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Bone mineral density (BMD) and neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), and platelet-lymphocyte ratio (PLR) in childhood thyroid diseases

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: This study aimed at investigating the laboratory parameters related to the pathogenesis of bone loss, including bone mineral density (BMD), neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), and platelet-lymphocyte ratio (PLR) in children with thyroid disease and healthy controls.

PATIENTS AND METHODS: Children and adolescents with hypothyroidism (n=63) and hyperthyroidism (n=30) as well as 32 age- and sex-matched healthy controls were included in the study. Auxological data, BMD, hemogram parameters, the levels of thyroid hormone, thyroid stimulating hormone (TSH), thyroid autoantibodies, parathyroid hormone, 25-hydroxy vitamin D, alkaline phosphatase, calcium, and phosphorus were analyzed.

RESULTS: The mean age of the patients was 12.12±2.7 years (range: 8-17). BMD Z-scores were within the normal range in all the patients and healthy controls. The BMD Z-scores were significantly higher in patients with hyperthyroidism than those in the control group and in patients with hypothyroidism. No significant difference was observed between the control and hypothyroid groups in terms of the BMD Z-scores. A correlation was observed between the BMD Z-scores and NLR, MLR, PLR, and free T4 levels. In patients with hypothyroidism, the BMD Z-scores were significantly positively correlated with the NLR, MLR, PLR, and the TSH level. In the control group, there was a moderate positive correlation between the BMD Z-scores and NLR. In the hyperthyroid group, there were no significant correlations between the BMD Z-scores and other variables.

CONCLUSIONS: The study data suggest that in children and adolescents with thyroid disease, the relationship between the BMD Z-scores and NLR, MLR, and PLR at the initial diagnosis in the hypothyroidism group was different from that in their healthy peers.

Key Words:
Bone mineral density, Thyroid diseases, NLR, MLR, PLR.

Introduction

Thyroid hormones have important effects on skeletal development, including linear growth and the maintenance of adult bone mass and strength. The fact that thyroid stimulating hormone (TSH) receptor is expressed in choroid follicular cells, as well as in chondrocytes, osteoblasts, and osteoclasts suggests that it has direct effects on skeletal metabolism[1].

Childhood hypothyroidism is associated with the impairment of bone maturation due to defective endochondral ossification, delay in skeletal development, and growth retardation and short stature[2]. The introduction of early thyroid hormone replacement therapy in such children helps them in moving toward a period of rapid "catching up growth" in which the skeletal maturation and bone age are accelerated as well. Ultimately, the expectation is normal adult size and bone mineral density (BMD)[1].

However, in childhood hyperthyroidism, an increase in skeletal maturation and growth rate is observed[3]. Adult hyperthyroidism is associated with a decrease in BMD and an increase in fracture risk[4]. Both clinical and animal studies[1,5] suggested that even the high-normal and/or low-normal TSH levels can lead to an increase in bone cycle and bone resorption, resulting in a decrease in the BMD and a higher risk of fractures.

As the new markers of systemic inflammatory response, the neutrophil-lymphocyte ratio (NLR)

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

and platelet-lymphocyte ratio (PLR)[6,7] were also associated with the reduced BMD and osteoporosis[8,9]. Currently, relevant studies[10] in the literature also use the monocyte-lymphocyte ratio (MLR) as an inflammation marker. The increase in the MLR proportional to the inflammation of the bone was reported to be associated with osteoporosis and bone-related diseases[11,12].

The present study investigated the relationship between the BMD and NLR, MLR, and PLR in children and adolescents with acquired hypothyroidism and hyperthyroidism prior to the treatment. To the best of our knowledge, this relationship has not been studied so far.

Patients and Methods

Patients

We designed as a cross-sectional research. The present study included 63 children and adolescents with acquired hypothyroidism (male, female) and 30 children and adolescents with hyperthyroidism (male, female). The control group consisted of 32 healthy (male, female) children and adolescents who were matched to the patient group in terms of age, sex, and body mass index (BMI).

The patients were screened for pathologies that would affect the BMD measurements in the orthopedic clinic. The patients were examined for spinal deformity, disproportion among extremities, skeletal dysplasia, genetic dysmorphism, developmental hip dysplasia, bone metabolism disease, pathological fracture history, and surgical intervention. Children and adolescents with pathologies that may affect BMD were excluded from the study. Furthermore, children and adolescents on drugs (such as steroids) that may affect bone mineral metabolism and those with chronic systemic diseases were excluded.

