

Bone Mineral Content at Birth Is Determined Both by Birth Weight and Fetal Growth Pattern

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ABSTRACT: Adult peak bone mass is related to birth weight, suggesting it could be affected by fetal growth pattern. Small-for-gestational-age (SGA) newborns have lower bone mineral content (BMC), but what about adapted-for-gestational-age (AGA) newborns with fetal growth restriction? The purpose of the study was to determine the respective role of birth weight and fetal growth pattern on BMC. Full-term newborns from SGA high-risk pregnancies were included ($n = 185$). Estimated fetal weight percentiles were measured monthly from mid-gestation to birth, and restricted fetal growth (FGR) was defined as a loss by more than 20 percentiles. BMC was measured at birth, using dual x-ray absorptiometry. Newborns were SGA ($n = 56$) or AGA ($n = 129$). Newborns with FGR ($n = 111$) were AGA ($n = 71$) or SGA ($n = 41$). BMC was significantly lower in SGA than AGA (1.48 ± 0.02 vs. 1.87 ± 0.04 g/cm) and lower when FGR irrespective of birth weight (1.66 g/cm ± 0.03 vs. 1.89 g ± 0.05). In multivariate analysis, FGR and SGA were significant and independent predictors of low BMC. In conclusion, fetal growth pattern affects BMC not only in SGA infants but also when birth weight is maintained in the normal range. (*Pediatr Res* 64: 86–90, 2008)

The peak bone mass of an individual depends upon growth and mineralization during the first two decades of life. However, a proportion of the variance of bone mineral content (BMC) found in the general population cannot be explained by genetic factors or childhood environment (1,2). Epidemiologic studies have suggested that part of this residual variation might be explained by the growth pattern in infancy (3) and probably during fetal development. Linear fetal growth is high during the last two trimesters of pregnancy, and fetal bone mineralization increases toward the end of pregnancy (4). Previous studies on a small number of newborns have shown that being born small for gestational age (SGA) was for a strong determinant of bone metabolism. BMC is lower in SGA infants at birth and is associated with a decrease in osteocalcin plasma level, suggesting that fetal mineralization is affected by fetal growth pattern (5,6). Moreover, prospective data in adult subjects indicate that bone mass and BMC

are associated with birth weight after adjustment for environmental factors and body size at the time of investigation (7). However, birth weight results from fetal growth *in utero*. In addition, to gestational age and gender, other pregnancy characteristics, such as maternal height and weight before pregnancy, parity and ethnicity account for a large part of variation in fetal growth velocity and weight at birth. On the one hand, small babies who are small simply as a result of adaptation to maternal size can be separated from those who have suffered from restricted fetal growth (FGR). On the other hand, infants with appropriate for gestational age (AGA) birth weight can fail to reach their genetic potential of growth because of a real FGR. Birth weight by itself is not sufficient to identify FGR then. It has recently been shown that customized fetal growth estimation, adjusting for maternal and fetal characteristics, allows precise evaluation of fetal growth restriction by identifying newborns who have failed to reach their genetic potential of growth (8–10) and newborns at high risk of adverse perinatal outcome. The purpose of this study was to determine the respective roles of birth weight and FGR on BMC at birth, using the method of customized fetal growth. We hypothesized that not only birth weight *per se* but also FGR would affect BMC at birth.

METHODS

Subjects. The study population consists of 185 newborns included between May 2004 and May 2007 in the CASyMIR cohort, a French prospective cohort exploring the metabolic consequences of being born SGA in early infancy. The infants were born from white women recruited during their first or second trimester of pregnancy in the maternity of the Robert Debré Hospital in Paris and considered as high risk of SGA pregnancies. The inclusion criteria were preexisting hypertension, smoking more than five cigarettes per day, a history of SGA in a previous pregnancy or among both parents, a history of pregnancy-induced hypertensive disorder, maternal height less than 152 cm corresponding to 2 SD for French women, uterine malformations, abnormal uterine or umbilical uterine arteries Doppler, and small fetal size at second trimester ultrasound examination. The date of conception was determined from the ultrasound examination performed at 12 wk of gestation.

