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The Long-Term Effect of Very Low Birth Weight and Prematurity On Bone Mineral Density In 5-7 Years Old Children

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Abstract

Objective: Very low birth weight (VLBW) infants are at increased risk of osteopenia of prematurity due to interruption of intrauterine bone mineralization. In this study aimed to evaluate the bone mineral density (BMD) by evaluating DXA in children aged 5-7 years with VLBW and preterm birth.

Methods: This study was conducted prospectively between February 2011 and September 2012. Seventy-five children aged 5-7 years, who were born under 1.500 grams were included.

Results: Bone density measurements of the study group (42 female 56%) were found to be low compared to the DXA reference values (p < 0.001). According to the L1-L4 Z score, bone density was found to be low in 21.33% (n: 16) of the cases. Total femur Z score (p = 0.018), femur neck BMD (p = 0.001), total femur BMD (p = 0.012) values were significantly lower in females than males. Whole body BMD values (p = 0.021) were significantly lower in patients receiving postnatal systemic steroids than in the non-receiving group. Femur neck BMD values of the patients who received only breast milk in the first six months were found to be statistically significantly higher than those who received only formula in the first six months (p = 0.034).A significant correlation was found between the current height, weight, BMI increase and BMD measurement.

Conclusion: In this study, it was shown that bone diseases in VLBW and preterm infants affect bone mineralization in long term. We determined the effects of drugs and nutrition used in treatments and current anthropometric measurements on bone health of preterm and VLBW.

Keywords: bone mineral density, osteoporosis, prematurity, very low birth weight

5-7 Yaş Arası Çocuklarda Düşük Doğum Ağırlığı ve Prematüretenin Kemik Mineral Dansitenin Üzerine Uzun Dönem Etkisi

Öz

Giriş: Çok düşük doğum ağırlıklı bebekler, intrauterin kemik mineralizasyonun kesintiye uğraması nedeniyle prematüre osteopeni riski altındadır. Bu çalışmada çok düşük doğum ağırlıklı ve preterm doğan 5-7 yaş arası çocuklarda kemik mineral yoğunluğunun DXA ile değerlendirilmesi amaçlandı.

Yöntemler: Bu çalışma, Şubat 2011 ve Eylül 2012 arasında prospektif olarak gerçekleştirildi. Bin beş yüz gramın altında doğan 5-7 yaş arası 75 çocuk dahil edildi.

Bulgular: Çalışma grubunun kemik yoğunluğu ölçümleri (42 kadın %56) DXA referans değerlerine göre düşük bulundu (p <0,001). L1-L4 Z skoruna göre, olguların %21,33'ünde düşük bulundu. Total femur Z skoru, femur boynu kemik mineral yoğunluğu, total femur kemik mineral yoğunluğu değerleri kadınlarda erkeklerden anlamlı olarak düşüktü(p = 0,018, p = 0,001, p = 0,012, sırasıyla). Tüm vücut kemik mineral yoğunluğu değerleri (p = 0,021) postnatal sistemik steroid alan hastalarda almayan gruba göre anlamlı derecede düşüktü. İlk altı ayda sadece anne sütü alan hastaların femur boynu kemik mineral yoğunluğu değerleri, ilk altı ayda sadece formül alanlara göre istatistiksel olarak anlamlı derecede yüksek bulundu (p = 0,034). Güncel boy, kilo, vücut kitle indeks ile kemik mineral yoğunluğu ölçümü arasında anlamlı bir korelasyon vardı.

Sonuç: Bu çalışmada çok düşük doğum ağırlıklı ve erken doğmuş bebeklerde kemik hastalıklarının uzun vadede kemik mineralizasyonunu etkilediği gösterilmiştir. Tedavide kullanılan ilaç ve beslenmenin ve güncel antropometrik ölçümlerin preterm ve çok düşük doğum ağırlıklı kemik sağlığına etkilerini belirledik.

Anahtar kelimeler: Çok düşük doğum ağırlık, kemik mineral yoğunluğu, osteoporoz, prematurite.

