

Original Article

Pediatric data for dual X-ray absorptiometric measures of normal lumbar bone mineral density in children under 5 years of age using the lunar prodigy densitometer

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Objectives: Knowledge of physiological variations of bone mineral density (BMD) in newborns and infants is necessary to evaluate pathological changes associated with fractures. Limited reference data for children under 5 years old are available. This study provides normative data of lumbar BMD for the Lunar Prodigy in young children under 5 years old. **Subjects and methods:** We assessed cross-sectionally 155 healthy children (77 boys, 80% Caucasian), ranging in age from newborn to the age of 5 years. Lumbar bone mineral content (BMC) and areal BMD were measured by dual-energy X-ray absorptiometry using a Lunar Prodigy absorptiometer. Volumetric BMD was calculated using the Kroeger and Carter methods. **Results:** BMC and areal BMD increased from birth to 5 years ($p < 0.001$). Volumetric BMD did not change with age. BMD and BMC correlated with age, weight and height ($R^2 \geq 0.85$ for all), with a maximum gain between the ages of 1 and 4 years, which did not follow the same pattern as height velocity. We did not find significant sex difference for any of the three measured parameters. **Conclusion:** This study provides normative data for lumbar spine densitometry of infants and young children using the Lunar Prodigy DXA system.

Keywords: Bone Mineral Density, Bone Mineral Content, Child, Lumbar Region

Introduction

Bone mass acquisition between childhood and adolescence is well known to be under the influence of numerous factors such as genetic, hormonal, nutritional, environmental and level of physical activity. There have been few studies examining bone mass accretion in the first years of life when rapid and important growth and neurodevelopment occur. In pediatric tertiary centers, the annual number of cases of young children referred for bone health evaluation is constantly increasing. Knowledge of physiological variations

and reliable reference data of bone mineral density (BMD) in newborns and infants are needed to evaluate and identify pathological changes in pediatric conditions associated with fractures¹. According to a recent Official Position of the International Society for Clinical Densitometry², lumbar spine is the recommended site for BMD measurement when evaluating children between 0 and 5 years. Indeed, a lumbar BMD scan is usually easily obtained without sedation even in newborns, and offers a rapid assessment with low radiation, good accuracy and reproducibility when compared with old pencil-beam measurements³⁻⁵. The Lunar Prodigy (GE Healthcare) is used by several pediatric centers and provides dual-energy X-ray absorptiometry (DXA) measurements in newborns and young children with good precision and reliability¹.

Extensive normative data on BMD exist for children aged 4 to 18 years old⁶⁻¹². Older data generated from pencil-beam densitometers in children younger than 5 years cannot be applied to scan results from fan-beam densitometers without adjustments. Very limited data exist for younger children with fan-beam technologies, most of them in infants, using the Hologic^{3,13-21} and Norland²² devices, whereas less exist for the Lunar Prodigy (GE Healthcare) densitometer^{1,23}. In

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a study including 207 neonates¹, total body BMD and BMC measures performed with Lunar Prodigy showed good accuracy. In the single study with data from young children with the Lunar Prodigy²⁴ the authors measured lumbar areal BMD in 147 children (69 boys and 78 girls) from 15 days to 4 years. BMD increased progressively from birth to 4 years and a statistically significant correlation was found between BMD and age, weight and length or height. BMD gains showed a similar pattern to height growth velocity.

The main objective of the present study was to provide normative data for BMC, areal BMD (aBMD) and volumetric BMD (vBMD) at the L2-L4 level for children in a Canadian population from birth to 5 years using the DXA Lunar Prodigy. Our secondary objective was to study how specific factors, such as gender, age, height, weight, type of diet and psychomotor development influence bone mass accretion in infants and young children.

Subjects and methods

Subjects

The study was a cross-sectional, single-observational assessment of 155 healthy Canadian children aged from birth to 5 years that was conducted between October 2004 and March 2006. All 155 children were either newborns, born at the Centre Hospitalier Universitaire (CHU) Mère-Enfant Sainte-Justine Hospital in Montreal, Canada, or infants and young children followed at the outpatient pediatric clinics of the same institution (single-center study). The families of the participants were contacted by a research nurse during their hospital stay or visit and were asked to participate by completing a single assessment during the immediate post-natal period, or the same day of their routine follow-up. Only one child was included per family that accepted to participate. Written informed consent was obtained from the parents of the participants. The study was approved by the Ethics Committee of the CHU Sainte-Justine.

