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Impact of intra- and extrauterine growth on bone mineral density and content in the neonatal period of very-low-birth-weight infants

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ABSTRACT

Background: Very-low-birthweight infants (VLBWIs) are at high risk for suboptimal bone mineral density (BMD) and bone mineral content (BMC). Small-for-gestational-age (SGA) status also causes reduced bone mineralization in full-term infants. However, the impact of intrauterine and postnatal extrauterine growth on BMD and BMC in VLBWIs is inconclusive.

Methods: We retrospectively investigated n = 68 VLBWIs, comprising 45 appropriate-for-gestational-age (AGA) and 23 SGA infants who underwent lumbar spine dual-energy X-ray absorptiometry at term-equivalent age.

Results: BMD and BMC did not differ between AGA and SGA VLBWIs. Subgroup analyses of infants with birthweight < 1000 g vs 1000–1500 g, and GA < 27 weeks vs ≥27 weeks also showed no differences in BMD and BMC between AGA and SGA infants. In contrast, infants with extrauterine growth restriction (EUGR) showed significantly lower values than those without (BMD: 0.124 ± 0.023 vs 0.141 ± 0.032 g/cm^2, P = 0.02; BMC: 0.80 ± 0.26 vs 0.94 ± 0.23 g, P = 0.04). There were no differences between AGA and SGA infants with EUGR. However, in the AGA cohort, infants with EUGR showed significantly lower values than those without (BMD: 0.121 ± 0.022; 0.141 ± 0.03 g/cm^2, P = 0.02; BMC: 0.73 ± 0.23 vs 0.94 ± 0.23 g, P = 0.005). Multiple regression analyses showed GA, weight and head circumference at birth, and weight percentile at term correlated with term BMD. Conversely, only weight percentile at term significantly correlated with term BMC.

Conclusion: EUGR, rather than IUGR, is a risk factor for reduced BMD and BMC in the neonatal period in VLBWIs.

1. Introduction

Metabolic bone disease of prematurity (MBDP) is a complication observed in preterm infants, causing subnormal bone mineral density (BMD) and bone mineral content (BMC) from birth until mid-childhood [1–4]. Although MBDP may be asymptomatic and self-limiting [5], evidence has emerged linking premature birth, especially in very-low-birthweight (<1500 g) infants (VLBWIs), and increased risk for osteoporosis in adulthood [4,6–9]. BMD, an areal density measurement, commonly refers to bone mass, while BMC, the actual mineral content, refers to the total amount of bone mineral [10]. Decreased BMC from infancy to adulthood in VLBWIs results in lower peak bone mass, which is associated with lower BMD in later life [4,6,7]. This risk is negatively associated with infant birthweight [3,6,7] and gestational age (GA) [4,6,11]. There is also evidence that small-for-gestational-age (SGA) status, predominantly resulting from intrauterine growth restriction (IUGR), could affect fetal bone metabolism [9,12–14]. IUGR is a consequence of a range of maternal or placental conditions that are known to predispose to inadequate intrauterine skeletal mineralization [9,15]. Postnatal growth is also an independent determinant of BMD and BMC in both term and preterm infants [6,16]. However, despite the contribution of improved nutrition to increased rates of neonatal survival of VLBWIs, these infants remain at risk of suboptimal postnatal growth, termed extrauterine growth restriction (EUGR) [17].

Nutritional imbalance and growth restriction during critical windows in the fetal and neonatal period are adversely associated with long-term developmental deficits and morbidity in later life [12]. Chronic deficiencies in transplacental minerals, nutrition and oxygen supply to the fetus result in reduced cord serum 1,25-dihydroxyvitamin D (1,25-$(OH)_2$D) and osteocalcin concentrations [18]. Subsequently, lower BMD [19,20] and BMC [18,21] are recorded in SGA infants from birth to early childhood compared with appropriate-for-gestational age (AGA) infants. The effects of IUGR on altered MBDP become diminished as gestation is prolonged [1], however recent epidemiological studies show that restricted growth patterns in early life may reduce

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bone accretion and deteriorate peak bone mass, resulting in increased risk of future osteoporosis [7–9]. Very few studies have investigated how intrauterine and subsequent extrauterine growth impact later bone health in VLBWIs [22,23]. The importance of this research is becoming more apparent as the first generation of VLBW survivors who received modern neonatal care reach middle age. We aimed to examine the impact of intrauterine and postnatal growth on bone mineralization and bone mass accretion in VLBWIs to find suitable strategies to improve their long-term skeletal outcome.

2. Patients and methods

Sixty-eight VLBWIs (GA 27.4 ± 2.5 weeks, birthweight 912 ± 250 g) discharged from the neonatal intensive care unit of Yodogawa Christian Hospital, Osaka, between 2006 and 2010 were retrospectively investigated. All infants underwent dual-energy X-ray absorptiometry (DXA) of the lumbar spine at term-equivalent age (36 weeks + 0 days to 41 weeks + 6 days of postmenstrual age, calculated with respect to the mother's last menstrual period). Children with major congenital malformations, metabolic diseases, moderate to severe cerebral palsy or who required total parenteral nutrition for >4 weeks were excluded. Each child's GA, birthweight, length, head circumference (HC), gender, singleton or twin status and weight and length at DXA measurement were documented. All anthropometric measurements were performed twice, and the mean value was used for analysis. Weight at birth and term age at DXA measurement were converted to percentiles based on Japanese anthropometric references for preterm-born infants and were adjusted for gender and GA [24]. Infants were classified as either AGA or SGA; AGA was defined as birthweight within the 10th to 90th percentiles of the reference values, and SGA below the 10th percentile [25]. EUGR was defined as weight below the 10th percentile of the reference values at term age on DXA measurement [17].