INTRODUCTION

In recent years, medical advances in prenatal care, assisted reproductive techniques, and neonatal intensive care units have increased the survival rate of preterm infants. Although the survival rates of infants with very low gestational age increased, there was no decrease in the main morbidity problems[1]. One of these problems is the metabolic bone disease of prematurity and early onset osteopenia and osteoporosis[2]. The 80% of maternal-fetal calcium phosphorus transport takes place within the third trimester' of intra-uterine life. Interruption of intrauterine bone mineralization in preterm and very low birth weight (VLBW) infants increases the frequency of osteopenia depending on prenatal (steroid use during pregnancy, diabetes, preeclampsia) and postnatal (use of surfactant, mechanical ventilation, duration of breastfeeding or formula feeding time, exposure to medications diuretic, theophylline, caffeine, aminoglycoside and time of total parenteral nutrition) reasons. Its effect on long-term bone health is not clear.

Preterm infants are at high risk in terms of bone mineralization and suboptimal growth when compared to term infants[3-5]. Different findings were obtained in the evaluation of bone density in the childhood age group of VLBW and preterm infants. Kurl et al.[6] in their study of 6-7 years old children with premature birth found similar lumbar bone mineral density (BMD) and bone mineral content (BMC) compared to the reference group. However, Armstrong et al.[7] reported very low lumbar BMD values of preterm children compared with term peers at the age of 6 to 7 years. However, it has been suggested that the delay in bone mineralization continues until 4-16 years of age[8].

The prevention or treatment of premature osteopenia has favorable effects such as, linear growth, increment of maximal bone mass and avoidance of bone fractures and should not be neglected[9-12].

The aim of this study is to interpret the bone mineral density in 5-7 years old children with premature and VLBW history by evaluating dual

energy X-ray absorptiometry (DXA) and to determine the relationships of DXA with prenatal, natal, postnatal and current variables.

METHODS

This study was carried out between February 2011 and September 2012 with 75 children aged between 5-7 years who were born lower than 1500 gram and admitted in the neonatal intensive care unit (NICU) of University Hospital.

The patients' data files were examined for the age of the mother, steroid use during pregnancy, diabetes, preeclampsia, diagnosis of hypertension, smoking and whether or not mothers were used headscarf in pregnancy. The birth date, sex, gestational week, birth weight, type of delivery, intrauterine development (SGA, AGA, LGA) were ascertained. A history of early membrane rupture, presence of chorioamnionitis and prenatal steroid use, duration of hospitalization of a baby, presence of RDS (respiratory distress syndrome), use of surfactant, mechanical ventilation, intubation and duration of nasal ventilation, presence and degree of BPD (bronchopulmonary dysplasia) were determined.

Whether the baby was receiving systemic steroid treatment during hospitalization, and if so, the time and duration were recorded. Early or late, clinical or culture-proven presence of sepsis, presence of second stage or more necrotizing enterocolitis (NEC), accompanying patent ductus arteriosus (PDA), presence of intracranial hemorrhage (ICH), and presence of retinopathy (ROP) of prematurity were questioned.

The use and administration times of total parenteral nutrition (TPN), transitions to enteral feeding of infants were recorded throughout the stays at hospital.

Diuretic, theophylline, caffeine, aminoglycoside use in the treatment of patients; if used, the duration was learned from the hospital files. The information about the duration of breastfeeding or formula feeding time, vitamin D and drug use history of the children were obtained from their files and families.

The child's home and environmental living conditions, school attendance, active outdoor playtimes, daily milk consumption were asked. Percentiles and Z scores of weight, height, and body mass index (BMI) information of the patients were recorded.

USA-made LUNAR BRAND model of 2010, 8743 BX-1L (GE Medical System™), DXA - dual energy X-ray absorptiometry device was used to measure bone density. All measurements were made by the same technician, all assessments were completed by the same nuclear medicine specialist based on source data schedules for children of device instruction manual. Total body (TB), total body less head (TBLH), L1-L4 vertebrae, femur neck and femur total bone mineral density (BMD) (gr/ cm^2), bone mineral content (gr) and Z score of all cases were measured. In studies showed that the trabecular bone mineral changes are more sensitive than cortical bone. So it has been used as the lumbar zone measurement area[6,7,13-16].

As the DXA had very low dose of radiation and the control group did not benefit from the study, the experimental group was compared with the reference values of the DXA device as a control group. In patients with the BMD Z score between 0 and -2,0 was normal, of the cases with lower than -2,0 are categorized as "low bone density by chronological age" and "lower value than expected by age".

* Ethical approval: The study was approved by the ethics committee of University Hospital (KAEK / 2011/168).