All 155 children were selected according to the following inclusion criteria: **1)** weight and height between the 3rd and 97th percentile for age based on the CDC 2000 growth reference, **2)** normal calcium and vitamin D intake reported in a dietary questionnaire and evaluated according to the guidelines of the Canadian Pediatric Society [14]) and **3)** normal psychomotor development. Exclusion criteria included conditions which could affect BMD, such as: **1)** growth delay, **2)** history of chronic diseases, **3)** use of corticotherapy or other osteotoxic medication, **4)** familial or personal history of bone diseases, **5)** suspicion of child negligence, abuse or violence, **6)** gross motor developmental delay.

Demographic data were collected from the children's medical files. The subjects were classified in 8 different age categories: **1)** newborns from day 2 to day 30, **2)** infants from 1 to 3 months, **3)** infants from 3 to 6 months, **4)** infants from 6 to 12 months, **5)** toddlers from 1 to 2 years, **6)** toddlers from 2 to 3 years, **7)** children from 3 to 4 years, **8)** children from 4 to 5 years.

Developmental assessment and questionnaires

Developmental milestones were assessed with the Denver Prescreening Developmental Questionnaire (PDQ I), completed by the parents²⁵. Children were excluded if they could not perform a skill that 90% of their age-matched counterparts could perform.

Calcium and vitamin D intake (dietary and supplement intake) were evaluated by original questionnaires developed for the study, administered to the parents during the interviews. This questionnaire was designed to gather information on the type (breast milk versus formula) and frequency of milk consumption during the past three months, as well as document a history of breastfeeding and amounts of supplemental calcium or vitamin D since birth. Patients with inadequate total calcium and vitamin D intake were excluded from the study.

Anthropometric measurements

Infant length was measured to the nearest 0.1 centimeter with the baby supine on the scale to calculate the distance from head to heel using a fixed head and a moveable foot-board. For children over 2 years of age, height was measured with a wall-mounted stadiometer.

Subjects were weighed while wearing minimal clothing on a digital scale to the nearest 0.01 kg.

Weight, length and height measurements were acquired in triplicate, and the mean was used to compute z-scores (standard deviation scores, SDS) using the CDC 2000 growth curves, which were the standard growth reference used at the time of recruitment of the participants.

Lumbar BMD assessment

Lumbar BMC and BMD values were respectively measured and calculated respectively by dual-energy X-ray absorptiometry (DXA) with a Lunar Prodigy (GE Healthcare) at the level of the lumbar spine (L2-L4), using the pediatric software. BMD, BMC and vBMD values were expressed in units of grams of hydroxyapatite/cm², grams of hydroxyapatite and grams of hydroxyapatite/cm³ respectively. All measurements were performed in the Department of Radiology of the CHU Sainte-Justine by the same technologist. Scan acquisition used the fast spine mode and fixed scan dimension of 12-cm length and 10-cm width. Each scan was completed in one to two minutes depending on the size of the infant and generally it took less than one minute in newborns. All scans for this study were performed with the child placed supine on top of the platform with a cotton blanket interposed between the subject and the platform and without sedation according to a previously described method²⁶. Children whose scans were considered of low quality due to movement artifacts did not have to repeat a scan and were excluded from the study. The precision of the above method for the Prodigy Lunar GE machine was validated for the needs of a large multi-center study²⁷ where our center had participated. Specifically, a spine phantom was cross-calibrated across

Table 1. Equations for the age-dependent coefficients of variation (S) and mean values (M) in boys. Age represents chronological age in years. vBMD: volumetric BMD.

	S	M
L2 to L4		
BMC (g)	$0.227 - 0.0225 \times \text{age}$	$1.69 + 1.99 \times \text{age}$
Areal BMD (mg/cm ²)	$0.131 - 0.01065 \times \text{age}$	$0.289 + 0.0869 \times \text{age} - 0.00446 \times \text{age}^2$
vBMD Kroger (mg/cm ³)	$0.134 - 0.00767 \times \text{age}$	$0.218 - 0.0417 \times \text{age} + 0.0303 \times \text{age}^2 - 0.00430 \times \text{age}^3$
vBMD Carter (mg/cm ³)	$0.113 - 0.00343 \times \text{age}$	$0.113 - 0.0334 \times \text{age} + 0.0210 \times \text{age}^2 - 0.00294 \times \text{age}^3$
Area (cm ²)	$0.127 - 0.00795 \times \text{age}$	$5.93 + 4.27 \times \text{age} - 0.370 \times \text{age}^2$