Hyperthyroidism was diagnosed based on the clinical findings and elevated free T4 (FT4), free T3 (FT3), and suppressed TSH levels in laboratory assays. Patients with hyperthyroidism were diagnosed either with Graves or Hashitoxicosis based on thyroid stimulating antibodies and thyroid autoantibodies [antithyroid peroxidase (anti-TPO), antithyroglobulin antibody (anti-TGA)]. Patients with hyperthyroidism with toxic adenoma or multinodular goiter were excluded from the study. Hypothyroidism diagnosis was based on the clinical findings and decreased free T4 (FT4), free T3 (FT3), and elevated TSH levels in laboratory assays. Patients were diagnosed with Hashimato and iodine deficiency based on positive thyroid autoantibodies and the urine iodine levels. Finally, the patients with congenital hypothyroidism were excluded from the study.

Height measurements were performed using a Harpenden stadiometer (Holtain, Crosswell, Crymych, UK) and weight measurements were performed using a digital scale, followed by using the formula for BMI measurement, which is BMI=-weight (kg)/height square (m^2). We referred to the 2015 Turkey National Growth Tables for weight, height, and BMI standard deviation scores[13]. Tanner staging method and Marshall staging method were used to determine the state of puberty in girls and boys, respectively[14].

BMD Z-scores and height, weight, BMI, the blood count levels (WBC: White blood cell, NEUT: neutrophils; LYMPH: lymphocytes; MON: monocytes, PLT: platelets), the levels of 25-OH vitamin D (25OHD), alkaline phosphatase (ALP), parathormone (PTH), phosphorus (P), phosphorus (P) of patients were collected from the medical records and the NLR, MLR, and PLR levels were calculated.

Complete blood counts were measured using auto-hematology analyzer (Abbott, Cell-Dyn Ruby, Chicago, IL, USA). Photometric analyzer (Abbott, c16000, Chicago, IL, USA) was used for biochemical parameters. Chemiluminescence immunoassay (Abbott, i2000sr, Chicago, IL, USA) was used for hormone parameters. The MLR, NLR, and PLR were calculated using the following formulas: monocyte count/lymphocyte count; neutrophil count/lymphocyte count; platelet count/lymphocyte count, respectively.

We conducted the study based on the principles of the Declaration of Helsinki and obtained the Ethics Committee Approval (Decision No. 2020-20) from the Health Sciences University Trabzon Kanuni Training and Research Hospital. We obtained the informed consent form in writing from all subjects and their parents.

Dual-Energy X-Ray Absorptiometry

We defined osteoporosis as the presence of clinically significant history of fracture and BMD Z-score of ≤2. We defined a clinically significant fracture history based on one or more of the following: ≥2 long bone fractures by the age of 10 years or ≥3 long bone fractures at any age up to 19 years[15]. In all patients, BMD (BMD unit: g/cm^2) was evaluated by Lunar Prodigy (General Electric, GE Healthcare, Lunar DPX, NT + 150301, Chicago, IL, USA) using dual-energy X-ray absorptiometry. We measured the BMD at the lev-

Table I. Clinical characteristics in patients with hypothyroidism-hypethyroidism and healthy controls.

Variable	Hyperthyroids (n=30)	Hypothyroids (n=63)	Healthy controls (n=32)	p-value
Age	13.7±2.0[a]	11.4±2.8[a]	12.2±2.7	**<0.001**
Sex (F/M)	24/6	57/6	23/9	0.063
Pubertal status				0.055
Tanner stage 1	3	21	6	
Tanner stage 2-5	27	42	26	
Height SDS	0.5 (-0.6-0.8)[b]	-0.4 (-1.2-0)[a,b]	0.3 (-1.2-1.1)[a]	**0.002**
Weight SDS	0 (-0.6-1.2)	0 (-0.9-0.6)	0.1 (-0.2-1)	0.084
BMI SDS	0.1 (-0.4-1.4)	0.3 (-0.9-1.1)	-0.2 (-0.3-0.9)	0.846

Values are expressed as n(%), mean±sd or median (25th and 75th percentile). For categorical variables Pearson's chi-square or Fisher's exact tests are used. Continuous variables were compared with one-way ANOVA followed by Tukey's test or Kruskal Wallis test followed by post-hoc Dunn's test. Bold p-values indicate statisticallly significant difference between three groups at α=0.05. [a,b,c]Same superscript letter indicate statistically significant difference between two groups at α=0.05 based on the post-hoc test. BMI: Body mass index.

el of lumbar spine segments L1-L4 (LS) through whole-body scan. The BMD Z-scores were calculated using the data on healthy Turkish children and adolescents (176 girls and 169 boys) after adjusting for height and age[16,17]. The same experienced operator performed all the scans.