STATISTICAL ANALYSIS

Statistical analysis was performed with the IBM SPSS 20.0 ™ program (SPSS Inc., Chicago, IL,

USA). Data with normal distribution were stated as mean ± standard deviation and data not showing normal distribution as median (range) values. Comparisons of independent binary groups with normal distribution were made with the t test, ANOVA variance analysis was applied to hypervariable groups. The Mann-Whitney U test was used to compare two groups of data not showing normal distribution, and over-variant groups. For the comparison of percentages of qualitative data, the Paired chi-square test and z-test were applied. A value of $p < 0.05$ was considered statistically significant. Pearson correlation test was used for correlation.

RESULTS

Of 75 patients included in the study, 42 (56%) were female and 33 (44%) were male. Bone density measurements of the subjects were found to be low compared to the reference values of the DXA device ($p < 0.001$) (Table I).

Table I: Comparison of Bone Density Measurements of 75 Cases with VLBW Aged 5-7 Years That Followed-Up in NICU.

	Females	Males	p value
L1-L4 BMD (g/cm²)	0.567±0.012	0.571±0.017	
Reference value	*0.650 (0.624-0.664)*	*0.633 (0.606-0.660)*	*<0.001*
Femur neck BMD (g/cm²)	0.582±0.012	0.656±0.018	
Reference value	*0.660 (0.640-0.680)*	*0.704 (0.678-0.730)*	*<0.001*
Femur total BMD (g/cm²)	0.572±0.013	0.629±0.017	
Reference value	*0.645 (0.630-0.660)*	*0.677 (0.649-0.705)*	*<0.001*
TB BMD (g/cm²)	0.769±0.084	0.774±0.010	
Reference value	*0.806 (0.793-0.819)*	*0.800 (0.780-0.820)*	*<0.001*
TBLH BMD (g/cm²)	0.586±0.007	0.599±0.009	
Reference value	*0.648 (0.622-0.674)*	*0.631 (0.600-0.662)*	*<0.001*

BMD: Bone mineral density, TBLH: total body less head

According to the Z score normal and -2.0 (low bone density by chronological age) bone density measurements of male and female cases were summarized in Table II. According to the L1-L4 Z score, % 78.66 (59) had normal bone density, and 21.33% (16) had low bone density (Table III).

Table II: Relationship of Gender with bone density measurements of 75 Cases with VLBW Aged 5-7 Years That Followed-Up in NICU.

	Females	Males	p-value
L1-L4 Z score	-1,050±1,64	-0,887±1,99	0.534
TB Z score	-1,100±0,23	-0,533±0,177	0.055
TBLH Z score	-1,211±0,121	-0,806±0,175	0.062
Femur neck Z score	-1,250±0,188	-0,684±0,226	0.057
Femur total Z score	-1,226±0,216	-0,551±0,174	*0.018*
L1-L4 BMD (g/cm²)	0,567±0,012	0,571±0,017	0.843
TB BMD(g/cm²)	0,769±0,084	0,774±0,010	0.674
TBLH BMD (g/cm²)	0,586±0,007	0,599±0,009	0.313
Femur neck BMD (g/cm²)	0,582±0,012	0,656±0,018	*0.001*
Femur total BMD (g/cm²)	0,572±0,013	0,629±0,017	*0.012*
L1-L4 BMC (g)	13,357±0,423	14,309±0,660	0.230
TB BMC (g)	576,10±177	625,93±266	0.125
TBLH BMC	336,34±13,47	372,76±21,83	0.313
Femur neck BMC (g)	0,94±0,37	1,04±0,05	0.117
Femur total BMC (g)	5,38±0,264	6,08±0,338	0.115
L1-L4 Z score (<-2)	10 (% 23.8)	6 (18.1%)	0.248
TB Z score (<-2)	6 (% 14.3)	1 (3%)	*0.023*
TBLH Z score (<-2)	6 (% 14.3)	4 (12.1%)	0.248
Femur neck Z score (<-2)	11 (26.2%)	4 (12.1%)	*0.003*
Total Femur Z score (<-2)	11 (26.2%)	1 (3%)	*0.001*

BMD: bone mineral density BMC: bone mineral content TB: total bone, TBLH: total body less head

Table III: Comparison of Characteristics of NICU Hospitalization According to the Results of Bone Density Measurements of 75 Cases with VLBW Aged 5-7 Years Old.