Birth weight of newborns was recorded within 10 g by midwives, using an electronic scale. Birth length was measured on a standard infants' measuring board within millimeter. Dual x-ray absorptiometry scan was performed in all

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Abbreviations: AGA, appropriate for gestational age; BMC, bone mineral content; CMC, cephalic mineral content; EFW, estimated fetal weight; FGR, restricted fetal growth; IG, intermediate fetal growth; NG, regular fetal growth; SGA, small for gestational age; TLMC, trunk and link mineral content

newborns on the third day of life. The study protocol was approved by the ethical committee of Paris—Saint Louis Medical School (Paris 7 University), and all parents gave written informed consent.

Assessment of fetal growth. Fetal growth was assessed every 4 wk by ultrasound from 22 to 36 wk of gestation. All four ultrasound scans were performed by the same observer for each woman under a standardized protocol according to the guidelines of College des Echographistes de France (Rapport du comité technique de l'échographie de diagnostic prénatal, collège français d'échographie fœtale, Avril 2005, www.cfef.org). Estimated fetal weight (EFW) was calculated using the second Hadlock formula, which includes abdominal, head circumferences, and femur length measurements (11). The customized fetal and birth weight percentiles were calculated for each case with a computer program that adjusts for parity, gender, maternal weight and height, and ethnic group March 2007 (Gestation related optimal weight program. Software version 5.15 and Centile calculator software v5.12.1 March 2007, www.gestation.net). Coefficients for these physiologic variables (based on 40,000 ultrasound-dated pregnancies from Nottingham) are contained in the software. Intrauterine growth velocity was calculated as the change in EFW percentiles from 22 wk of gestation until birth (12). Fetal growth restriction was defined as a reduction of EFW by 20 percentiles or more and newborns were divided into three groups: newborns with no reduction of EFW percentile [regular growth (NG)], newborns with a reduction in EFW by less than 20 percentiles [intermediate growth (IG)], and newborns with a reduction in EFW by 20 percentiles or more (FGR). At birth, SGA was defined as birth weight equal or below the 10th and AGA—above the 10th percentile according to the French reference curves (13).

Measurement of body composition. All BMC measurements were performed by using the same dual x-ray absorptiometry scan (Lunar Prodigy DXP Pro, GE medical Systems, Madison, WI). Scans were analyzed by using a specific software for small body weight (14,15). Radiation dose was 1.8 μ Gy according to the constructor. Coefficient of variation for BMC measurement is around 1.95% in animal studies (16) and around 2.4% for newborns *in vivo*, according to literature (17). Daily quality assurance tests were performed prior measurements. Newborns were placed in the supine position and the whole body was scanned, beginning at the top of the head and moving in a rectilinear pattern down the body to the feet. No sedation was used. Measurements were performed having the baby asleep. If significant movement were encountered, the scan was stopped and repeated. Total body mineral content was measured in grams. The total body scan area was divided into two regions of interest selected and analyzed separately: the head or cephalic mineral content (CMC) and the rest of the body (trunk, pelvis, upper and lower limbs) or trunk and limbs mineral content (TLMC). For head segmentation, a horizontal line above the shoulders was adjusted to immediately below the chin. BMC, CMC, and TLMC were measured in grams and are expressed as grams per centimeter of body size to adjust to body size.

Statistical analysis. All analyses were performed using the JMP software version 5.1 (SAS Inc. Meylan, France). Data are given as mean \pm SD. Chi-square test was used to compare proportions between groups. Continuous variables were compared using analysis of variance in univariate models. To further assess the effect of birth weight and fetal growth restriction on BMC, a multivariate linear model was built including gestational age, gender, maternal smoking, and seasonality at birth as covariates.

RESULTS

Mineral content related to birth weight and fetal growth.

The subjects' characteristics are shown in Table 1. One hundred eighty-five full-term newborns have been included in this study (92 boys and 93 girls). In this population, 56 infants were classified as SGA and 129 as AGA. Using our criteria, 73 newborns experienced normal or subnormal growth. By contrast, 112 newborns experienced FGR. Gestational age and gender were not different between the three groups, whereas caesarean sections were more frequent in the FGR group than in the IG and NG groups (28.6% vs. 18.7% and 10.2%, respectively $p = 0.0028$). FGR was present in most of the SGA newborns (77%) and in 55% of AGA subjects. In both SGA and AGA, the main risk factors of fetal growth restriction were maternal smoking, abnormal Doppler measurements, and history of SGA in previous pregnancies.