2.1. Dual-energy X-ray absorptiometry

BMD (g/cm^2) and BMC (g) for the lumbar spine (L2–L4) were measured in the supine position with DXA using Hologic QDR Discovery-A (Hologic, Bedford, MA), which was calibrated daily. BMD was derived by dividing BMC by vertebral cross-sectional area. Measurements were performed while the baby was asleep whenever feasible; if required, sodium triclofos (50–80 mg/kg) was used as a sedative to avoid movement artifacts.

2.2. Nutritional management during admission

Fluids with glucose and electrolytes were intravenously administered after birth, and parenteral nutrition with amino acids and lipids started within 72 h after birth. Breast milk supplemented with human milk fortifier (HMS-1; Morinaga, Tokyo) and/or premature formula (GP-P, Morinaga, Tokyo) were given enterally. Serum calcium, inorganic phosphorus, and alkaline phosphatase (ALP) levels were measured at least once a week, and calcium gluconate and potassium phosphate were supplemented orally or intravenously to keep calcium levels within 8.0–10.5 mg/dl, and inorganic phosphorus levels within 3.5–6.0 mg/dl. Alfacalcidol (200 IU/kg) was also given to all infants daily. Serum alkaline phosphatase levels were measured once a week.

2.3. Clinical data during admission

The need for oxygen at ≥36 weeks of corrected GA, PDA ligation, history of intestinal perforation, need for furosemide for ≥2 weeks, total dose of hydrocortisone administered (the only steroid administered) and the maximum serum ALP level during admission were documented.

2.4. Statistical analyses

All analyses were performed with JMP 11 statistical software (SAS, Cary, USA). BMD and BMC at term were examined in SGA and AGA infants together with their anthropometric measurements and clinical features and in subgroups of birthweight < 1000 g vs. 1000–1500 g, GA < 27 weeks vs. ≥27 weeks and with EUGR vs. without EUGR. The Student's *t*-test or non-parametric Mann–Whitney test was used for quantitative parameters and Fisher's exact test for qualitative variables. Data are presented as mean ± standard deviation. $P < 0.05$ was considered statistically significant. Multiple linear regression analysis was performed to determine independent variables significantly explaining the variance in BMD and BMC at term age. Multiple correlation coefficient, r, was used to assess the associations.

2.5. Ethics

The study was approved by the Ethics Committee of Yodogawa Christian Hospital, and written parental informed consent was obtained for all infants.

3. Results

3.1. Demographic data, anthropometric measurements and clinical features (Table 1)

Of the 68 VLBWIs, 45 were classified AGA and 23 SGA. While GA was higher in SGA than in AGA infants, no significant differences in birthweight, length, HC or clinical features were found. For DXA measurements at term age, SGA infants had significantly lower weights than did AGA infants. No differences in BMD (Fig. 1-a), BMC (Fig. 1-b) or length between AGA and SGA were observed.

Table 1
Comparison of demographic data, clinical features during admission, BMD, and BMC between AGA and SGA VLBWIs.

	AGA (n = 45)	SGA (n = 23)	P-value
Characteristics at birth			
GA (weeks)	26.7 ± 2.0	28.6 ± 3.0	0.004
Weight (g)	946 ± 241	844 ± 259	0.11
Weight (percentile)	47.5 ± 21.1	4.1 ± 5.0	<0.001
Length (cm)	33.7 ± 4.4	33.2 ± 3.0	0.67
HC (cm)	24.4 ± 2.8	25.3 ± 2.9	0.25
Female, n (%)	27 (60)	15 (65)	0.79
Twin, n (%)	12 (27)	8 (35)	0.58
Clinical features during admission			
Need for oxygen at ≥36 weeks of GA, n (%)	16 (36)	10 (43)	0.60
PDA ligation, n (%)	10 (22)	1 (5)	0.09
Intestinal perforation, n (%)	3 (7)	0 (0)	0.55
Total dose of hydrocortisone administration (mg/kg)	10.3 ± 14.4	9.5 ± 15.9	0.85
Furosemide administration ≥ 2 weeks, n (%)	32 (71)	16 (70)	1.00
Maximum serum ALP level (IU/l)	2222 ± 853	2437 ± 871	0.16
DXA measurements at term			
Postmenstrual age (weeks)	39.6 ± 1.4	40.0 ± 1.2	0.29
Weight (kg)	2.41 ± 0.36	2.08 ± 0.30	<0.001
Height (cm)	44.1 ± 2.6	43.0 ± 3.3	0.18
BMD (g/cm^2)	0.129 ± 0.028	0.128 ± 0.024	0.89
BMC (g)	0.82 ± 0.25	0.87 ± 0.27	0.46

AGA: appropriate for gestational age; ALP: alkaline phosphatase; BMC: bone mineral content; BMD: bone mineral density; DXA: dual-energy X-ray absorptiometry; GA: gestational age; HC: head circumference; PDA: patent ductus arteriosus; SGA: small for gestational age.