Table 2. Equations for the age-dependent coefficients of variation (S) and mean values (M) in girls. Age represents chronological age in years. vBMD: volumetric BMD. An example of how to use these data: Assume that a 2.3 year-old girl has a total L2 to L4 BMC of 5.9 g. As shown in Table 3, S can be calculated as $0.141 - 0.00142 \times 2.3 = 0.138$ and M is $1.60 + 2.23 \times 2.3 = 6.73$. The z-score of this girl therefore is $\text{Ln}(5.9/6.73)/0.138 = -0.95$. These calculations may appear complicated, but once the equations from Tables 2 and 3 have been entered into a spreadsheet program, z-scores can be computed automatically.

	S	M
L2 to L4		
BMC (g)	$0.141 - 0.00142 \times \text{age}$	$1.60 + 2.23 \times \text{age}$
Areal BMD (mg/cm ²)	$0.084 - 0.00566 \times \text{age}$	$0.291 + 0.105 \times \text{age} - 0.00490 \times \text{age}^2$
vBMD Kroger (mg/cm ³)	$0.084 - 0.00735 \times \text{age}$	$0.219 - 0.00652 \times \text{age} + 0.0111 \times \text{age}^2 - 0.00125 \times \text{age}^3$
vBMD Carter (mg/cm ³)	$0.076 - 0.00643 \times \text{age}$	$0.124 - 0.00454 \times \text{age} + 0.00606 \times \text{age}^2 - 0.00075 \times \text{age}^3$
Area (cm ²)	$0.081 - 0.00087 \times \text{age}$	$5.68 + 4.29 \times \text{age} - 0.374 \times \text{age}^2$

study sites including our center, and in vivo precision for lumbar spine BMD ranged from 0.003 to 0.01 g/cm² ²⁷.

Statistical analysis

The results were expressed in both mean and SD, as they presented a Gaussian distribution. Volumetric BMD was calculated according to the recommended formula for Lunar device $\text{vBMD} = \text{BMD} \times [4 / (\pi \times L)]$; L=width according to the Kroger method²⁸. Linear models were used to compare BMD, BMC and vBMD values between the breastfed versus non-breastfed groups adding age as a covariate. ANOVA study was used to explore differences in BMD, BMC and vBMD and in height and weight standardized z-scores among the 8 different age groups. A two-way ANOVA was performed with a “sex x age group” interaction term to determine if a sex difference emerges in the entire sample. Linear regression analyses were used to determine the correlation between factors such as age, weight and height with BMD and BMC. A sensitivity analysis was performed, to evaluate a distinct correlation between BMD and BMC z-scores and height and weight z-scores, using linear models. Differences were considered statistically significant at $P < 0.05$. Data were analyzed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA).

Cole's LMS method was used to derive age- and sex-dependent normative data²⁹. This method assumes that the data can be transformed to a normal distribution by a suitable power transformation (L). The distribution is then summarized by the median (M) and the coefficient of variation (S). BMD normative curves were created relative to age using LMS Chartmaker Pro version 2.3 (London, UK)²⁹. Specifically, the equations for M and S that describe these age-dependent curves are given in Tables 1 and 2. As indicated by Cole²⁹, a given test result can be converted into the age- and sex-specific z-score using the formula:

$\text{Z-score} = [\text{Ln}(\text{patient's test result}/\text{M})]/\text{S}$ where Ln is the natural logarithm, M corresponds to the age- and sex-specific mean value as derived from the equation in Tables 1 and 2 and S is the age- and sex-specific coefficient of variation derived from the same tables.

Results

Clinical and demographic characteristics

We studied 77 boys and 78 girls (sex ratio= 1:1.01), with an age range from 24 hours of life to 5 years old (mean age at time of DXA: 1.6 years). Among the 165 initially contacted families, 8 refused to participate. One hundred and fifty seven

Table 3. Demographic and BMD results in the 8 age categories.