Figure 1 shows BMC according to birth weight. As ex-

Table 1. Characteristics of the subjects (data are given as mean \pm SD)

	Mean	SD
N	185	
Gestational age (wks of gestation)	38.9	1.87
Sex (M/F)	92/93	
Birth weight (g)	3004	561
Birth length (cm)	48.5	2.39
Head circumference (cm)	33.97	1.52
Ponderal index (g/cm ³)	26.42	2.33
Caesarean section n (%)	45 (24.3)	
Fetal growth and birth weight pattern	N	
AGA	129	
+ Regular growth (NG*)	44	
+ Intermediate growth (IG [†])	14	
+ Restricted growth (FGR [‡])	71	
SGA	56	
+ Regular growth (NG*)	8	
+ Intermediate growth (IG [†])	7	
+ Restricted growth (FGR [‡])	41	

* No reduction of estimated fetal weight percentile.

[†] IG: reduction of estimated fetal weight by less than 20 percentiles.

[‡] FGR: reduction of estimated fetal weight by 20 or more percentiles.

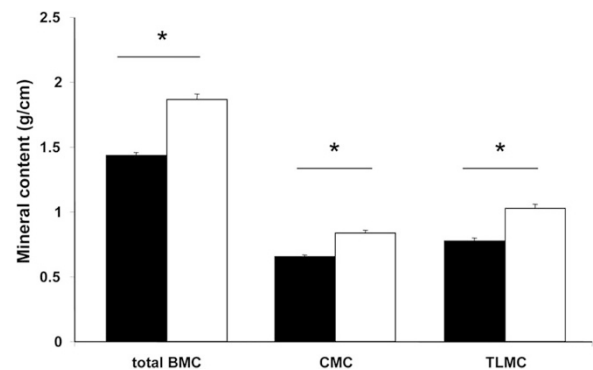


Figure 1. Total bone mineral content (total BMC), Cranium mineral content (CMC) and trunk and limbs mineral content (TLMC) in SGA newborns (■) and AGA newborns (□). * $p < 0.05$, adjusted for gestational age and gender.

pected, total BMC was lower in SGA infants than in AGA newborns (1.48 ± 0.02 g/cm vs. 1.87 ± 0.04 g/cm). CMC and TLMC were studied separately, to further analyze which body compartment was affected by fetal growth restriction. CMC and TLMC were both lower in SGA children (CMC: 0.66 g/cm \pm 0.01 in SGA vs. 0.84 g/cm \pm 0.02 in AGA; TLMC: 0.78 g/cm \pm 0.02 in SGA and 1.03 g/cm \pm 0.03 in AGA).

Figure 2A shows total BMC, CMC, and TLMC of the infants with respect to fetal growth irrespective of birth weight. BMC was not significantly different between NG and IG groups. However, it was decreased in case of FGR irrespective of birth weight. Total BMC was lower in FGR group (1.66 g/cm \pm 0.03) compared with IG and NG group, (1.86 g \pm 0.04 and 1.89 g \pm 0.05 , respectively). The lower total BMC in newborns with restricted growth was associated with a decrease in BMC of trunk and limbs. TLMC was lower in FGR group (TLMC: 0.89 g/cm \pm 0.02 in FGR, 1.04 g/cm \pm 0.03 in IG, and 1.06 g/cm \pm 0.03 in NG), whereas CMC was not significantly different between the groups. Similar results were found when comparing BMC, CMC, and TLMC in AGA newborns among different patterns of fetal growth (Fig. 2B). BMC and TLMC were lower

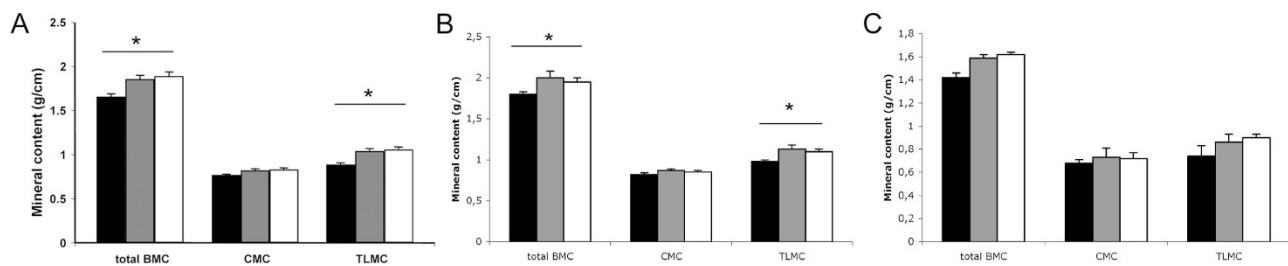


Figure 2. Total bone mineral content (total BMC), Cranium mineral content (CMC) and limbs and trunk mineral content (TLMC) and fetal growth pattern, in the whole cohort (A) and in relation with birth weight: AGA newborns (B) or SGA newborns (C) regular growth (NG, □); intermediate growth (IG, ▒); restricted growth (FGR, ■) (* $p < 0.05$, adjusted for gestational age and gender).

