, 25-OH vitamin D (25OHD), alkaline phosphatase (ALP), parathormone (PTH), phosphorus (P), calcium (Ca), cholesterol, triglyceride, fasting blood glucose, insulin, HbA1c, and BMD Z-scores of patients from the medical records and calculated the NLR, MLR, PLR, MPV, MPV/PC, and MHR levels.

We performed the present study under the principles of the Declaration of Helsinki and received Ethics Committee Approval (Decision No.: 2020-11) from Health Sciences University Trabzon Kanuni Training and Research Hospital. We received written informed consent form from all subjects and their parents or guardians.

Dual-Energy X-Ray Absorptiometry

We defined osteoporosis as a history of clinically significant fracture with a BMD Z score of-2. We defined a history of clinically significant frac-

tures as follows: ≥2 long bone fractures by the age of 10 years or ≥3 long bone fractures at any age up to 19 years[28]. In all subjects, BMD (BMD unit: g/cm^2) was evaluated using Lunar Prodigy (General Electric, GE Healthcare, Lunar DPX, NT + 150301, Madison, WI, USA) with dual-energy X-ray absorptiometry. We measured BMD at the level of lumbar spine segments L1-L4 (LS) through whole-body scans. BMD Z-scores were calculated using data on healthy Turkish adolescents and children after adjusting for age and height[29,30]. The same experienced operator performed all the scans.

Statistical Analysis

The descriptive data are presented as frequencies (percentages) or median and range (minimum-maximum) or mean ± standard deviation. Normality of the continuous variables was assessed with Shapiro Wilk tests and histogram graphs. Independent samples *t*-tests or non-parametric Mann-Whitney U-tests were used for the comparison of continuous variables between two groups. The relationship between the categorical variables was assessed with Pearson's chi-square test. The degree of association between the continuous variables was estimated by the Pearson's correlation coefficient. The analyses were performed using the Statistical Package for Social Sciences 26.0 for Windows (SPSS Inc., Chicago, IL, USA). The results were considered to be significant at a level of $p < 0.05$.

Results

The statistical analysis of the study population characteristics for the patients in obese and control groups were presented in Table I. The mean BMD Z-score in the obese and normal weight group was within the normal limits (2.40 ± 1.10 and 1.03 ± 0.68,

Table I. Clinical characteristics in control and obese groups.

	Control group (BMI<85th per) (n=36)	Obese Group (BMI ≥95th per) (n=112)	*p*
Gender			0.795
Male	12 (33.3%)	40 (35.7%)	
Female	24 (66.7%)	72 (64.3%)	
Age (years)	12.88 ± 2.59	12.35 ± 3.09	0.354
Pubertal stage (1-5)	3.0 (1.0-5.0)	4.0 (1.0-5.0)	0.200
Lumbarspine BMD (g/cm^2)	0.80 ± 0.18	0.97 ± 0.22	**<0.001**
BMD Z score (SDS)	1.03 ± 0.68	2.40 ± 1.10	**<0.001**
Calcium(mg/dL)	9.46 ± 0.30	9.63 ± 0.41	**0.025**
Phosphorus(mg/dL)	4.44 ± 0.57	4.14 ± 0.58	**0.008**
Alkaline phosphatase (IU/L)	220.22 ± 94.51	170.04 ± 72.89	**0.001**
Parathyroid hormone (pg/mL)	56.11 ± 8.73	48.50 ± 18.02	**0.001**
HDL-cholesterol (mg/dL)	41.0 (37.0-83.0)	41.5 (28.0-60.0)	0.420
WBC	7.20 (6.60-9.00)	8.05 (5.10-15.20)	0.152
Hgb	13.22 ± 1.30	13.50 ± 1.00	0.232
MCV	79.63 ± 9.48	81.50 ± 5.30	0.265
PLT	313.56 ± 43.72	308.86 ± 65.91	0.625
MPV	8.07 ± 0.99	8.28 ± 0.88	0.250
PLR	110.98 ± 28.41	117.42 ± 36.19	0.331
NLR	1.32 (0.58-2.50)	1.51 (0.48-5.37)	0.074
MLR	0.17 (0.14-0.33)	0.22 (0.03-0.78)	**0.041**
MPV/PC	0.02 (0.01-0.04)	0.02 (0.02-2.71)	**<0.001**
MHR	0.01 (0.01-0.01)	0.01 (0.01-0.03)	**<0.001**
RDW	13.2 (11.8-14.9)	13.6 (12.4-130.0)	**<0.001**