Category: Age category	1 0-1 month	2 1.1-3 months	3 3.1-6 months	4 6.1-12 months	5 1.1-2 years	6 2.1-3 years	7 3.1-4 years	8 4.1-5 years	Total
Number (total N)	30	12	14	22	20	18	20	19	155
Boys	15	6	8	10	10	8	10	10	77
Height SD	0.07	0.23	0.75	0.29	-0.09	-0.21	0.12	0.55	0.19
Weight SD	0.06	0.69	0.59	-0.18	-0.44	-0.08	0.26	0.46	0.11
BMD Minimum	0.23	0.26	0.27	0.29	0.32	0.39	0.47	0.50	0.23
BMD Maximum	0.37	0.37	0.37	0.43	0.50	0.67	0.70	0.77	0.77
BMD Mean	0.30	0.31	0.32	0.35	0.41	0.52	0.58	0.62	0.43
BMD Median	0.30	0.31	0.33	0.34	0.40	0.51	0.58	0.58	0.38
BMD SD	0.04	0.03	0.03	0.04	0.05	0.07	0.05	0.08	0.13

children were enrolled and valid BMD assessments were obtained for 155 children among which 30 (19.3%) were newborns (15 girls/15 boys). All children were born in Canada with an ethnic distribution of 80% Caucasian, 8% Black, 5% Hispanic, 5% Arabic and 2% Asian. There was no significant difference in the height z-scores among the 8 age categories ($p=0.181$), whereas there was a significant difference in weight z-score, between age categories 2 (1-3 months) and 5 (1-2 years) ($p=0.043$), with the younger age category having a higher weight z-score (Table 3).

Among the children older than one month of age (125 out of 155 patients), 93 (74.4%) had been previously or were currently breastfed. The average duration of breastfeeding in this group was 6.9 months (SD: 4.84 months). Twenty-two children (17.6%) had never been breastfed and there were missing data from 10 patients (8%).

Normative curves

For each age category, BMD and BMC measures presented a Gaussian distribution. The linear model revealed that there was a significant difference in lumbar BMD between boys and girls after adjusting for age group, with girls having higher BMD values as compared to boys ($p=1.4 \times 10^{-4}$). Furthermore, we also sought to determine whether increasing age among boys and girls had an effect on BMD and we observed a significant interaction between age group and sex (p -value for interaction= 0.009). Therefore, although sex per se does not appear to influence BMD, its interaction with age does. However, these results should be interpreted with caution owing to our limited sample size.

According to the LMS method described above, we have plotted curves based on the normative data from our cohort. Therefore, age- and sex-specific reference data for BMD, BMC and volumetric BMD are shown graphically in Figures 1, 2 and 3.

The distribution of BMD values according to age for boys and girls appears in Figure 1. BMD values (grams of hydroxyapatite/cm²) increased with age from birth to 5 years

old ($p<0.001$), with a maximum gain between the age of 1 and 4 years.

