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EDITORIAL

Growth, bone health, and later outcomes in infants born preterm☆,☆☆

Crescimento, saúde óssea e resultados mais recentes em neonatos prematuros

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One in ten babies worldwide are born preterm every year; over 90% of these are born in low and middle-income countries such as Brazil.[1] Improvements in neonatal intensive care and increased survival of preterm infants has led to an increasing focus on the long-term impacts of preterm birth, specifically with respect to metabolic outcomes such as bone mineral density (BMD) and timing and extent of catch-up growth.

Metabolic bone disease of prematurity

Preterm infants are particularly susceptible to metabolic bone disease for two key reasons: Firstly, 80% of fetal bone mineral accumulation occurs during the last trimester of pregnancy, with a surge in placental transfer of calcium, magnesium, and phosphorus to the neonate.[2] A preterm infant *ex-utero* must accrete bone mineral during this period without the support of the regulatory placental environment, and almost all these infants will have significantly lower bone mineral content (BMC) than those born at term. Secondly, *ex-utero* living conditions make it more difficult for infants to move and stress their bones as they would have done in-utero.[3] As well as mineral insufficiency, lower BMD is also a consequence of other factors such as medication (e.g. steroids, diuretics, etc.), respiratory compromise,[4] and infection,[5] which may damage bone trabeculae. Although metabolic bone disease of prematurity is often asymptomatic and described as self-limiting,[6] concern remains that under-mineralization during such a critical period could increase the risk of childhood fracture. Perhaps more importantly, it may result in reduced peak bone mass,[7] which is a key predictor for risk of osteoporosis in adulthood.

Impact of preterm birth on later metabolic bone outcomes

In this issue of *Jornal de Pediatria*, Quintal et al.[8] have conducted a comprehensive longitudinal study, examining bone mineralization and body composition using dual X-ray absorptiometry (DXA) in 14 preterm infants over the first six postnatal months, and compared them to infants born full term. This is important, as previous research studies have produced conflicting data on the effect of prematurity on later BMD. Consistent with data from this study, previous studies in preterm infants have shown a lower bone mass,[9]

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BMD,[7] and BMC[4] at the corrected age of term, as well as a lower weight and ponderal index.[7] Several studies, however, have failed to demonstrate an association between preterm birth and later bone strength,[5,10,11] whilst others have shown greater BMC and BMD in term children compared to preterm, at follow-up.[4,12] A possible explanation for the variation in study results may be in the timing of follow-up as catch-up in bone mineralization may occur throughout childhood and adolescence.[13] Of note, in Quintal et al.'s study,[8] catch-up bone mineralization appears to have occurred in early infancy; thus, data from preterm and full-term infants were comparable by 6 months of age. This may be attributable to the persisting benefits of growth factors present in breast milk, as Quintal et al.'s cohort were all breastfed, compared to much of the published data from formula fed babies. Continued follow up of this cohort with further DXA scans in later childhood and adulthood would provide additional insights into their peak bone mass.

The exact influence of birth weight on later BMD remains unclear. Some studies have found that, although preterm-born infants were lighter during childhood than their term counterparts, their BMD was appropriate for size. Adults who were born preterm remain on average slightly shorter than their term-born peers. As some studies may not have made appropriate adjustments for current size, it may be difficult to determine whether BMD is appropriate or not. There is also evidence that very low birth weight (VLBW) infants, whether preterm or not, attain a sub-optimal peak bone mass in part due to their small size, but also due to their subnormal skeletal mineralisation.[5] The Hertfordshire cohort study (which formed the basis for several of Barker's studies) showed that birth weight was independently associated with bone density at 60-75 years of age. Although another study found no association with preterm birth and peak bone mass,[14] an effect of being small for gestational age was apparent, suggesting that a proportion of later bone mass is determined by *in utero* events, such as fetal growth.

The challenges of optimizing neonatal nutrition

The use of fortified breast milk in this study and exclusive breastfeeding post-discharge is commendable. Maternal breast milk is associated with a range of benefits both in the short-term (e.g. reduction in the incidence of necrotizing enterocolitis) and long-term (e.g. improved cognitive outcome.) A study by Fewtrell at al.[15] showed that the variable with the greatest effect on adult BMD was the proportion of breast milk intake. Given that breast milk has a much lower mineral content than formula, and requires fortification to meet nutrient requirements, the data of Fewtrell et al. suggests a possible beneficial role for non-nutrient components such as growth factors. The cohort of Quintal et al.[8] highlights the challenges of providing adequate nutrition to enable growth in preterm infants. Although many units now strive to start early feeds, parenteral nutrition (PN) is now common place in most NICUs and provides nutrients whilst enteral tolerance is achieved: in this study, although enteral feeds were started soon after birth, most received PN support with an average PN duration of 12 days.