Values are expressed as n (%), means ± sd or median (min – max). For the categorical variable, Gender Pearson's chi-square test is used. For continuous variables, if values are reported in means, *p*-values are calculated using independent samples *t*-test; if values are given in medians, *p*-values are calculated using Mann Whitney U test. Bold *p*-values indicate statistical significance at $\alpha<0.05$. BMD: Bone mineral density, WBC: White blood cell, NLR: neutrophil-to-lymphocyte ratio, MLR: monocyte-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, MPV/PC: mean platelet volume-to-platelet count ratio, MHR: monocyte-to-high-density lipoprotein ratio, RDW: Red Cell Distribution Width, MCV: Mean Corpuscular Volume, Hgb: Hemoglobin, PLT: Platelet, MPV: mean platelet volume (MPV), PCT: plateletcrit PDW: Platelet Distribution Width.

Table II. Correlation analyses between BMD Z score and other variables in obese and control groups.

	Control group (n=36)		Obese Group (n=112)	
	R	*p*	R	*p*
25OHD	-0.205	0.231	-0.198	**0.036**
Calcium (mg/dL)	0.421	**0.010**	-0.126	0.184
Phosphorus (mg/dL)	-0.185	0.281	-0.203	**0.032**
Alkaline phosphatase (IU/L)	-0.305	0.07	-0.294	**0.002**
Parathyroid hormone (pg/mL)	0.212	0.215	-0.142	0.135
HDL-cholesterol (mg/dL)	-0.061	0.726	-0.18	0.058
WBC	-0.098	0.571	0.03	0.756
NLR	0.647	**<0.001**	-0.057	0.553
MLR	0.470	**0.004**	-0.221	**0.019**
PLR	0.553	**<0.001**	-0.226	**0.016**
MPV/PC	0.086	0.617	0.138	0.146
MHR	-0.167	0.332	-0.044	0.644
RDW	-0.278	0.101	0.001	0.995
MCV	0.339	**0.043**	0.039	0.684
Hgb	0.342	**0.041**	-0.082	0.389
PLT	-0.126	0.463	-0.169	0.075
MPV	0.172	0.314	0.081	0.393

r: Pearson's correlation coefficient. Bold *p*-values indicate statistically significant correlation between the variable and BMD Z score at $\alpha<0.05$. BMD: Bone mineral density, WBC: White blood cell, NLR: neutrophil-to-lymphocyte ratio, MLR: monocyte-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, MPV/PC: mean platelet volume-to-platelet count ratio, MHR: monocyte-to-high-density lipoprotein ratio, RDW: Red Cell Distribution Width, MCV: Mean Corpuscular Volume, Hgb: Hemoglobin, PLT: Platelet, MPV: mean platelet volume (MPV), PCT: plateletcrit PDW: Platelet Distribution Width.

respectively). The lumbar spine BMD (g/cm^2) and BMD Z score were significantly higher in obese group, compared to control group (p <0.001, p <0.001, respectively). Among the biochemical and hemogram parameters, Ca (p=0.025), P (p =0.008), ALP (p =0.001), PTH (p =0.001), MLR (p =0.041), MPV/PC (p <0.001), MHR (p <0.001), RDW (p <0.001) were found to be statistically significantly different between obese and control groups.

In the correlation analysis significant negative correlations were observed between the BMD Z score and 25OHD (r=-0.198, p =0.036), P (r=-0.203, p =0.032), ALP (r=-0.294, p =0.002), in the obese group (Table II).

While MLR and PLR were negatively correlated with BMD Z score in the obese group (r=-0.221, p =0.019; r=-0.226, p =0.016, respectively), positive correlations were observed between BMD Z score and MLR, and PLR in control group (r=0.470, p =0.004; p =0.553, p <0.001, respectively) (Table II) (Figures 1 and 2).