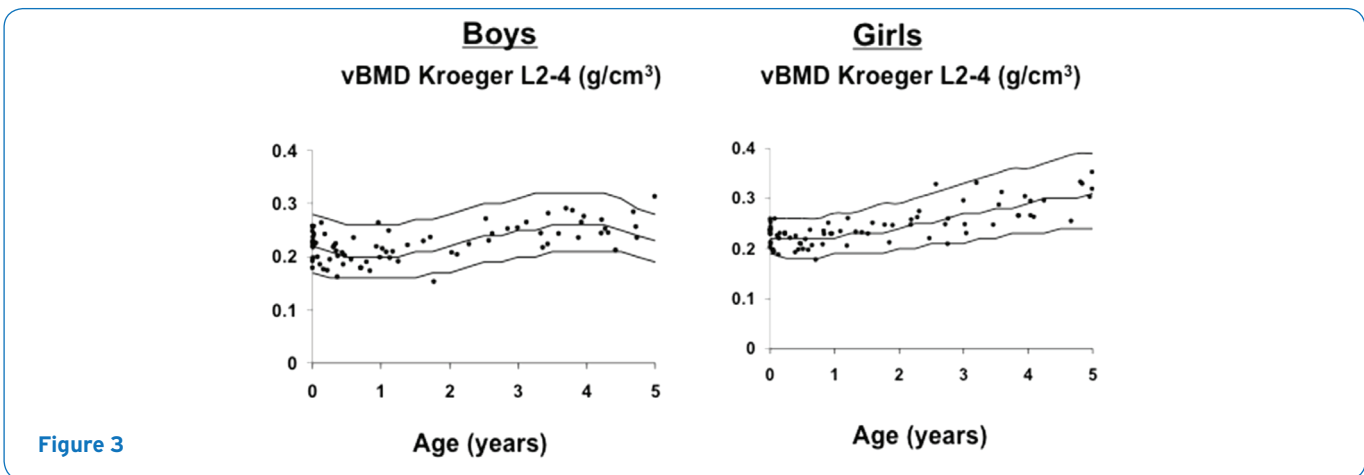
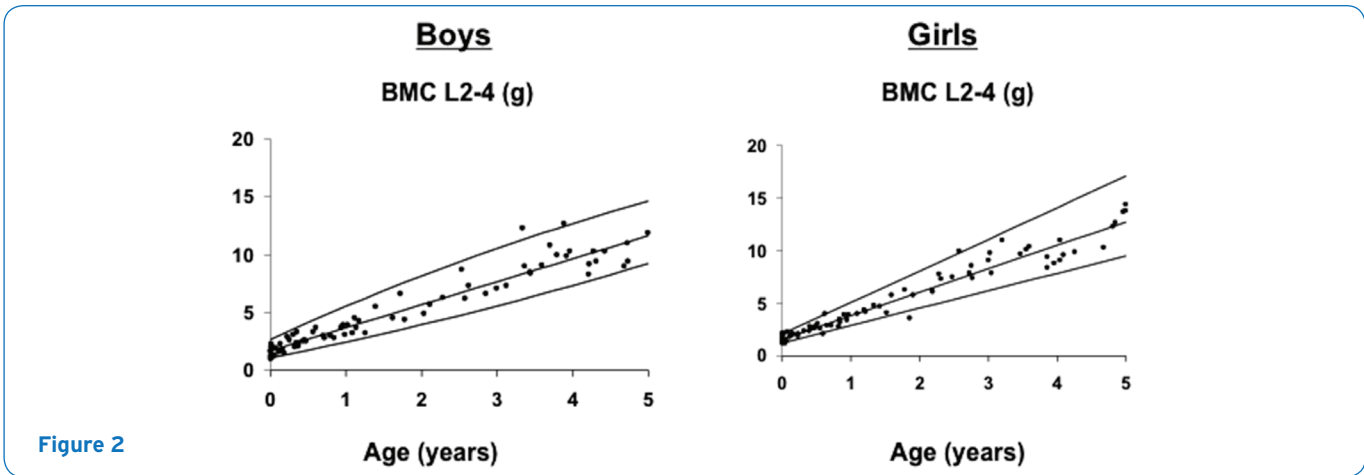
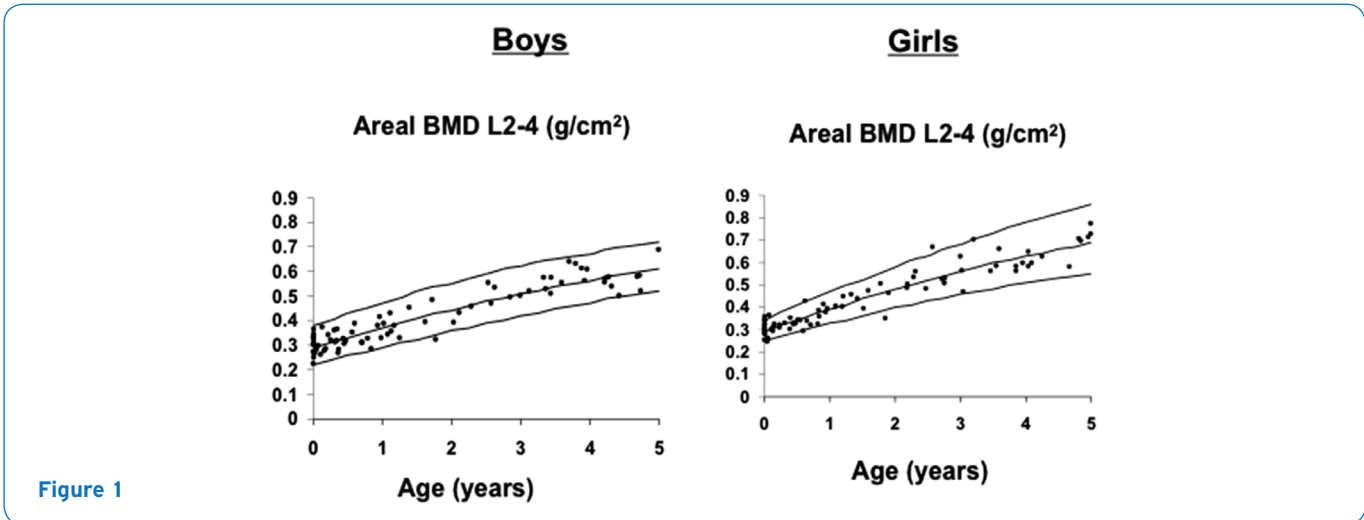
The distribution of BMC values according to age for boys and girls appears in Figure 2. BMC values (grams of hydroxyapatite) increased with age from birth to 5 years old as well ($p<0.001$), with a maximum gain between the age of 2 and 3 years. Respectively, we found a significantly higher lumbar BMC in girls ($p=0.015$) in the entire sample in our linear model with age group and sex as covariates. Again, when we sought to determine whether increasing age among boys and girls had an effect on BMC, we observed a significant interaction between age group and sex (p -value for interaction= 0.016), implying that, although sex itself does not appear to influence BMC, its interaction with age does.