	L1 - L4 Normal	L1-L4 Low	p value
Birth weight (gr)	1199±31.77	1089±47.32	0.058
Birth week	30.28±0.31	29.81	0,422
PPV	21(35.6%)	6(37.5%)	1,000
Preeclampsia	24(40.7%)	4(25%)	0,383
Chorioamnionitis	12(20.3%)	0	0.059
Prenatal steroid	46 (78%)	12(75%)	0.749
SGA	13(22%)	5(31.2%)	0.513
RDS	45(76.3%)	13(81.2%)	0.668
Mechanical Ventilation	50(84.7%)	15(93.8%)	0.449
Sepsis	37(62.7%)	10(62.5%)	1.000
PDA	7(11.9%)	2(12.5%)	1.000
NEC	17(28.8%)	2(12.5%)	0.060
ICH	46(78%)	11(68.8%)	0.513
Inhaled steroid	24(40.7%)	6(37.5%)	1.000
Systemic steroid	11(18.6%)	2(12.5%)	0.784
ROP	6 (10.2%)	2(12.5%)	0.676
Theophylline and caffeine	31 (52.5%)	7(43.8%)	0.068
Breast milk (month)	6.02±1.09	9.77±2.76	0.215
Vitamin D (month)	14.46±0.09	17.24±2.16	0.209
Formula use (month)	12.03±2.08	14.74±2.66	0.314
Current height (cm)	111.33±0.95	107.0±1.03	*0.003*
Current weight (kg)	19.80±0.62	16.5±0.40	*0.000*
Current BMI	15.98±0.32	14.48±0.20	*0.000*
Total	59(78.66%)	16(21.33%)	

PPV: positive pressure ventilation, SGA: Small for gestational age, RDS: respiratory distress syndrome, PDA: patent ductus arteriosus, NEC: necrotizing enterocolitis, ICH: intracranial hemorrhage, ROP: retinopathy of prematurity, BMI: Body mass index

The femur total Z score (p = 0.018), femur neck BMD (p = 0.001) and femur total BMD (p = 0.012) measurements were significantly lower in females than in male patients (Figure 1).
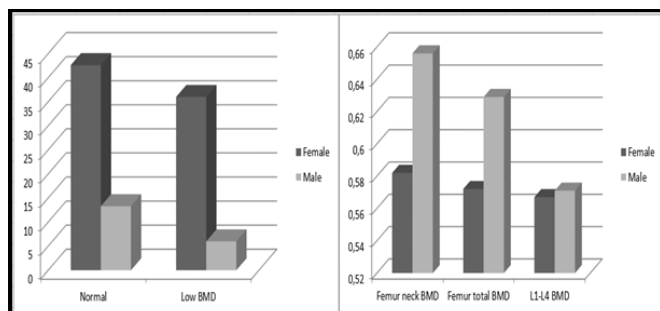

Figure 1: Classification According to Gender and Bone Density Measurement of 75 Cases with VLBW Aged 5-7 Years Old That Followed-Up in NICU and Relationship Between Femur Neck, Total Femur and L1-L4 BMD Values.

There were statistically significant differences only in current height, weight, BMI values when prenatal, natal and postnatally followed-up parameters of two groups with low and normal bone density are compared (Table III).

When bone mineral density measurements (TB, TBLH, L1-L4, femur neck and femur total BMD, BMC and Z score) of the cases were compared with the prenatal, natal and postnatal parameters no statistically significant difference was found (Table III).

When small for gestational age (SGA) and appropriate for gestational age (AGA) are compared according to the application of positive pressure ventilation (PPV) and/or mechanical ventilation, and for the history of PDA, NEC, ROP in intensive care unit follow-ups no statistical significance was found.

In a cluster receiving postpartum steroid the total body BMD value was significantly lower (p = 0.021) than the cluster non-steroid group.

When the measurements of bone density of the patients who received only breastmilk (femur neck BMD 0.662 ± 0.025) for the first six months were compared with those who received only formula (femur neck BMD 0.598±0.016) for the

first six months, those who received the breastmilk were found to be statistically significantly higher (p= 0.034) (Figure 2).
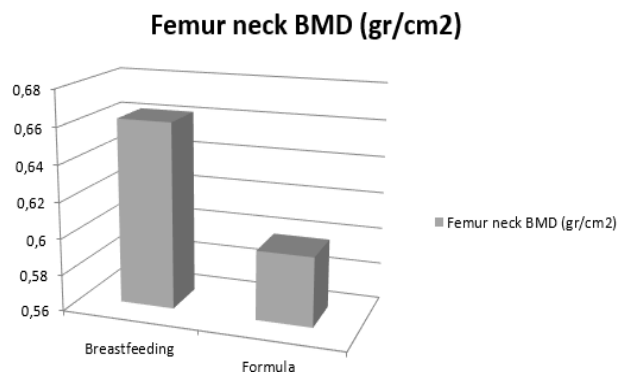

Figure 2: The Relationship of BMI, Weight, Height Percentiles with L1-L4 BMD of 75 Cases with VLBW that Followed-Up in NICU.

