The long-term impact of very preterm birth on adult bone mineral density

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\begin{abstract}
Introduction: Preterm infants are at increased risk of osteopenia of prematurity due to insufficient bone mineral accretion. Data on long term effects of prematurity on bone health are conflicting. This study aimed to compare bone mineral density (BMD) in young adults born very preterm and full-term controls and to examine factors associated with long-term bone health.

Methods: This observational cross-sectional study enrolled 101 young adults (18–29 years) born < 29 weeks of gestation and 95 sex- and age-matched full-term controls. Participants underwent dual-energy X-ray absorptiometry to measure areal BMD and body composition. Generalized estimated equations were used to compare groups adjusting for height Z-score, lean body mass and fat mass.

Results: Adults born preterm were shorter and lighter than full-term controls. Areal BMD was reduced at the lumbar spine, the femoral neck and whole body in the preterm versus full-term group, but after adjustment, areal BMD Z-score was only significantly lower at the femoral neck by $-0.3$ unit (95% confidence interval $-0.6$ to $-0.0$). Low BMD (Z-score $\leq -1$ standard deviation) at any site was observed in 53% of adults born preterm versus 28% of full-term controls, but this was not statistically significantly different. We did not identify any neonatal factors associated with lower BMD within the preterm group.

Conclusions: Very preterm birth is associated with lower areal BMD at the femoral neck in young adulthood, even after accounting for body size. Whether this will translate into higher risk of osteoporotic fractures later in life remains unknown.
\end{abstract}

1. Introduction

Nearly one-third of infants born < 1500 g develop bone mineral disease of prematurity, a clinical condition characterized by a significant reduction in bone mineral density without radiological signs. The lower the gestational age (GA), the higher the risk (Sharp, 2007; Nallagonda et al., 2017; Done, 2012). Worldwide, 1 in 10 babies are born preterm before 37 weeks of gestation with 1–2% born very (< 28 weeks’ GA) or extremely (< 28 weeks’ GA) preterm (Goldenberg et al., 2008). Preterm birth occurs during the third trimester of pregnancy when placental transfer of calcium, magnesium and phosphorus to the foetus is particularly important to foster bone mineralization (Sharp, 2007). However, neonates born preterm are rather exposed to lower amount of minerals from parenteral nutrition and limited enteral intake. In addition, restricted spontaneous movements \textit{ex utero} reduce mechanical stimulation (Sharp, 2007). Prematurity-related conditions such as pre-eclampsia, sepsis, and lung disease, all known to be associated with high levels of oxidative stress, along with treatments like postnatal steroids or diuretics further contribute to the pathophysiology of metabolic bone disease (Embleton and Wood, 2014; Figueras-Aloy et al., 2014; Bowden et al., 1999; Chan et al., 2008; Viswanathan et al., 2014; Torres-Cuevas et al., 2017). These events can permanently alter programming of bone growth and mineralization (Cooper et al., 2000). Altogether, preterm birth may affect attainment of peak bone mass thus increasing later risk for osteoporosis.

Studies examining the impact of preterm birth on long-term bone health have yielded diverging results. Both Hovi (Hovi et al., 2009) and...
Balasuriya (Balasuriya et al., 2017) showed that young adults born preterm with birth weight < 1500 g had lower areal bone mineral density (aBMD) relative to term controls, which concurred with findings fromFewtrall who compared participants born preterm to population norms (Fewtrall et al., 2009). In contrast, others did not find any difference (Weiler et al., 2002; Erlandson et al., 2011; Dalziel et al., 2006; Breukhoven et al., 2011). Furthermore, very few studies have specifically examined perinatal factors that could be associated with aBMD in young adults born preterm.

We aimed to assess aBMD in young adults aged 18–29 years born at < 29 weeks in comparison to controls born full-term. We further sought to investigate perinatal factors associated with bone health. We postulated that in this group of adults born very preterm, lower aBMD would be observed in relation to term controls. In addition, indicators of neonatal illness would be linked to reduced aBMD among the very preterm group.

2. Methods

2.1. Study design and participants

This research is part of a larger observational cross-sectional study aiming to comprehensively assess several body systems in young adults born very preterm. Approval from our Research Ethics Board was obtained. All participants provided informed written consent.

