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Small-for-gestational-age preterm-born infants already have lower bone mass during early infancy ☆,☆☆,★

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ABSTRACT

Background: In preterm-born infants, low birth weight and diminished bone accretion deteriorate peak bone mass. Whether low birth weight is already associated with decreased bone mass during infancy is unknown.
Objective: To study the effect of birth weight on bone accretion between term age (40 weeks postmenstrual age) and six months post-term in preterm-born infants.
Design: In 139 preterm-born infants (51% male, gestational age 30.3 ± 1.5 weeks, birth weight 1341 ± 288 g) weight and whole-body bone mineral content (BMC, gram) were measured at term age and six months post-term. At birth, infants were small-for-gestational-age (SGA, n = 33, weight and/or length < −2 SDS) or appropriate-for-gestational-age (AGA, n = 98, weight and length ≥ −2 SDS).
Results: At term age and six months post-term, BMC adjusted for gender and gestational age was lower in SGA than AGA infants (term age: 38.1 ± 9.5 versus 48.6 ± 10.1 g, β = −0.26, 95% CI −0.37; −0.16, p < 0.001; six months: 130.1 ± 25.7 versus 145.4 ± 22.9 g, β = −0.16, 95% CI −0.25; −0.08, p < 0.001). At six months post-term, BMC remained lower in SGA infants after adjustment for actual weight and length. Between term age and six months post-term, BMC gain adjusted for gender and gestational age was lower in SGA than AGA infants (91.7 ± 22.8 versus 98.2 ± 20.7 g; β = −0.12, 95% CI −0.24; −0.003, p = 0.044). BMC gain remained lower in SGA infants after adjustment for weight and length gain.
Conclusion: The first six months post-term, SGA preterms have lower bone accretion, independent of body size, suggesting that prenatal conditions for bone accretion cannot be replicated postnatally.

Introduction

Preterm-born infants are prone to suboptimal bone mass. Preterm birth is frequently preceded by intra-uterine growth retardation, which is associated with inadequate intra-uterine bone formation and a smaller skeleton at birth. In addition, preterm-born infants are deprived of the intra-uterine third trimester, which is essential for 80% of the total bone mass of the newborn [1]. During the postnatal extra-uterine third trimester, mineral intake of preterm-born infants is insufficient for bone mass accretion, which aggravates the already present bone mineral deficit. During infancy and childhood, preterm-born children have lower bone mass accretion compared to their term-born peers [2–5]. This decreased bone mass tracks from infancy to adulthood resulting in lower peak bone mass in preterm-born adults [6–8], which is associated with a higher risk of osteoporosis [9].

During infancy, bone mass accretion can to a certain extent be modified by feeding and growth. The type of feeding provided during early infancy influences bone mass accretion, as emphasized by lower bone mineral content (BMC) in preterm-born infants fed human milk compared to formula [10–12] and by higher BMC in preterm-born infants fed nutrient-enriched formula compared to standard formula [13–15].

Bone mass accretion can also be modified by prenatal and postnatal growth trajectories. In term-born infants, fetal growth and low birth weight, as a proxy of intra-uterine growth, are associated with lower bone mass and decreased estimated bone strength at adult age [16–19]. In preterm-born infants, low birth weight is associated with decreased bone mass at term age and with lower bone mineral density (BMD) at 20 years of age [7,20]. In particular, preterm-born infants that are small-for-gestational-age have decreased bone size and lower BMD at 20 years of age [7,21]. In both term-born and preterm-born infants, growth during infancy and childhood determines bone mass in childhood and adulthood [17,22–28].

Abbreviations: AGA, appropriate-for-gestational-age; BA, bone area; BMC, bone mineral content; BMD, bone mineral density; SDS, standard deviation score; SGA, small-for-gestational-age.

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Whether low birth weight in preterm-born infants is already associated with decreased bone mass during early infancy is unknown. Therefore, we studied the effect of birth weight on bone mass accretion between term age (40 weeks postmenstrual age) and six months post-term in preterm-born infants and investigated if this relation was modified by post-term growth and type of feeding.

Subjects and methods

Subjects

The present study was part of a randomized controlled trial that evaluated the effect of postdischarge formula, term formula, and human milk on growth and body composition of preterm-born infants. The design of the randomized controlled trial has been described in detail elsewhere [29]. In short, 152 infants with a gestational age of 32 weeks or less and/or a birth weight of 1500 g or less were included shortly after birth. Infants with congenital malformations or conditions that affected growth and body composition were not included. The present study aimed to investigate size at birth in relation to prospectively collected anthropometry and bone mass between term age and six months post-term and included all infants with available data on anthropometry and bone mass between these time-points. Infants were evaluated at our outpatient clinic at term age (40.3 ± 0.7 weeks postmenstrual age), at three months post-term (53.0 ± 0.5 weeks postmenstrual age) and at six months post-term (66.0 ± 0.5 weeks postmenstrual age). At six months post-term, 139 preterm-born infants completed the randomized controlled trial (51% boys, gestational age 30.3 ± 1.5 weeks, birth weight 1341 ± 288 g) (Fig. 1). Thirteen infants did not complete the randomized controlled trial for various reasons (Fig. 1).