Additionally, Ca (r=0.421, p =0.010), NLR (r=0.647, p <0.001), MCV (r=-0.339, p =0.043), and Hgb (r=0.342, p =0.041) were significantly and positively correlated with BMD Z score in control group.

Discussion

In this study, we examined the relationship between BMD with NLR, MLR, PLR, MHR, MPV, and MPV/PC in children and adolescents with obesity. BMD Z score showed correlations with MLR and PLR, in children with obesity and normal weight children.

Chronic inflammation is associated with low BMD, osteoporosis, and fractures[31]. Leukocyte subgroup tests are generally used to determine inflammatory diseases[32]. However, a recent study[33] showed that PLR, NLR, and MLR are more favorable markers of inflammation than leukocyte subsets.

Diagnostic values have been reported for MLR in many immunological diseases, reflecting the severity of systemic inflammation and immune damage[14]. To the best of our knowledge, there was only one adult study examining the relationship between osteoporosis and MLR. The

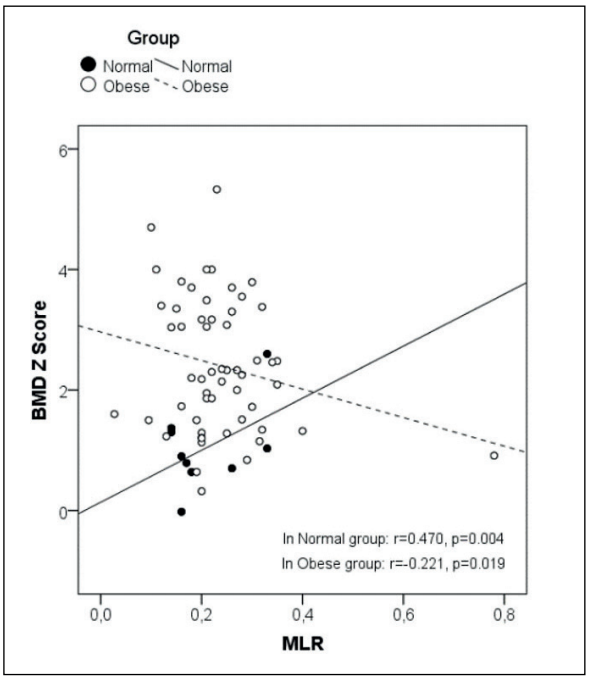

Figure 1. Correlations between BMD Z-score and MLR.

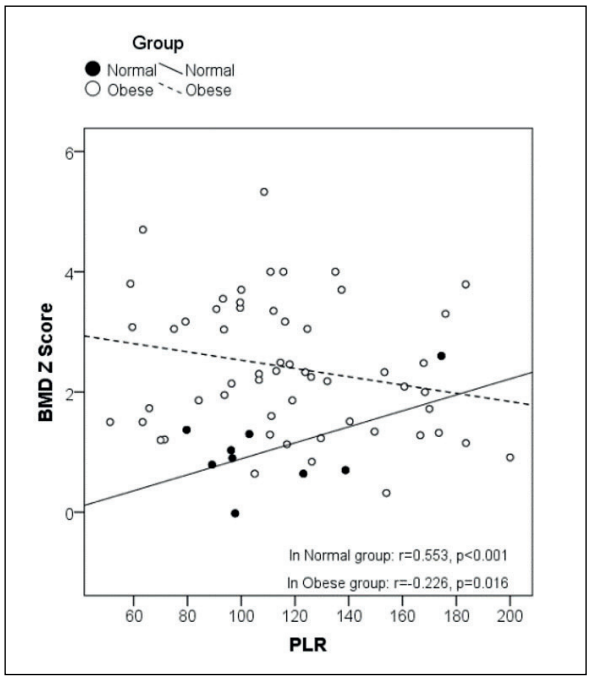

Figure 2. Correlations between BMD Z-score and PLR.

study revealed that when patients were classified as osteopenia and osteoporosis according to their BMD Z-scores, higher MLR, NLR, and PLR levels were found in the osteoporosis group. Gao et al[16] reported that the diagnostic value of MLR in terms of osteoporosis was found to be higher than the other two parameters. In the present study, MLR was significantly associated with BMD Z score in both obese and control groups.