Participants were traced and recruited from a list of 485 patients born below 29 weeks’ gestational age between 1987 and 1996 at Centre Hospitalier Universitaire Sainte-Justine, Montreal, Canada, who had survived to 18 months corrected age. Currently pregnant women and individuals with severe neurosensory impairment precluding test completion were excluded. The 83 recruited participants were comparable to the 402 non-participants in terms of GA, birth weight, small-for-gestational-age, and presence of bronchopulmonary dysplasia prior to the onset of pathological diseases. In addition, we estimated volumetric density (BMDvol) at the lumbar spine to account for bone size using the following Kroger formula: aBMD × (4/π × width of measurement area in lumbar spine) (Kroger et al., 1995).

Physical examination was limited to height and weight measurement in triplicate. Height in Z-score was obtained using World Health Organization growth standards (World Health Organization, 2006). Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

2.4. Statistical analysis

Descriptive statistics were summarized as means and 95% confidence intervals (CI), medians and interquartile range (IQR) or proportions. Given the matched study design, between-group comparisons for the 95 pairs were performed with dependent Student’s t-test for continuous variables and McNemar test for categorical variables. Within pair comparisons of aBMD Z-scores with adjustment for adult height Z-score, lean body mass, and fat mass were done with generalized estimating equations. To examine factors associated with low aBMD in young adults born preterm (n = 101), independent t-test, Chi-square or Mann-Whitney U test were used. Given the exploratory nature of the latter analyses, we did not correct for multiple testing. All analyses were carried with IBM SPSS 24 (North Castle, NY, USA).

3. Results

3.1. Neonatal characteristics

Table 1 displays neonatal characteristics of our study population. Mean GA and birth weight were 27.1 weeks and 957 g for the preterm group; 44% were male. Almost half of preterm infants were exposed to antenatal steroids, a similar proportion had received surfactant, and 28% received postnatal steroids. Parenteral nutrition was given for a median of 17 days (IQR: 8, 40). Median length of hospitalization was 83 days (IQR: 66, 108).

3.2. Adult characteristics

Participants were assessed at a mean age of 23 years. Young adults born preterm, as a group, had significantly lower weight, height, and lean body mass than controls (Table 1). Of note, only 83% of preterm participants reached mid-parental height, as compared to 98% of controls. Estimated cardiorespiratory fitness and smoking were reportedly similar between the two groups. Inhaled steroids were used by 7% and 8% individuals born preterm and full-term, respectively. A subgroup of participants (n = 34 pairs) had complete dietary data and were comparable to others in terms of age, sex, weight and height. There was no difference in daily calcium and protein intake between participants.
**Table 1**

Neonatal characteristics and current health for the 95 matched pairs.

| Neonatal characteristics                          | Very preterm      | Term          |
|--------------------------------------------------|-------------------|---------------|
|                                                   | \(N = 95\)        | \(N = 95\)    |
| Male sex, n (%)                                   | 42 (44)           | 42 (44)       |
| Gestational age, weeks                            | 27.1 (26.9, 27.4) | 39.5 (39.3, 39.8) |
| Birth weight, g                                   | 957 (912, 1002)   | 3391 (3307, 3472) |
| Small for gestational age, n (%)                  | 6 (6)             | 6 (6)         |
| Antenatal steroids, n (%)                         | 41 (44)           | 0             |
| Surfactant, n (%)                                 | 43 (45)           | 0             |
| Postnatal steroids, n (%)                         | 27 (28)           | 0             |
| Bronchopulmonary dysplasia, n (%)                 | 35 (37)           | 0             |
| Necrotizing enterocolitis, n (%)                  | 5 (5)             | 0             |
| Weight Z-score at discharge                      | −2.1 (−2.3, −1.8) | NA            |
| Weight at discharge < 10th percentile, n (%)      | 67/83 (81)        | NA            |