The distribution of vBMD values according to age for boys and girls appears in Figure 3. The vBMD values (grams of hydroxyapatite/cm³) showed a slight increase but did not change significantly with age. Girls had a higher vBMD in the entire sample ($p=6.5 \times 10^{-5}$) in the linear model with age group and sex as covariates. After adding the age group \times sex interaction term we did not observe any difference in the models (p -value for interaction= 0.098), meaning that sex appears to influence vBMD independently from age group. Specifically, we found a significantly higher vBMD in girls in the age groups of 3-4 years old ($p=2.7 \times 10^{-7}$) and 4-5 years old ($p=2 \times 10^{-10}$). Again, these results should be interpreted with caution given the limited sample size.

Factors associated with BMD and BMC

A univariate linear regression analysis was used to identify factors associated with the lumbar BMD. A statistically significant correlation was found between BMD values and age ($R^2=0.86$, $p<0.0001$), weight ($R^2=0.86$, $p<0.0001$), and height ($R^2=0.85$, $p<0.0001$) (Figure 4). As showed in this figure, BMD increase did not follow the same pattern as that of height. Maximum BMD increase appeared in heights between 75 cm and 105 cm, which correspond to ages from 12 months to 4 years. The most significant BMD increase was

Figures 1,2,3. Age-dependant reference ranges for DXA results of the lumbar spine (BMD, BMC, vBMD) for boys and girls. Shown are the mean and the range of 2 standard deviations around the mean.



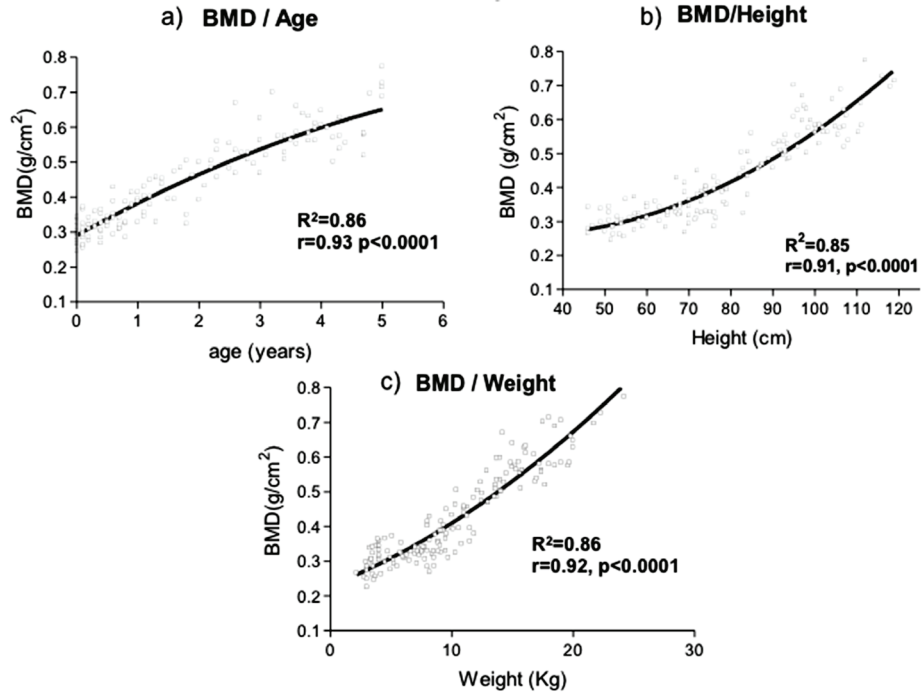


Figure 4. Correlation of BMD to age (a), height (b) and weight (c).