Preterm infants miss out on the important phase of mineral accretion in the third trimester and are therefore even more vulnerable to the effects of inadequate mineral provision in the postnatal period. Although PN solutions have improved dramatically since the first reports of neonatal use in the late 1960's, problems with respect to mineral provision exist because calcium and phosphate are insoluble in high concentrations. The increased availability of organic salts, such as sodium glycerophosphate, has improved solubility (and therefore mineral provision), and increased intakes of amino acids are both likely to result in higher lean mass and bone mass accretion than in the past, but PN provision continues to lack a strong evidence base and several concerns persist.[16] In particular, aluminium contamination remains a very common problem, and is independently associated with reduced BMC in later childhood.[15]

Bone mineral and other growth deficits accrued whilst enteral nutrition is established often increase during NICU stay. Mineral uptake is compromised through the low content in un-fortified breast milk (especially phosphate) and inefficient absorption due to an under-developed gastrointestinal tract.[6] This results in a greater loss of long bone density than observed in term infants and further increases the risk of metabolic bone disease. There is compelling evidence that optimizing early growth through nutritional interventions generates positive and lasting effects on bone mineralization,[10] which may partially counteract preterm bone deficits. A systematic review by Kusckel and Harding in 2009 showed that fortifying the nutrition of preterm babies improves growth and bone mineral aggregation.[17] International guidelines from groups such as ESPGHAN recommend that those receiving unfortified breast milk should receive multivitamin, iron, folic acid, phosphate, and sodium supplementation.[18]

Several studies have emphasized the importance of early growth on later bone health,[2] so it is encouraging to observe in this study that the preterm infants demonstrated significant catch-up growth with an increase in mean weight Z-score from -2.58 at 40 weeks to -0.49 at 6 months, and an increase in mean length Z-score from -2.22 to -0.59 at the 6-month follow-up. In a study by Cooper et al, those who were lightest at 1 year of age had the lowest BMC.[2] In a further study, weight gain during the first two years of life predicted BMD at age 9-14.[19] Fewtrell et al. suggested that preterm infants with the most substantial increase in height (length) between birth and follow-up showed the greatest bone mass at follow-up.[12] They also demonstrated that birth length alone was a strong predictor of later bone mass, suggesting that optimizing linear growth early may be beneficial to later bone health. However, the mean weight Z-score at term of -2.58 in Quintal et al.'s study[8] highlights the major challenges of promoting adequate growth during NICU stay. Even though the infants showed impressive catch-up growth up to 6 months of age, the dramatic fall in growth centiles during NICU stay, followed by a period of rapid growth acceleration, represents a pattern that is very different to that observed following normal pregnancies. Whether this type of growth trajectory represents an independent risk for later adverse metabolic outcome requires further study, but highlights that growth, rather than absolute size, is the key variable determining longer-term health.

The use of DXA scanning as an adjunct to biochemistry in the detection of metabolic bone disease

Quintal et al. demonstrate that DXA scanning is a reliable and well-validated technique to estimate BMC and BMD. It is well tolerated due to its non-invasive nature and short scan times, and the radiation levels involved are lower than background levels. The newer DXA machines with enhanced image resolution enable accurate calculation of fat and lean mass indices, although they cannot reliably determine adipose tissue partitioning. Plain radiographs in preterm infants on NICU frequently demonstrate osteopenia, but are insensitive markers of BMD. Biochemical markers may help determine the presence of metabolic bone disease; for example, high levels of alkaline phosphatase can be useful as a prompt to check serum calcium and phosphate.[20] However, the complexity of processes involved in metabolic bone disease of prematurity mean that biochemical measures are similarly insensitive. The key to management is to focus efforts that minimize its occurrence as much as is feasible in busy NICU settings, rather than perfecting sensitive detection methods. This can be done by encouraging the use of aluminium-free, high quality mineral supplemented PN solutions with adequate amounts of amino acids, combined with the early and sustained use of breast milk, and supplemented by the routine use of fortifiers that meet nutrient requirements.

Epigenetics and bone metabolism

Many of the long-term effects on bone health may be due to programming and modulated by epigenetic mechanisms – mitotically-heritable alterations in gene expression potential that are not caused by changes in DNA sequence. The classic examples are DNA methylation and histone acetylation[21] and result in differences in gene expression and transcription, but may also involve post-transcriptional effects on other processes such as protein translation. Early life growth and nutritional exposures appear to affect cellular memory and result in variation in later life phenotypes. Much of this work is preliminary, but initial data suggest that epigenetic mechanisms may underlie the process of developmental plasticity and its effect on the risk of osteoporosis. One of the models that has been postulated is the role of maternal vitamin D status and postnatal calcium transfer. Early work on methylation and vitamin D receptors and placental calcium transporters suggests that epigenetic regulation might explain how maternal vitamin D levels affect bone mineralization in the neonate.[21] Much of the current research is in animal models, but if the changes can be replicated in humans, epigenetic or other biomarkers may provide risk assessment tools to enable targeted intervention to those at greatest risk of osteoporosis.

Future clinical and research priorities

Longitudinal studies with minimal attritional losses, and especially those conducted within randomized controlled trial settings are needed if we are to improve health outcomes of preterm infants across the globe. This research needs to be high quality and conducted in low-, middle-, and high-income countries so generalizability can be maximized. Risk benefit ratios of medical interventions are sensitive to the individual and the healthcare context. Nevertheless, the importance of early bone and body growth on the later development of metabolic diseases such as osteoporosis means that optimizing nutrition both pre- and post-hospital discharge must remain a clinical priority. Importantly, greater efforts must be applied to support research and quality improvements initiatives within and between countries – we need to improve our collaborative working!

Conflicts of interest

The authors declare no conflicts of interest.

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