Statistical Analysis

Descriptive data are presented as number (percentages) or median and interquartile ranges (25th-75th percentiles) or mean ± standard deviation. The normality of continuous variables was assessed by Shapiro-Wilk test. Statistical differences between groups were evaluated using one-way ANOVA or Kruskal Wallis test. When significant differences were found, post-hoc Tukey HSD test or Dunn's test were applied for pairwise group comparisons of normally and non-normally distributed variables, respectively. The categorical variables were analysed with Pearson's chi-square

Table II. BMD Z-scores, biochemical parameters and blood count levels in patients with hypothroidism-hypethroidism and healthy controls.

Variable	Hyperthyroids (n=30)	Hypothyroids (n=63)	Healthy controls (n=32)	p-value
BMD Z-Score	2.1 (1.4-2.3)[a,b]	0.5 (-0.3-1.7)[b]	1 (0.6-1.4)[a]	**0.001**
25.OH D Vit (ng/mL)	15.1 (11-18)	15 (12-17)	14 (12-19)	0.931
Calcium (mg/dL)	9.5 (9.5-9.6)	9.3 (9.2-9.8)	9.6 (9.2-9.7)	0.456
Phosphorus (mg/dL)	3.8 (3.7-4.2)[a]	4.6 (4.3-5)[a]	4.4 (3.8-4.7)	**<0.001**
Alkaline phosphatase (IU/L)	90.5 (63-115)[a,b]	178 (117-239)[b]	213 (111-252)[a]	**<0.001**
Parathyroid hormone (pg/mL)	34 (23-46)[a,b]	43 (35-54)[b]	42 (39-75.8)[a]	**0.006**
WBC(10^3/µL)	6.3 (5.5-8.1)	6.9 (6.1-7.6)	7.2 (6.9-8)	**0.038**
NEUT(10^3/µL)	3.2 (2.9-3.8)[b]	3.1 (2.9-3.4)[a]	3.8 (3.1-4.5)[a,b]	**0.004**
LYMPH(10^3/µL)	2.2 (2-2.3)[a,b]	2.5 (2.3-3)[b]	2.7 (2.3-3.1)[a]	**0.019**
MON(10^3/µL)	0.6 (0.5-0.7)	0.6 (0.5-0.7)	0.6 (0.5-0.6)	0.700
TSH	0.01 (0.01-0.01)[b,c]	13.00 (11.00-18.20)[a,c]	1.80 (1.60-2.20)[a,b]	**<0.001**
FT4	2.0 (1.4-2.5)[b,c]	0.8 (0.7-0.9)[a,c]	0.9 (0.8-1)[a,b]	**<0.001**
NLR	1.6 (1-1.8)	1.3 (0.9-1.6)	1.3 (1.1-2)	0.189
MLR	0.27 (0.25-0.28)[a]	0.22 (0.19-0.26)[a]	0.19 (0.16-0.32)	**0.014**
PLR	126.2 (105.1-139.1)	113.9 (94.2-123.7)	97.7 (96.3-123.1)	0.142

Values are expressed as n(%), mean±sd or median (25th and 75th percentile). For categorical variables Pearson's chi-square or Fisher's exact tests are used. Continuous variables were compared with one-way ANOVA followed by Tukey's test or Kruskal Wallis test followed by post-hoc Dunn's test. Bold p-values indicate statisticallly significant difference between three groups at α=0.05. [a,b,c]Same superscript letter indicate statistically significant difference between two groups at α=0.05 based on the post-hoc test.
BMI: Body mass index, BMD: Bone mineral density, WBC: White blood cell, NEUT: neutrophils; LYMPH:lymphocytes; MON: monocytes, NLR: neutrophil-to-lymphocyte ratio, MLR: monocyte-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio,), TSH: Thyroid stimulating hormone, FT4: free T4.