Köseoğlu et al[12] investigated the relationship between NLR and PLR and BMD in postmenopausal women and found that PLR values as inflammatory markers were significantly higher in the low BMD group. In addition, they found a correlation between PLR levels and BMD and suggested that PLR is a distinguishing factor for low BMD. In our study, similar to the above-mentioned study, BMD and PLR appeared to be negative correlated in children with obesity.

Few studies have evaluated the relationship between NLR and BMD. Typically, higher NLR values have been detected in patients with osteoporosis, and a correlation with BMD has been previously reported. However, some other studies[11,12] did not any relationship. In our study, we did not find any relationship between NLR and BMD Z score in children with obesity, but a positive correlation was found in normal weight children.

Ye et al[34], in 2020, examined the relationship between BMD and complete blood count rates in adult patients and reported that the BMD T score showed a negative correlation with the neutrophil and monocyte ratios, and the neutrophil and monocyte ratios increased with the increase in osteoporosis severity.

Osadnik et al[35] studied obese adults and found a strong relationship only between BMI and MHR, among other inflammatory hemogram-based biomarkers. In addition, in multiple intergroup comparisons of other hemogram-based inflammatory markers showed weak associations with BMI, only borderline significance was observed for PLR in men. In our study, there was no correlation between BMI and NLR and MPV. These results and those of Osadnik et al[35], which is the only study on obesity and hemogram-based biomarkers, suggest that the increased inflammation in obesity may be effective especially on monocytes and HDL. There is increasing evidence that adiposity affects bone health in children. Obese children and adolescents have higher bone mineral content than their normal weight counterparts; thus, adipose tissue positively affects bone tissue[36]. However, the rates of limb fractures increase in obese children, indicating that they have poor bone quality[37].

Fang et al[38] found that NLR is an independent risk factor for postmenopausal osteoporosis and in-

creases the risk of fracture. There are also studies[39] showing that a high NLR is associated with poor prognosis in osteoporotic individuals. Furthermore, a high NLR is proven to be indicative of an independent fracture in orthogeriatric patients[40]. According to our study, there is no significantly correlation in obese children and adolescents.

Malgorzata et al[41] investigated the relationship of BMD with NLR and PLR in girls with anorexia nervosa. In their studies, they found that total body BMD Z score and NLR and PLR were negatively correlated ($r = -0.239$, $p = 0.042$; $r = -0.231$, $p = 0.049$, respectively). They found that only PLR showed a negative correlation with the lumbar spine BMD Z score ($r = -0.236$, $p = 0.044$). In our study, there was a negative correlation between the lumbar spine BMD Z score and both NLR and PLR in obese children and adolescents ($r = -0.221$, $p = 0.019$; $r = -0.226$, $p = 0.016$, respectively). These findings suggest the interaction of chronic inflammation and impaired bone quality in both anorexia nervosa and obesity.

Study Limitations

This is a single-center study. Larger sample groups are needed to determine the diagnostic values of parameters that were found to be significant. We could not evaluate the investigated markers along with the other indicators of inflammation, such as C-reactive protein, erythrocyte sedimentation rate, and interleukin-6. We found that BMD Z score was associated with these markers regardless of BMI; however, comparison in healthy children without obesity will have a more impactful contribution to the literature.

Conclusions

In children with obesity, the negative impact of obesity on bone mass needs to be anticipated. This is due to the fact that fractures in children with obesity, especially upper and lower extremity fractures, constitute a large proportion of fracture groups. Considering the knowledge about the relationship between osteoporosis and blood count rates in adults, the data from our study suggest that these inexpensive, simple prognostic markers can be used to estimate bone mineral status in children and adolescents with obesity. In addition, long-term studies on children with obesity are needed to provide essential data for early interventions to prevent risks associated with obesity and impaired bone health.

Conflicts of Interest
The authors declare that they have no conflitc of interest.

ORCID ID
Mehmet Murat Bala, OrcID: https://orcid.org/0000-0002-7213-5647.
Keziban Aslı Bala, OrcID: https://orcid.org/0000-0001-8755-7714.