in the FGR groups (BMC: $1.8 \text{ g} \pm 0.03$ in FGR, $2.0 \text{ g} \pm 0.08$ in IG, and 1.95 ± 0.05 in NG; TLMC: $0.98 \text{ g/cm} \pm 0.02$ in FGR, $1.13 \text{ g/cm} \pm 0.05$ in IG, and $1.10 \text{ g/cm} \pm 0.03$ in NG). In SGA newborns, BMC and TLMC were lower as well in FGR (Fig. 2C), but this difference did not reach statistical significance because of the small number of SGA babies in IG and NG groups (BMC: $1.42 \text{ g/cm} \pm 0.04$ in FGR, $1.59 \text{ g/cm} \pm 0.03$ in IG, and $1.62 \text{ g/cm} \pm 0.09$ in NG; TLMC: $0.74 \text{ g/cm} \pm 0.03$ in FGR, $0.86 \text{ g/cm} \pm 0.08$ in IG, and $0.9 \text{ g/cm} \pm 0.07$ in NG).

Determinants of mineral content. Determinants of mineral content at birth were assessed using a multivariate analysis (β coefficients and adjusted p values are shown in Table 2, where BMC was adjusted for neonatal and maternal factors). Fifty-seven percent of the variance of BMC at birth was explained by the significant determinants included in the model: gestational age, being SGA, FGR, and maternal smoking ($r^2 = 0.57$, $p < 0.0001$). As expected, BMC was strongly correlated to SGA status, but was also associated to fetal growth restriction in both SGA and AGA newborns. SGA was independently and significantly associated with a decreased of BMC by -0.0099 g/cm ($p < 0.0001$) and FGR with a decreased by -0.006 g/cm ($p = 0.001$). Moreover, the effect of FGR was further accentuated in SGA newborns (-0.003 g/cm , $p < 0.0001$) as evidenced by the statistical negative interaction between SGA or AGA and FGR. BMC was also significantly associated to lower gestational age and maternal smoking during pregnancy. BMC, however, was not related to the season of birth or to the way of delivery nor to maternal BMI.

DISCUSSION

Factors associated with BMC were studied in newborns and we report that both birth weight and fetal growth pattern affect BMC. BMC is reduced not only in SGA but also when birth weight is maintained in the normal range after fetal growth restriction. BMC in children and in adults is affected by intrauterine and early postnatal events. In a cohort of adults, it has been reported that birth weight was a significant predictor of BMC some seven decades later (7). This relationship was independent of known adult lifestyle determinant of bone loss such as physical activity, low calcium intake, or cigarette smoking. It also remained significant after adjustment for age, gender, and adult height, suggesting that intrauterine environmental factors that influence the fetal growth pattern could have long-term effects. This lower BMC seems to be present already at birth in subjects born SGA. Indeed, in the present

Table 2. Determinants of BMC at birth by multivariate analysis

	BMC at birth (g/cm)	
	β coefficient	p
Total model		<0.0001
Gestational Age (weeks)	0.103	<0.0001
Gender		
Female (vs. Male)	-0.02	0.16
Birth weight pattern		
SGA (vs. AGA)	-0.099	<0.0001
Fetal Growth pattern		
Restricted growth FGR (vs. regular growth NG)	-0.06	0.001
Intermediate growth IG (vs. regular growth NG)	0.007	0.78
Season of birth		
Spring (vs. Winter)	0.02	0.93
Summer (vs. winter)	-0.03	0.1
Autumn (vs. winter)	0.04	0.15
Maternal smoking	-0.037	0.04
Maternal BMI (kg/m ²)	0.006	0.13
Caesarian section	-0.002	0.85
Interaction between Birth weight pattern and fetal growth pattern	-0.003	<0.0001

Total r^2 of the model = 0.57.