| Current health                                    |                   |               |
| Age, year                                         | 23.2 (22.8, 23.7) | 23.2 (22.8, 23.7) |
| Weight, kg                                        |                   |               |
| Male                                              | 67 (63, 71)       | 77 (73, 82)   |
| Female                                            | 58 (55, 58)       | 65 (61, 68)   |
| Height, cm                                        |                   |               |
| Male                                              | 172 (170, 175)    | 178 (175, 180) |
| Female                                            | 160 (158, 162)    | 166 (164, 167) |
| Height, Z-score                                   | −0.6 (−0.9, −0.2) | 0.2 (−0.1, 0.5) |
| Female                                            | −0.5 (−0.7, −0.2) | 0.4 (0.2, 0.6) |
| Body mass index, kg/m²                             |                   |               |
| Male                                              | 22 (21, 24)       | 24 (23, 26)   |
| Female                                            | 23 (22, 24)       | 24 (22, 25)   |
| % body fat, Z-scores                              | 0.7 (−0.2, 1.4)   | 1.0 (0.1, 1.6) |
| Female                                            | 0.8 (0.6, 1.3)    | 0.8 (0.5, 1.3) |
| Lean body mass, kg                                |                   |               |
| Male                                              | 51 (48, 54)       | 57 (54, 59)   |
| Female                                            | 35 (35, 37)       | 39 (38, 41)   |
| Reached potential height, n (%)                   |                   |               |
| Male                                              | 23 (77)           | 25 (100)      |
| Female                                            | 30 (88)           | 32 (97)       |
| Smoking, n (%)                                    | 22 (23)           | 17 (18)       |
| Estimated VO_{2max}, mL/kg/min                    | 43 (41, 48)       | 46 (45, 51)   |
| 25-hydroxyvitamin D, nmol/L                       | 61.5 (55.9, 67.1) | 59.6 (54.2, 64.9) |

Data expressed as mean (95% confidence interval) unless specified otherwise.

#Maximal O2 consumption (VO_{2max}) estimated using Huet Physical Activity Questionnaire.

NA: Not applicable.

* Means between very preterm and term significantly different at < 0.05.

**3.3. Bone mineral density in young adulthood**

BMC, aBMD and aBMD Z-scores were significantly lower in the preterm group for all measures taken (Table 2). Given the correlation between aBMD Z-scores at all sites and height Z-score (Pearson's r between 0.26 and 0.39), lean body mass (r = 0.25-0.36), and fat mass (r = 0.22-0.42), we adjusted for these three variables; only the difference in aBMD in Z-score at the femoral neck remained significant. We further adjusted aBMD for levels of serum vitamin D and cardiorespiratory fitness, but discerned no additional change in our results (not shown).

**3.4. Characteristics of preterm participants with lower aBMD**

We carried out a subgroup analysis for the preterm group (n = 101), comparing those with aBMD ≤ −1 SD in any of the three regions in young adulthood (n = 51) to those with normal aBMD i.e. a Z-score higher than −1 SD (n = 50). As shown in Table 3, we did not identify any neonatal factors associated with lower aBMD.

**4. Discussion**

Young adults born very preterm had reduced aBMD. This was mostly accounted for by lower adult weight and height in comparison to full-term controls, except at the level of the femoral neck. Our study is unique as it examined a cohort of young adults born at earlier GA (≤29 weeks) than what has been previously reported (Hovi et al., 2009; Balasuriya et al., 2017; Fewtrell et al., 2009; Breukhoven et al., 2011; Butazzoni et al., 2016). In addition, we matched participants by age and sex, using siblings and friends, thus reducing differences in environmental factors such as smoking (correlation of 86% among pairs), physical activity (r = 0.70), and vitamin D levels (r = 0.38). This facilitated isolation of the effects of very preterm birth. Finally, the collection of complete neonatal history also allowed us to explore indicators of long-term bone health though current study could not identify any specific risk factors.