References

1) Ogden CL, Carroll MD, Lawman HG, Fryar CD, Kruszon-Moran D, Kit BK, and Flegal KM. Trends in Obesity Prevalence Among Children and Adolescents in the United States, 1988-1994 Through 2013-2014. JAMA 2016; 315: 2292-2299.
2) Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, Lee A, Marczak L, Mokdad AH, Moradi-Lakeh M, Naghavi M, Salama JS, Vos T, Abate KH, Abbafati C, Ahmed MB, Al-Aly Z, Alkerwi A, Al-Raddadi R, Amare AT, Amberbir A, Amegah AK, Amini E, Amrock SM, Anjana RM, Arnlov J, Asayesh H, Banerjee A, Barac A, Baye E, Bennett DA, Beyene AS, Biadgilign S, Biryukov S, Bjertness E, Boneya DJ, Campos-Nonato I, Carrero JJ, Cecilio P, Cercy K, Ciobanu LG, Cornaby L, Damtew SA, Dandona L, Dandona R, Dharmaratne SD, Duncan BB, Eshrati B, Esteghamati A, Feigin VL, Fernandes JC, Furst T, Gebrehiwot TT, Gold A, Gona PN, Goto A, Habtewold TD, Hadush KT, Hafezi-Nejad N, Hay SI, Horino M, Islami F, Kamal R, Kasaeian A, Katikireddi SV, Kengne AP, Kesavachandran CN, Khader YS, Khang Y-H, Khubchandani J, Kim D, Kim YJ, Kinfu Y, Kosen S, Ku T, Defo, BK, Kumar GA, Larson HJ, Leinsalu M, Liang X, Lim SS, Liu P, Lopez AD, Lozano R, Majeed A, Malekzadeh R, Malta DC, Mazidi M, McAlinden C, McGarvey ST, Mengistu DT, Mensah GA, Mensink GBM, Mezgebe HB, Mirrakhimov EM, Mueller UO, Noubiap JJ, Obermeyer CM, Ogbo FA, Owolabi MO, Patton GC, Pourmalek F, Qorbani M, Rafay A, Rai RK, Ranabhat CL, Reinig N, Safiri S, Salomon JA, Sanabria JR, Santos IS, Sartorius B, Sawhney M, Schmidhuber J, Schutte AE, Schmidt MI, Sepanlou SG, Shamsizadeh M, Sheikhbahaei S, Shin M-J, Shiri R, Shiue I, Roba HS, Silva DAS, Silverberg JI, Singh JA, Stranges S, Swaminathan S, Tabares-Seisdedos R, Tadese F, Tedla BA, Tegegne BS, Terkawi AS, Thakur JS, Tonelli M, Topor-Madry R, Tyrovolas S, Ukwaja KN, Uthman OA, Vaezghasemi M, Vasankari T, Vlassov VV, Vollset SE, Weiderpass E, Werdecker A, Wesana J, Westerman R, Yano Y, Yonemoto N, Yonga G, Zaidi Z, Zenebe ZM, Zipkin B, Murray CJL. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. N Engl J Med 2017; 377: 13-27.
3) Ma NS, Gordon CM. Pediatric osteoporosis: where are we now? J Pediatr 2012; 161: 983-990.
4) Fintini D, Cianfarani S, Cofini M, Andreoletti A, Ubertini GM, Cappa M, Manco M. The Bones of