study, BMC at birth was lower in SGA newborns than in AGA newborns. We hypothesized that BMC could be additionally affected by fetal growth restriction, a feature that can be observed not only in SGA infants but also in AGA infants. For the purpose of the study, FGR was defined as the failure to reach the genetic potential of growth using the customized fetal growth method. Fetal growth was monitored in a prospective way in all pregnant women. The EFW and the corresponding percentile were calculated from the data collected during antenatal ultrasound examinations using the method of the customized percentiles. Using this method, we were able to identify fetal growth restriction both in AGA and SGA newborns. FGR was associated with decreased total BMC (both in AGA and SGA newborns), which was related to a reduced mineral content in limbs and trunk, whereas CMC was maintained as previously reported (18). Moreover, fetal growth restriction remained a significant and independent predictor of low BMC irrespective of birth weight. Finally, both reduction in birth weight and in fetal growth affect BMC, the effect of FGR being even amplified in SGA newborns, as attested by the statistical interaction between these two parameters.

It has been previously reported that children born SGA have lower BMC and decreased bone formation marker (osteocalcin) compared with those born AGA even after allowing for seasonal variation (5). Osteocalcin gene is expressed in the late phase of bone formation (differentiation and mineralization period). Cord serum 1,25-(OH)₂ vitamin D, the active metabolite of vitamin D that enhances uteroplacental calcium transfer, is lower in SGA than in AGA infants (19). One could think that the lower IGF-1 levels reported in SGA could affect collagen synthesis and bone matrix apposition rates. Indeed, IGF-1 stimulates preosteoblast cell replication and enhances osteoblastic collagen type 1 synthesis by increasing type 1 collagen transcript levels in osteoblasts (20,21). But, serum biochemical indices of collagen synthesis and degradation are similar in SGA and AGA children (22). Taking together, these data emphasize that reduced BMC in SGA infants is predominantly related to low mineral supply rather than defective matrix synthesis. We can speculate that in the present study, BMC is lower in the FGR group for the same reason.

During pregnancy, minerals are actively transported across the placenta to the fetal circulation against a concentration gradient and the fetus is totally dependent on maternal resources to acquire Ca²⁺, P, and Mg. The rate of maternofetal Ca²⁺ transfer increases dramatically during the last trimester of pregnancy (from 24 wk to term gestation), with a peak accretion rates between 36 and 38 wk gestation (19). Approximately, two-thirds of total body Ca²⁺ accumulated in a healthy term human fetus is transported during the last trimester of pregnancy (23). Conditions affecting placenta nutrient transfer at that time are also likely to affect fetal bone mineralization. According to our results, in the FGR group, the main risk factors were uteroplacental vascular abnormalities and maternal smoking. Maternal smoking, reported to influence skeletal growth, acts through different mechanisms. The most widely cited are impaired placental function, reduced uteroplacental blood flow, or effects on fetal oxygen carrying capacity (24,25). Another reported mechanism is a potential toxic effect of the heavy metal cadmium on fetal skeletal growth. Cadmium is present in high concentration as a contaminant in tobacco and has specific effects on trophoblast calcium transport (26).

Determination of factors affecting BMC is important because osteoporosis as a risk factor for fracture is still a public health problem (27). The strong association between birth weight and BMC is pointing to the importance of fetal growth on skeletal development. Here, we have reported for the first time that impaired fetal growth has an impact on BMC irrespective of birth weight. An association between early postnatal growth and BMC was previously reported (28,29). Weight at 1 y has been reported as a significant predictor of BMC in the lumbar spine and femoral neck of women and lumbar spine in men some seven decades later in the Hertfordshire cohort (3). Accelerated growth in the first year has been furthermore associated with greater bone size and strength as assessed by peripheral quantitative computed tomography (30). In a Finnish cohort, childhood growth velocity was a major determinant of hip fracture risk in elderly (31). Taking together, these data support the concept that fetal and

early postnatal growth determines BMC, bone growth, and the risk of osteoporosis later in life. Our results suggest that fetal growth could modulate this risk even when birth weight is protected within the normal range. Calcium supplementation in women with adequate dietary calcium intake during the pregnancy has shown to have no effect on BMC in newborn (32). The effect of calcium supplementation during childhood on fracture risk is still debated (33,34). Therefore, appropriate diet and medical assessment of postnatal growth seems to be the best medical practice in this situation.

In conclusion, fetal growth restriction is an important determinant of BMC at birth and can be considered as an independent predictor of fetal bone mineralization even when birth weight is maintained within the normal range. This effect is independent of low birth weight making the SGA babies with fetal growth restriction the more at risk of low BMC.

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