Table III. Correlation analysis in all patients.

		NLR	MLR	PLR	TSH	FT4
BMD Z Scores	**rho**	0.339	0.457	0.309	-0.172	0.232
	p	**<0.001**	**<0.001**	**<0.001**	0.056	**0.009**

Rho: Spearman's correlation coefficient between BMD Z-scores and other variables. Bold *p*-values indicate statisticallly significant correlation at α=0.05.
BMD: Bone mineral density, NLR: neutrophil-to-lymphocyte ratio, MLR: monocyte-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, TSH: Thyroid stimulating hormone, FT4: free T4.

or Fisher'exact tests, where appropriate. Relationships between continuous variables were assessed by Spearman's correlation analysis. The analyses were performed using the Statistical Package for Social Sciences 25.0 for Windows (IBM, Armonk, NY, USA). The results were considered to be significant at a level of $p < 0.05$.

Results

The mean age of the patients included in the study was 12.12± 2.7 years (range: 8-17.0 years). There was no significant difference between the control group and the hyperthyroidism and hypothyroidism groups in terms of age, sex distribution, BMI and standardized BMI (BMI SDS), and puberty staging (Table I).

BMD Z-scores were within the normal range in all the patients, as well as the individuals in the control group. The significant differences between groups were observed in BMD Z-Score (p<0.001), P (p<0.001), ALP (p<0.001), PTH (p=0.006), WBC (p=0.038), NEUTH (p=0.004), LYMPH (p=0.019), TSH (p<0.001), ST4 (p<0.001) and MLR (p=0.014) (Table II). Post-hoc analysis revealed that BMD Z-scores was significantly higher in patients with hyperthyroidism compared to control subjects [median (IQR): 2.1 (0.9) *vs.* 1 (0.8), p=0.041] and patients with hypothyroidism [median (IQR): 2.1 (0.9) *vs.* 0.5 (2.0), p<0.001]. No significant difference was observed between control and hypothyroid groups in terms of BMD Z-scores. Patients with hyperthyroidism had significantly higher MLR compared to the patients with hypothyroidism [median (IQR): 0.27 (0.03) *vs.* 0.22 (0.07), p=0.014].

The correlations between BMD Z-scores and other variables were assessed (Table III and Table IV). When all patients were evaluated, a correlation was found between BMD Z-score and NLR, MLR, PLR and ST4. In the patients with hypothyroidism, BMD Z-scores was significantly positively correlated with NLR (rho=0.526, p<0.001), MLR (rho=0.490, p<0.001), PLR (rho=0.279 p=0.027), and TSH (rho=0.415, p=0.001) (Figure 1). In the control group, a moderate positive correlation between BMD Z-scores and NLR was observed (rho=0.378, p=0.033). In hyperthyroid group, no significant correlations were found between BMD Z-scores and other variables.

Table VI. Correlation analysis in groups.

	BMD Z Scores					
	Control		Hypothyroid		Hyperthyroid	
Variables	*rho*	*p*	*rho*	*p*	*rho*	*p*
NLR	0.378	**0.033**	0.526	**<0.001**	-0.316	0.089
MLR	0.210	0.249	0.490	**<0.001**	-0.214	0.256
PLR	0.189	0.301	0.279	**0.027**	-0.073	0.702
TSH	0.202	0.268	0.415	**0.001**	0.233	0.216
FT4	0.059	0.748	-0.048	0.707	-0.207	0.272

Rho: Spearman's correlation coefficient between BMD Z-scores and other variables. Bold *p*-values indicate statisticallly significant correlation at α=0.05.
BMD: Bone mineral density, NLR: neutrophil-to-lymphocyte ratio, MLR: monocyte-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, TSH: Thyroid stimulating hormone, FT4: free T4.