Children With Obesity. Front Endocrinol (Lausanne) 2020; 11: 200.
5) Phillips CM, Perry IJ. Does inflammation determine metabolic health status in obese and non-obese adults? J Clin Endocrinol Metab 2013; 98: E1610-9.
6) Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. J Clin Endocrinol Metab 2004; 89: 2548–2556.
7) Mundy GR. Osteoporosis and inflammation. Nutr Rev 2007; 65: S147-51.
8) Anandacoomarasamy A, Caterson I, Sambrook P, Fransen M, March L. The impact of obesity on the musculoskeletal system. Int J Obes (Lond) 2008; 32: 211-222.
9) Gary T, Pichler M, Belaj K, Hafner F, Gerger A, Froehlich H, Philipp Eller, Rief P, Hackl G, Pilger E, Brodmann M. Platelet-to-lymphocyte ratio: a novel marker for critical limb ischemia in peripheral arterial occlusive disease patients. PLoS One 2013; 8: e67688.
10) Grau AJ, Boddy AW, Dukovic DA, Buggle F, Lichy C, Brandt T, Hacke W. Leukocyte count as an independent predictor of recurrent ischemic events. Stroke 2004; 35: 1147-1152.
11) Öztürk ZA, Yeşil Y, Kuyumcu ME, Bilici M, Öztürk N, Yeşil NK, Özkaya M, Kısacık B, Kepekçi Y, Arıoğul S. Inverse relationship between neutrophil lymphocyte ratio (NLR) and bone mineral density (BMD) in elderly people. Arch Gerontol Geriatr 2013; 57: 81-85.
11) Koseoglu SB. Bone loss & platelet-to-lymphocyte ratio. Biomark Med 2017; 11: 5-10.
13) Limmer A, Wirtz DC. Osteoimmunology: Influence of the Immune System on Bone Regeneration and Consumption. Z Orthop Unfall 2017; 155: 273-280.
14) Huang Y, Deng W, Zheng S, Feng F, Huang Z, Huang Q, Guo X, Huang Z, Huang X, Pan X, Li T. Relationship between monocytes to lymphocytes ratio and axial spondyloarthritis. Int Immunopharmacol 2018; 57: 43-46.
15) Yapar A, Ulucaköy C, Sezgin EA, Atalay İB, Ekşioğlu MF. Diagnostic role of neutrophil-to-lymphocyte ratio and monocyte-to-lymphocyte ratio in patients with enchondroma and low-grade chondrosarcoma. Jt Dis Relat Surg 2020; 31: 286-290.
16) Gao K, Zhu W, Liu W, Ma D, Li H, Yu W, Li, Q, Cao Y. The predictive role of monocyte-to-lymphocyte ratio in osteoporosis patient. Medicine (Baltimore) 2019; 98: e16793.
17) Gasparyan AY, Ayvazyan L, Mikhailidis DP, Kitas GD. Mean platelet volume: a link between thrombosis and inflammation? Curr Pharm Des 2011; 17: 47-58.
18) Akbal A, Gökmen F, Gencer M, Inceer BS, Kömürcü E. Mean platelet volume and platelet distribution width can be related to bone mineralization. Osteoporos Int a J Establ as result Coop between Eur Found Osteoporos Natl Osteoporos Found USA 2014; 25: 2291-2295.
19) Kamath S, Blann AD, Lip GY. Platelet activation: assessment and quantification. Eur Heart J 2001; 22: 1561-1571.
20) Guenancia C, Hachet O, Stamboul K, Béjot Y, Leclercq T, Garnier F, Yameogo NV, de Maistre E, Cottin Y, Lorgis L. Incremental predictive value of mean platelet volume/platelet count ratio in in-hospital stroke after acute myocardial infarction. Platelets 2017; 28: 54-59.
21) Usta A, Avci E, Bulbul CB, Kadi H, Adali E. The monocyte counts to HDL cholesterol ratio in obese and lean patients with polycystic ovary syndrome. Reprod Biol Endocrinol 2018; 16: 34.
22) Papachristou NI, Blair HC, Kypreos KE, Papachristou DJ. High-density lipoprotein (HDL) metabolism and bone mass. J Endocrinol 2017; 233: R95-R107.
23) Li S, Guo H, Liu Y, Wu F, Zhang H, Zhang Z, Xie, Z., Sheng Z, Liao E. Relationships of serum lipid profiles and bone mineral density in postmenopausal Chinese women. Clin Endocrinol (Oxf) 2015; 82: 53-58.
24) Ackert-Bicknell CL. HDL cholesterol and bone mineral density: is there a genetic link? Bone 2012; 50: 525-533.
25) Faienza MF, D'Amato G, Chiarito M, Colaianni G, Colucci S, Grano M, Corbo F, Brunetti G. Mechanisms Involved in Childhood Obesity-Related Bone Fragility. Front Endocrinol (Lausanne) 2019; 10: 269.
26) Neyzi O, Bundak R, Gokcay G, Gunoz H, Furman A, Darendeliler F,Bas F. Reference Values for Weight, Height, Head Circumference, and Body Mass Index in Turkish Children. J Clin Res Pediatr Endocrinol 2015; 7: 280-293.
27) Wheeler MD. Physical changes of puberty. Endocrinol Metab Clin North Am 1991; 20: 1-14.
28) Bachrach LK, Gordon CM. Bone Densitometry in Children and Adolescents. Pediatrics 2016; 138: e20162398. doi: 10.1542/peds.2016-2398.
29) Goksen D, Darcan S, Coker M, Kose T. Bone mineral density of healthy Turkish children and adolescents. J Clin Densitom Off J Int Soc Clin Densitom 2006; 9: 84-90.
30) Demir K, Konakci E, Ozkaya G, Kasap Demir B, Ozen S, Aydin M, Darendeliler F. New Features for Child Metrics: Further Growth References and Blood Pressure Calculations. J Clin Res Pediatr Endocrinol 2020; 12: 125-129 doi:10.4274/jcrpe.galenos.2019.2019.0127.
31) Lencel P, Magne D. Inflammaging: the driving force in osteoporosis? Med Hypotheses 2011; 76: 317-321.
32) Weitzmann MN, Ofotokun I. Physiological and pathophysiological bone turnover - role of the immune system. Nat Rev Endocrinol 2016; 12: 518-532.
33) Bozan N, Alpaycı M, Aslan M, Cankaya H, Kıroglu AF, Turan M, Ayral A, Senkoy E, Ilter S. Mean platelet volume, red cell distribution width, platelet-to-lymphocyte and neutrophil-to-lymphocyte ratios in patients with ankylosing spondylitis and their relationships with high-frequency hearing thresholds. Eur Arch oto-rhino-laryngology Off J Eur Fed Oto-Rhino-Laryngological Soc Affil with Ger Soc Oto-Rhino-Laryngology - Head Neck Surg 2016; 273: 3663-3672.