In children going to school (n=34) L1-L4 Z score, L1-L4 BMD, L1-L4 BMC, TB BMD, TB BMC, TBLH Z score, TBLH BMD, TBLH BMC, femur neck BMD, femur neck BMC, total femur BMD, total femur BMC values were significantly higher than who did not attend to school (p = 0.040, p < 0.001, p < 0.001, p = 0.009, p < 0.001, p = 0.041, p = 0.001, p = 0.001, p = 0.012, p = 0.004, p = 0.012, respectively).

Vitamin D, calcium, phosphorus, ALP and PTH levels that affect bone mineral density also was evaluated. There was no significant difference in BMD levels between patients (p = 0.576, p =.356, p = 0.274, p=0.255, p= 0.341, respectively).

There was a correlation between femur neck Z score (r: 0.259 p= 0.028), BMC (r: 0.276 p = 0.019), BMD (r: 0.260 p= 0.027), femur total Z score (r: 0.259 p = 0.028), BMD (r: 0.258 p = 0.028) and milk consumption in the last 2-3 weeks of the cases.

When the current height (except total body Z score), weight, BMI increment and bone density measurements were compared, significant differences were found in terms correlation between them (Table IV). There was a statistically significant difference when all bone

density parameters were compared with current height, weight and BMI percentiles smaller and greater than 10th percentile.

Table IV Evaluation of Correlation Analysis

	Birth weight	Birth week	Hospitalization duration	TPN	Breast-feeding time	Formula feeding period	Vitamin D use period	Height	Weight	BMI	Daily milk consumption
L1-L4 Z score	r:0.520 p:0.658	r:0.072 p:0.540	r:0.022 p:0.852	r:0.002 p:0.986	r:0.042 p:0.719	r:0.091 p:0.441	r:0.009 p:0.940	*r:0.490* *p:0.000*	*r:0.590* *p:0.000*	*r:0.410* *p:0.000*	r:0.133 p:0.254
TB Z score	r:0.140 p:0.232	r:0.163 p:0.162	r:0.004 p:0.972	r:0.540 p:0.647	r:0.001 p:0.992	r:0.114 p:0.329	r:0.082 p:0.483	*r:0.277* *p:0.16*	*r:0.407* *p:0.000*	*r:0.351* *p:0.002*	r:0.121 p:0.321
L1-L4 BMD	r:0.044 p:0.708	r:0.025 p:0.829	r:0.018 p:0.876	r:0.025 p:0.831	r:0.098 p:0.401	r:0.013 p:0.910	r:0.033 p:0.782	*r:0.577* *p:0.000*	*r:0.603* *p:0.000*	*r:0.320* *p:0.005*	r:0.0.88 p:0.453
L1-L4 BMC	r:0.168 p:0.149	r:0.017 p:0.817	r:0.103 p:0.378	r:0.690 p:0.554	r:0.094 p:0.422	r:0.083 p:0.481	r:0.018 p:0.880	*r:0.775* *p:0.000*	*r:0.733* *p:0.000*	*r:0.308* *p:0.007*	r:0.213 p:0.066
TB BMD	r:0.018 p:0.313	r:0.123 p:0.293	r:0.031 p:0.791	r:0.130 p:0.267	r:0.053 p:0.649	r:0.017 p:0.882	r:0.101 p:0.388	*r:0.356* *p:0.002*	*r:0.447* *p:0.000*	*r:0.306* *p:0.008*	r:0.133 p:0.254
TB BMC	r:0.116 p:0.321	r:0.080 p:0.692	r:0.046 p:0.698	r:0.026 p:0.823	r:0.142 p:0.226	r:0.065 p:0.578	r:0.006 p:0.960	*r:0.786* *p:0.000*	*r:0.811* *p:0.000*	*r:0.418* *p:0.000*	r:0.222 p:0.056

TB BMC: Total Body bone mineral content, TB BMD: total bone mineral density, TPN: Total parenteral nutrition

DISCUSSION

In recent years, osteopenia has become an important topic in childhood. One of the risk factors causing osteopenia is premature birth[15]. In the literature, in the evaluations of bone mineralization of preterm infants in childhood age group osteopenia rates are not given but BMD and BMC ratios of these cases were evaluated. In this study, in comparison of 5-7 years children born preterm and VLBW with healthy children of the same age, the bone densities according to L1-L4 Z score was low in 21.33%.