Our findings confirmed previous research from Hovi et al. and Balasuriya et al. showing lower peak bone mass in young adults born preterm and with birth weights < 1500 g (Hovi et al., 2009; Balasuriya et al., 2017). In the Helsinki Study of Very Low Birth Weight Adults, Hovi et al. examined 144 individuals born between 24 and 36 weeks' GA (mean GA of 29 weeks) and 139 controls born full-term (Hovi et al., 2009). They observed a reduction of 0.51 unit in Z-score at the level of the lumbar spine, 0.56 unit at the femoral neck, and 0.33 unit for whole body in young adults born preterm, which is comparable to our unadjusted results. This difference remained statistically significant only at the lumbar spine and femoral neck after they adjusted for sex, adult height and BMI. Similarly, Balasuriya et al. studied 52 very-low-birthweight young adults with mean GA of 29 weeks and 75 full-term controls (Balasuriya et al., 2017). Mean difference in aBMD Z-score, adjusted for adult weight and height, was statistically significantly lower at the level of the femoral neck and whole body, but not the lumbar spine. Overall, findings suggest lower than average aBMD Z-scores in young adults born preterm at a time when bone mass accrual should be at its peak. These results may be partly explained by lower adult weight and height in individuals born preterm. Indeed, BMD assessed by DXA scan measures areal density and is thus influenced by bone size. As a result, DXA scan underestimates aBMD in lighter and shorter individuals (Compston et al., 1995). In a young population such as ours, in addition to aBMD, clinicians also need to consider past medical history of fractures to predict future risk of recurrent fractures (Shepherd et al., 2015). Consistent with previous work (Balasuriya et al., 2017), there was no difference between young adults born preterm versus full-term in their previous history of fractures. Unlike Balasuriya et al., we did not distinguish between high- and low-impact injuries. Nevertheless, participants were seen at a relatively young age for osteoporotic fractures, which incidence usually starts rising beyond
Interestingly, in all three studies on young adults born preterm (Hovi et al., 2009; Balasuriya et al., 2017; Fewtrell, 2011), decreased aBMD at the femoral neck remained significant even after accounting for weight and height, thus suggesting other pathological pathways linking preterm birth and lower aBMD in adulthood. Other variables such as physical activity and timing of gross motor milestones could also be determinants of aBMD at the femoral neck (Mori et al., 2014; Pocock et al., 1986; Ireland et al., 2016; Ireland et al., 2017). Indeed, in the Avon Longitudinal Study of Parents and Children, infants with impaired gross motor skills at 18 months had lower hip BMD and strength at 17 years of age (Ireland et al., 2016). Given that preterm birth is associated with motor delays (Synnes et al., 2017), lower habitual loading of the lower limbs, which is determined by early-life motor competence, could result in subsequent decreased in femoral aBMD. Unfortunately, we did not collect data on gross motor development.

Earlier studies which did not find any effect of preterm birth on adult bone health recruited individuals of higher gestational ages (Dalziel et al., 2006; Breukhoven et al., 2011). Buttazzoni et al. did observe that adults born preterm (mean GA 32 weeks) and small-for-gestational-age had reduced bone mass, but not those with birth weight appropriate for GA (Buttazzoni et al., 2016). Hovi et al. found that for each additional gestational week, BMD Z-score at the lumbar spine increased by 0.19 units (Hovi et al., 2009). Given that maximal fetal bone accretion occurs in the last trimester of pregnancy, infants born at earlier GA are at increased risk of neonatal illness which may result in poor nutrition, increased inflammation, and exposure to medications that hinder bone mineralization. All these factors may contribute to osteopenia of prematurity (Sharp, 2007; Nallagonda et al., 2017; Done, 2012). However, we could not find any association between neonatal factors and adult bone health.

Study limitations must be acknowledged. First, despite efforts in recruitment, there may be selection bias as our cohort was a small sample set of the historical population. Young adults with severe neuromotor developmental issues were excluded due to challenges in completing the research protocol. Therefore, we might have underestimated the true difference in aBMD between young adults born very preterm and full-term. Second, we could not explore the relationship between current aBMD and neonatal diagnosis of osteopenia of prematurity because the latter was not systematically documented in the charts. Third, we did not have sufficient data to explore the impact of childhood growth on current aBMD. Fourthly, history of fracture was documented but the frequency and the cause of the fracture were not requested in the questionnaire. This information could have facilitated our understanding of the impact of lower BMD on bone health. Our study has important clinical implications for current generations of young adults born prematurely. However, nutritional interventions in neonatal intensive care units and post-discharge have changed in the past 20 years.
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