34) Ye X, Jiang H, Wang Y, Ji Y, Jiang X. A correlative studies between osteoporosis and blood cell composition: Implications for auxiliary diagnosis of osteoporosis. Medicine (Baltimore) 2020; 99: e20864.
35) Osadnik T, Bujak K, Osadnik K, Czarnecka H, Pawlas N, Reguła R, Fronczek M, Lejawa M, Gawlita M, Gonera M, Góral M, Strzelczyk JK, Gierlotka M, Lekston A, Kasperczyk J, Poloński L, Gąsior M. Novel inflammatory biomarkers may reflect subclinical inflammation in young healthy adults with obesity. Endokrynol Pol 2019; 70: 135-142.
36) Leeuwen J, Koes BW, Paulis WD, Middelkoop M. Differences in bone mineral density between normal-weight children and children with overweight and obesity: a systematic review and meta-analysis. Obes Rev an Off J Int Assoc Study Obes 2017; 18: 526-546.
37) Kessler J, Koebnick C, Smith N, Adams A. Childhood obesity is associated with increased risk of most lower extremity fractures. Clin Orthop Relat Res 2013; 471: 1199-1207.
38) Hong F, Hanqing Z, Zhi W, Zhongming Z, Yunjun L, Lin L. Systemic immune-inflammation index acts as a novel diagnostic biomarker for postmenopausal osteoporosis and could predict the risk of osteoporotic fracture. J Clin Lab Anal 2020; 34: e23016.
39) Huang Chenshu H, Li Shaolin L. Association of blood neutrophil lymphocyte ratio in the patients with postmenopausal osteoporosis. Pakistan J Med Sci 2016; 32: 762-765.
40) Alexander F, Wichat S, Leon F, Paul S. The Neutrophil to Lymphocyte Ratio on Admission and Short-Term Outcomes in Orthogeriatric Patients. Int J Med Sci 2016; 13: 588-602.
41) Morawiecka-Pietrzak MT, Malczyk Ż, Dąbrowska E, Blaska M, Pietrzak M, Gliwińska A, Góra A, Ziora K, Pluskiewicz W, Ostrowska Z. The Relationship of Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio with Bone Mineral Density in adolescent girls suffering from anorexia nervosa. Endokrynol Pol 2021; EP.a2021.0036.