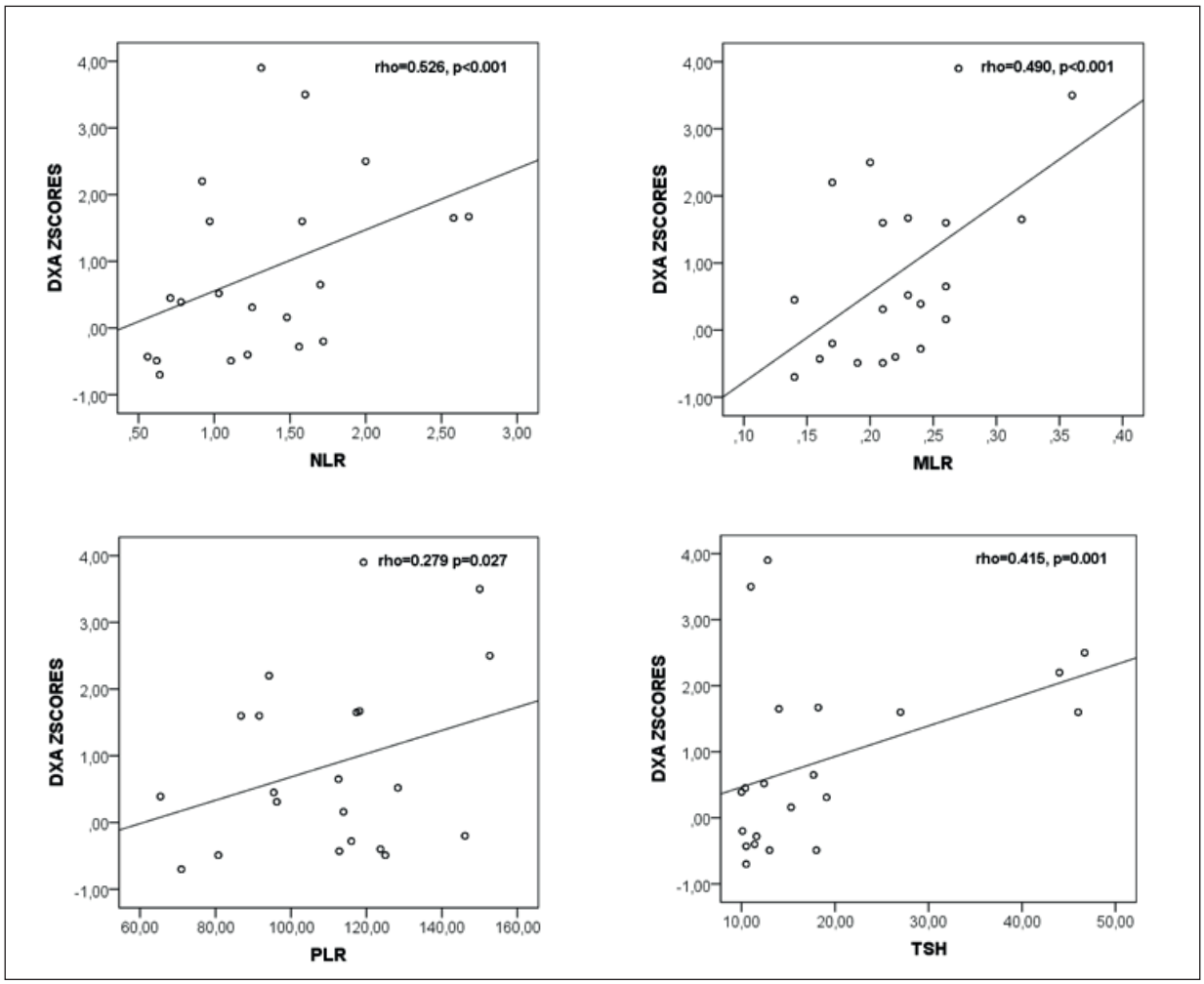

Figure 1. Correlation plots between DXA Z-Scores (Dual-energy X-ray absorptiometry=BMD Z-Scores) and other variables for hypothyroid group. (rho: Spearman's correlation coefficient).

Discussion

The present study achieved two main results. First, the BMD Z-scores were higher in the hyperthyroidism group than in the hypothyroidism group and healthy controls, whereas there was no difference between the hypothyroidism group and control group. Secondly, the BMD Z-scores were found to be correlated with NLR, MLR, and PLR in children with hypothyroidism.

A meta-analysis[4] that investigated the relationship of fracture risk with subclinical thyroid dysfunction reported an increase in the risk of hip and other fractures, especially in individuals with the TSH levels <0.10 mIU/L and with endogenous subclinical hyperthyroidism.