The study protocol was approved by the ethics committee of VU University Medical Center, Amsterdam, The Netherlands. All the parents of the participating children gave written informed consent.

Methods

Anthropometry, severity of illness, and type of diet

At birth, at term age, and at three and six months post-term, weight (gram) was measured with a digital scale, length (cm) was measured with a length board, and head circumference was measured with a non-stretchable measuring tape [29]. At birth, weight, length, and head circumference were expressed as standard deviation score (SDS) based on Swedish references for preterm-born infants, which adjusted for gender and gestational age [30]. Infants were classified as small-for-gestational-age (SGA) if birth weight and/or length were below −2 SDS and as appropriate-for-gestational-age (AGA) if birth weight and length were −2 SDS or above. The relative gain in weight and length between term age and six months post-term was calculated as follows: (gain between term age and six months post-term) / measurement at term age ∗ 100%.

The Neonatal Therapeutic Intervention Scoring System was used to evaluate severity of illness during hospital admission. The Neonatal Therapeutic Intervention Scoring System has a maximum score of 130 points and is a valid indicator of severity of illness in neonates, independent of birth weight [31]. In the present study, infants were fed different feeding regimens between term age and six months post-term according to the study protocol of the randomized controlled trial, namely postdischarge formula, term formula, or human milk [29].

Dual-energy X-ray absorptiometry (DXA)

At term age and at six months post-term, bone mass was measured with whole-body dual-energy X-ray absorptiometry (DXA; Hologic QDR4500A, Hologic Inc., Bedford, MA, USA), as described previously [29]. In short, naked infants were swaddled in a cotton sheet and placed in supine position on the scanning area. Infants were not sedated and were scanned after feeding when the infant was settled. A research nurse was in attendance during the scanning procedure to ensure an adequate position of the infant.

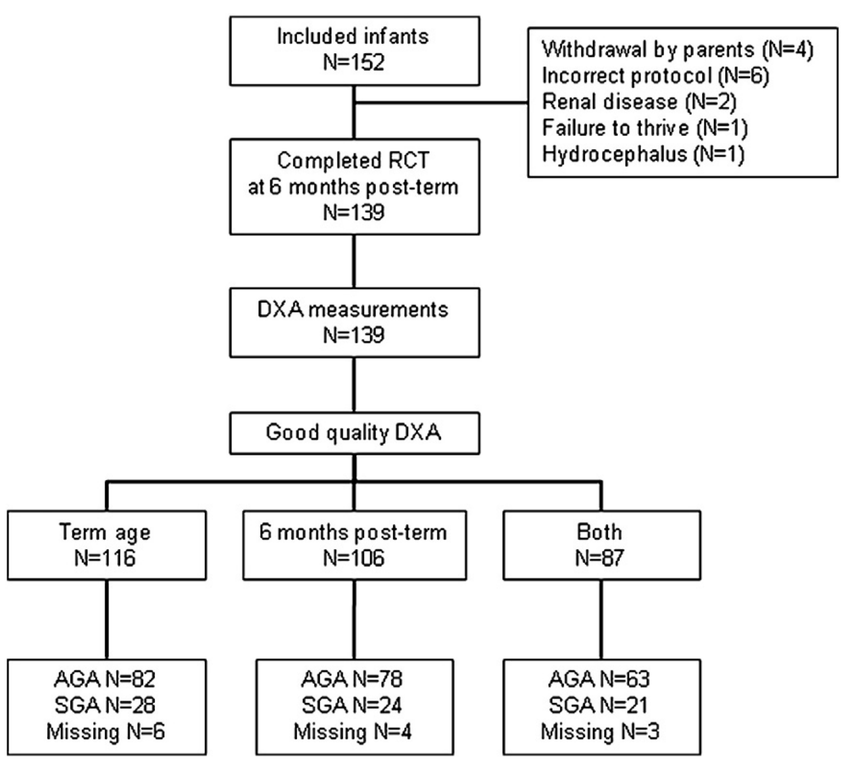

Fig. 1. Flow diagram of study subject recruitment. N = number of infants; AGA = appropriate-for-gestational-age (weight and length ≥ −2 SDS); SGA = small-for-gestational-age (weight and/or length < −2 SDS); missing = not classified as AGA or SGA due to unknown birth length.