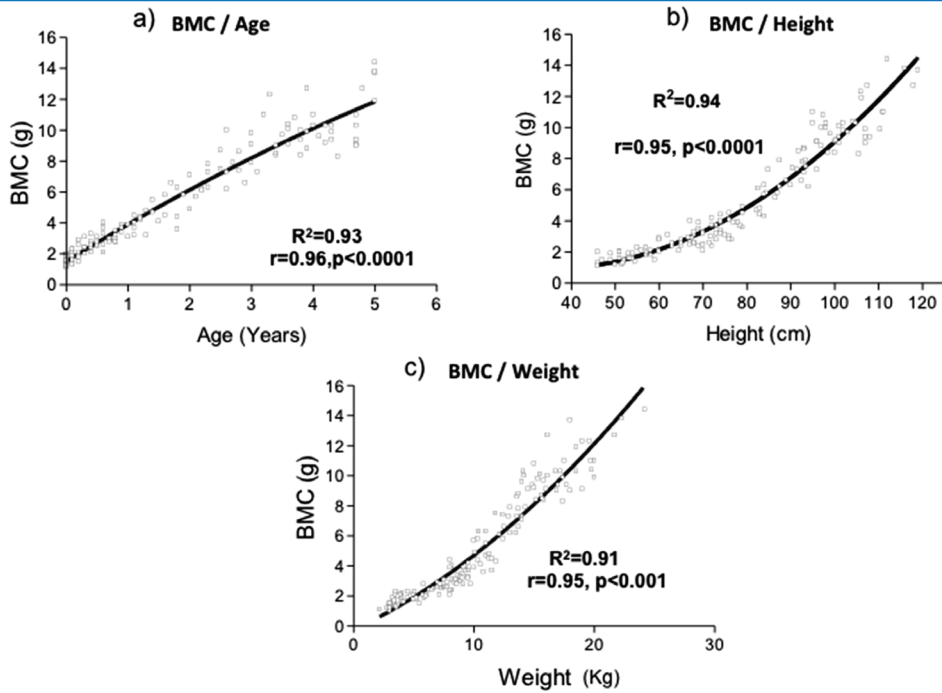


Figure 5. Correlation of BMC to age (a), height (b) and weight (c)

observed between age categories 4-5 and 5-6 (during the second and third year of life).

When we looked at the correlation of BMC and age, weight and height, significant correlations were also found with all three parameters (Figure 5). The strongest correlation was found between BMC and height ($R^2=0.94$, $p<0.0001$). Concurrently with the BMD results, the maximal BMC increase appeared after reaching the height of 75 cm. The average BMC increase for a height gain of 25 cm was 2.3 grams for a height from 50 cm to 75 cm, 5.9 grams for a height from 75 cm to 100 cm, and 11.3 grams from 100 cm to 125 cm.

To further explore the correlation between BMD and BMC and growth parameters taking into account the effect of age and sex, we carried out a sensitivity analysis evaluating the correlation between BMD and BMC z-scores and height and weight z-scores. We found that BMD z-scores were correlated to height z-scores ($p=0.002$) and weight z-scores ($p<0.0001$), but the R^2 scores were lower ($R^2=0.06$ and $R^2=0.19$) than the ones we previously reported. The analysis revealed similar results for the association between BMC z-scores and height and weight z-scores ($R^2=0.13$ and $R^2=0.22$ respectively, p -value <0.0001 for both associations). This discrepancy can be explained by the fact that age and sex themselves explain a part of the variability in the bone outcomes. By standardizing weight and height values, a part of the variability in the bone outcomes previously attributed to these growth parameters disappeared. Nevertheless, the correlation between BMD and BMC and height and weight persisted after standardization for age and sex.

When we looked at the effect of breastfeeding on BMD, BMC and vBMD after adjusting for age, we found no significant difference ($p=0.443$, $p=0.789$ and $p=0.493$ respectively). However, the ratio of breastfed versus non-breastfed was extremely skewed in our cohort since the nutritional impact was not our primary objective. Thus we could not evaluate the impact of breastfeeding in our study.