Bone density measurement values of our cases were lower than the reference values of DXA device. Breukhoven et al.[17] reported in their study of 18-24 years old patients with preterm birth that preterm birth did not affect their adult bone health. In the study of Erlanson et al.[18], in children between the ages of 8-15 years proximal femur BMC value was significantly lower in males with preterm birth, but there was no difference between groups when age,

maturity, weight, physical activity and nutrition were added into consideration. However, Bowden et al.[15] showed in their study that children with preterm birth had low lumbar vertebrae BMC values at the age of 8 years. In the study of Weiler et al.[19] children born with low birth weight at their 16-19 years, total body, lumbar and total femur BMC values were reported to be lower than children with born at term. Xie et al.[20] showed that low BMD at any site was observed in 53% of adults born preterm versus 28% of full-term controls.

When the total femur Z score, femur neck BMD, total femur BMD values of females were compared, it was found that they were significantly lower than the males; it might be related to the lower BMI and weight of females.

In a group receiving postoperative systemic steroids TB BMD had lower values than the non-steroid group; it may be associated with negative effects of steroid use and chronic lung diseases on bone health. In the study of Eeloo et al.[16], similar to our study, significantly low

lumbar spinal bone mineral density measurements were found according to DXA evaluation when children aged 5-8 years with VLBW who received steroid therapy due to chronic lung disease compared with preterm control group not receiving steroid therapy.

In the comparison of cases receiving only breastmilk or formula in the first six months, the femur BMD value was significantly higher in the group receiving only breastmilk. In one study, 5-year-old children with VLBW with breast milk after birth have been reported to have higher bone mineral content in wrists.[21] Fewtrel et al.[22] reported in their study of 12-years old children with preterm birth that there was no correlation between total body BMC and early life feeding. Christmann et al.[23] were found that at 9 to 10 years the mean bone mass SDS measured for total body and lumbar vertebrae was within the normal range and seemed not related to nutritional intake.

In children attended school, L1-L4 BMD, L1-L4 BMC, TB BMD, TB BMC values were significantly higher than who did not attend school. Cells that are sensitive to mechanical stress needed to be stimulated for bone production. For this reason, physical movements such as running, jumping, rope jumping and gymnastic movements which make the bone surfaces stretch, are of great importance especially in childhood and adolescence period where bone formation is accelerated. Therefore, there is an absolute need to improve the duration and quality of physical education classes in schools[24].

One of the reasons why it is hard to determine the effect of preterm birth on bone mineralization is the effect of current body mass of the person[25]. In this study, weight, BMI and height of the cases were within normal ranges according to norms of healthy Turkish children of their age[26]. Current weight and BMI of females were found to be lower than males. Erlandson et al.[18] in their study found that preterm females had lower weight when compared to males and control group.

In this study, the correlation was found between height, weight, BMI and bone measurements. As in the study by Kurl et al.[6], significant variables between BMC, BMD and Z scores were due to current weight, height and BMI of the cases. The most important determinants of the effects of preterm birth on bone mineralization are current weight, height and BMI[24].

CONCLUSION

Osteoporosis is a public health problem that has an increasing importance in both developed and developing countries. The fact that VLBW and premature children cannot surviving the last trimester of pregnancy, negatively affects bone health both postpartum and in childhood. In our study, it was shown that bone diseases, which are one of the increasing complications in VLBW and preterm infants, affect growth and bone mineralization in postpartum and long term. We determined the effects of the diseases seen in VLBW and premature births, drugs used in the treatment and nutrition, current anthropometric measurements (height, weight and BMI) on bone health. VLBW and premature births should be monitored closely until the adolescence period in order to reduce the risk of decrement either in bone mineralization and peak bone mass in the adult period.

Ethics Committee Approval: The local research and ethics committee approved the study protocol, and the study was conducted following the ethical principles described by the Declaration of Helsinki.

Declaration of Conflicting Interests: The authors declare that they have no conflict of interest.

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