Lee et al[18] evaluated the BMD Z-scores that were adjusted for height at the time of initial diagnosis in children and adolescents with Graves' disease and found that their BMD levels were lower than those of their healthy peers. Based on these results, they suggested that BMD measurement could be necessary for the initial evaluation in this population. In our study, the BMD levels were within the normal range in the hyperthyroidism group; however, they were still higher than those of the healthy controls. The limited size of our patient group and the fact that bone mineralization could have been unaffected due to early diagnosis might account for this different result. As a matter of fact, presently, osteoporosis caused by untreated thyrotoxicosis is rare because of the early diagnosis and treatment; however, undiagnosed hyperthyroidism remains an important risk factor for secondary bone loss and osteoporosis in patients presenting to hospital with fractures[19,20].

Veldscholte et al[21] prospectively showed in a large population study that a higher level of FT4

during childhood was associated with the lower BMD levels. Population studies on both euthyroid and hyperthyroid adults suggested that the higher and/or lower TSH levels were associated with the lower BMD levels[2]; however, these findings did not directly apply to a healthy pediatric population. In the present study, there was a positive correlation between the FT4 and BMD Z-scores after the evaluation of all the patients.

Di Mase et al[22] investigated the bone mineral levels using dual-energy X-ray densitometry (DXA) and quantitative ultrasound over a 3-year follow-up period in children with subclinical hypothyroidism. The above study proved that bone health was not affected in children and adolescents with subclinical hypothyroidism who did not undergo any long-term treatment. In our study, there was no significant difference in the BMD Z-scores between the hypothyroidism group and healthy controls.

Kim et al[5] investigated the relationship between the BMD and TSH levels in euthyroid men. They found that the serum TSH levels close to the lower threshold of the normal range were associated with the lower BMD levels in adults.

Correlation was reported between BMD and the values of the PLR, an inflammatory marker in postmenopausal women, based on which the PLR was suggested as a distinctive factor for the low levels of BMD[9]. In our study, there was a positive correlation between the PLR and BMD when all groups were evaluated (p<0.001, r=0.309).

Only a limited number of studies have investigated the relationship between the NLR and BMD. Generally, higher NLR levels were reported in osteoporosis, showing an association with BMD, whereas other studies did not find any association[8,9]. In our study, there was a positive correlation between the NLR and BMD in the healthy controls and hypothyroidism group (p<0.001, r=0.526).

In the literature, the relationship between the BMD with NLR and PLR in childhood was only investigated in girls with anorexia nervosa[23]. Those studies reported that there was a negative correlation between the total body BMD Z-scores and NLR and PLR (r=−0.239, p=0.042; r=−0.231, p=0.049, respectively). PLR was reported to have a negative correlation with the lumbar spine BMD Z-score (r=−0.236, p=0.044).

A study[24] investigated the relationship between the complete blood count rates and BMD in adults. They reported that the BMD T-score was negatively correlated with the monocyte and neutrophil rates in both sexes and that the rates increased with the increasing bone loss and severity of osteoporosis. In our study, a positive correlation was observed between the BMD and MLR in the hypothyroidism group (p<0.001, r=0.490).

Limitations

This study has some limitations, including the fact that the sample group was relatively small and that there were no follow-up data on post-treatment bone condition in individuals who received medication for thyroid disease. In addition, factors that affected the bone cycle, including nutritional habits (calcium and vitamin D intake) and physical activities, were not considered.

Optimizing the peak bone mass gain in children and adolescents is essential to prevent osteoporosis and also prevent fractures that may occur in advanced age. Therefore, simple diagnostic tests are needed to predict the bone condition in thyroid diseases that have an effect on bone mineralization.

Conclusions

The study data suggest that in children and adolescents with thyroid disease, the relationship between the BMD Z-scores and NLR, MLR, and PLR at the initial diagnosis in the hypothyroidism group was different from that in their healthy peers.

These results indicate that the easily accessible parameters, such as the NLR, MLR, and PLR, can help clinicians predict bone density at the first diagnosis of thyroid disorders in children and adolescents. Thus, possible fractures can be prevented upon following appropriate treatment.

The present study is the first pediatric study in this field; hence, we believe that it will contribute to further studies involving larger groups.

ORCID ID

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

Conflict of Interests

The authors declare that they have no conflict of interest.

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