Discussion

Although several previous studies have established normal reference data for DXA for children and adolescents, relatively little is known about BMD acquisition during the first years of life. In the ISCD Positions of 2007³⁰ guidelines for densitometry in infants and children younger than 5 years old were not included due to lack of sufficient densitometric data on this age group. In the Official Positions of the ISCD published in 2013², recommendations for infants and young children have been added, reflecting the need of research in this area. Infancy and early childhood are important and special periods of growth, of neuromuscular change and of development. But similarly to adolescents and adults, infants and young children may experience diverse chronic medical conditions and/or require pharmaceutical agents that increase bone fragility and fracture risk. When fractures occur without a history of high-energy trauma, identification of abnormal bone structure and/or density may lead to diagnosis

of conditions of bone fragility.

Very few data exist for this age group for the Lunar Prodigy densitometer. Our major aim was to provide normative data for lumbar BMD/BMC values measured with DXA made by this manufacturer in a well-defined Canadian pediatric population from the newborn period to 5 years of age. In our study, all ages were equally represented and a single bone density technologist performed all scans. Our results confirm that DXA performed by Lunar Prodigy can measure lumbar BMC and calculate BMD in this age range.

We also assessed the influence of factors such as age, weight and height on BMD and BMC. According to our results, BMD and BMC values increase with age, weight and height in healthy boys and girls, with the steepest increase observed during the second, third and fourth post-natal year despite the decrease in growth velocity. In this age range, motor development is also maximized with rapid acquisition of important milestones, such as the ability to sit, walk, run and jump. This may explain an increase in bone mass through several pathways, which is well resumed in the model proposed by Rauch et al³¹, based on Frost's mechanostat theory³².

Our results are partially compatible with the study of Xu et al.²². In this study implicating 11,898 Chinese children aged 0 to 3 years, lumbar BMD increased with age among both boys and girls, with the fastest gain observed during the first postnatal year. In the same study, weight appeared to be the strongest factor influencing BMD, in accordance with our results. For BMC, height seemed to have the strongest association in our study. Our results were similar to the findings of Kalkwarf et al², where the maximum increase in BMC and BMD was observed between the ages of 1 and 36 months.

In accordance with previous studies^{1,4,5,22}, we observed that the sex of the child did not appear to influence lumbar BMD independently of the age group, which may be explained by the relatively low influence of circulating sex hormones at the ages of our study population. Although in some studies^{3,33} lumbar BMC was found to be greater in males than in females in the young age groups, no sex difference was observed in BMD or vBMD, but these studies can be hampered by their relatively small sample size^{3,33}. Interestingly, in our study no difference was detected in the BMC values between the two genders, but vBMD was significantly higher in females than in males. A possible explanation for this result could be a polymorphism of the Vitamin D receptor (VDR). According to Tao and colleagues' work³⁴ VDR alleles contribute to lumbar spine volumetric BMD variance in prepubertal girls, but the areal BMD effect reflects the relation between areal BMD and growth. Another explanation could be a relatively smaller vertebral size in females, resulting in a higher volumetric BMD value for the same BMC. In accordance with this hypothesis, a recent study showed a significant sex dimorphism in vertebral size in newborns, with females having smaller vertebral cross-sectional areas compared to boys³⁵.

The weaknesses of our study include our relatively small sample size extending over a large age span which does not allow to classify our findings as reference data. We therefore report our findings as normative values and they should be

interpreted with caution. Nevertheless, these findings should be considered as indicative of trends in the general population and in this sense, they can act as a useful tool to evaluate bone health in young patients. Another limitation of this study is the fact that correlations between birth weight, ethnicity, and vitamin D levels, as possible influential parameters of BMD, could not be studied. We chose lumbar spine for the BMD assessments, but did not look at the total body skeleton for the children aged more than 3 years old, mainly for two reasons: first, the nutritional impact was not our primary outcome and secondly, total body scans are more challenging to perform in young children. Bone age was not assessed but did not appear to be pertinent in our study since we excluded children who were SGA, born prematurely and had a growth delay or chronic condition, all of which could delay bone maturation.

In conclusion, our study provides normative data with DXA for lumbar BMD values in infants and young children and shows that BMD and BMC accretions are not explained by skeletal growth alone. At this specific stage of major physical development, mechanical and motor skill factors appear as possible major contributors to the BMC and BMD gains, in agreement with the mechanostat theory. These data provide useful clues in evaluating bone health and following children at risk of bone pathology during infancy and early childhood in clinical practice. Additional larger studies are needed to establish solid reference data, to determine the place of DXA in the evaluation of bone fragility in young children, to improve DXA interpretation and further our understanding of bone physiology.

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