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ORIGINAL ARTICLE

The development of bone mineral lateralization in the arms

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Abstract

Summary Bone mineral content (BMC) is known to be greater in the dominant arm after the age of 8 years. We studied a group of children and found that BMC sidedness gradually increased up to the age of 6 years and then remained stable into late adolescence.

Introduction Bone mineral content (BMC) exhibits sidedness in the arms after the age of 8 years, but it is not known whether BMC is greater in the dominant arm from birth or whether lateralization develops in early childhood. To address this, we examined bone mineral status in relation to handedness and age.

Methods Subjects ($N=158$) were children recently initiating glucocorticoids for underlying disease (leukemia 43 %, rheumatic conditions 39 %, nephrotic syndrome 18 %). Handedness was determined by questionnaire and BMC by dual-energy X-ray absorptiometry.

Results Median age was 7.2 years (range, 1.5 to 17.0 years), 49 % was male, and the spine BMD Z-score was −0.9 (SD, 1.3). By linear regression, BMC sidedness in the arms was significantly related to age ($r=0.294$, $p=0.0005$). Breakpoint analysis revealed two lines with a knot at 6.0 years (95 % CI, 4.5–7.5 years). The formula for the first line was: dominant:nondominant arm BMC ratio$=0.029\times$age [in years]$+0.850$ ($r=0.323$, $p=0.017$). The slope of the second line was not different from 0 ($p=0.332$), while the slopes for the two lines were significantly different ($p=0.027$).

Conclusions These results show that arm BMC sidedness in this patient group develops up to age 6 years and then remains stable into late adolescence. This temporal profile is consistent with mechanical stimulation of the skeleton in response to asymmetrical muscle use as handedness becomes manifest.

Keywords Biomechanics · Body composition · Bone densitometry · Handedness · Pediatrics

Introduction

> The natural potential of each arm is just about the same, and the difference between them is our own fault, because we've habitually misused them. Plato [1]

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Bone mineral content (BMC) exhibits sidedness in the arms of adults in that the dominant arm has greater BMC than the nondominant limb [2–7]. This lateralization has been shown to be present in children as young as eight, but there is no data prior to this age, so it is not known whether sidedness of arm BMC exists from birth or whether it develops consequent to increasing limb use as handedness becomes manifest [4]. Some studies on human fetal bones suggest that right-sided arm bones may be slightly bigger and heavier than corresponding bones on the left, while other anatomical data indicates no lateralization at birth [8–11]. It has long been recognized that mechanical stimulation influences bone structure to maximize efficiency of load-bearing [12–17]. Hand-use preference appears early in life in some individuals, but it is not fully established until 4 to 5 years of age in most people [18–22]. Consequently, if the dominant arm acquires greater muscle mass and strength than the nondominant one in early childhood through increasingly preferential use, there may be greater muscle-induced load on the bones of the dominant side, and this may, in turn, lead to the higher BMC compared to the nondominant arm [3, 4, 12, 23]. On the other hand, if arm BMC sidedness is present from birth, then this would argue against muscle stimulation from increasingly selective arm use being the determining factor. To evaluate the ontogeny of bone sidedness, we have examined the bone mineral status of the limbs in relation to handedness in children across a range of age.

Materials and methods

Study subjects

Subjects were participants in the Canadian Steroid-associated Osteoporosis in the Pediatric Population (STOPP) research initiative [24–26]. We studied those STOPP subjects from seven research sites for whom whole body dual-energy X-ray absorptiometry (DXA) was available, who completed handedness evaluations, and who had no significant limitations to limb use. This study was approved by the Research Ethics Board in each participating institution and local consent processes were followed. Height and weight Z-scores were determined as previously described [24–26].

Bone mineral densitometry

Bone mineral density (BMD) and BMC were measured by whole body DXA using either Hologic QDR 4500 (four centers) or Lunar Prodigy (three centers). Spine in vivo precision was performed at five centers, with root mean square standard deviation precision values of 0.006 to 0.017 g/cm^2 for spine BMD and 0.63 to 1.69 g for spine BMC. Total body sub-region precision was done at two research sites, with root mean square standard deviation values of 0.011 to 0.015 g/cm^2 for arm BMD and 3.21 to 4.27 g for arm BMC, and 0.010 to 0.017 g/cm2 for leg BMD and 5.05 to 5.38 g for leg BMC. “Arm” and “leg” regions were delineated by the DXA programs. The arm included the upper arm, lower arm, and hand. The leg included the upper leg, lower leg, and foot. Since the densitometric parameter used for analysis was the ratio between right and left limbs (for either BMC or BMD), no cross-calibration of machines was required for limb measurements (since both numerator and denominator would be multiplied by the same correction factor, which would reduce to one). Spine BMD was also measured to characterize the population, with cross-calibration and Z-score determination as previously described [24]. Bone age was assessed on radiographs of the left hand and wrist [24].

Handedness assessment

Handedness was determined by questionnaire, done a median of 2 years 7 months after the DXA scan (range, 9 months to 5 years 1 month) to allow for maturation of handedness preference. For children aged 6 years or older at the time of handedness assessment (n=149), a variation of a modified Edinburgh Handedness Inventory questionnaire was used that was answered by subjects or parents [20, 21]. Nine activities were classified as done using the left hand, right hand, or both for writing or printing, drawing, throwing a ball, using scissors, using a TV remote control, holding a toothbrush, holding a knife without a fork, holding a spoon, and pulling a tab on a can or twisting the cap off a bottle. A shortened 5-point version that omitted questions about activities unlikely to be performed by younger children was used for subjects aged 4 to 5 years (n=9). This questionnaire included drawing, throwing a ball, using scissors, holding a toothbrush, and holding a spoon. For both age groups, each item was scored 1 point if the right hand was used to perform that activity, 0 if the left hand was used, and 0.5 point if both hands were used. The overall handedness results for each individual were expressed as the percentage of the maximum pure right hand score. Left hand dominance was arbitrarily defined as a handedness score of ≤5.5 % in order to include both those who did all activities with the left hand (score of 0 %) and those age six or older who did most activities with the left hand but a single activity using either hand (which gave a score of 5.5 %). Right hand dominance was arbitrarily defined as a handedness score ≥88.9 %. This included those completely right handed (score of 100 %); those 6 years or older who did most activities with the right hand but a single activity using either hand (which gave a score of 94.4 %); and those 6 years or older who did most activities with the right hand but one activity solely with the left hand or two activities using either hand (both combinations of which produced a percentage score of 88.9 %). All intermediate scores were considered mixed handedness. Analysis was also done on individuals with pure left or right handedness (0 % or 100 %). The dominant leg was assigned based on the side of hand dominance [27–30].

Statistical methods

Analyses were conducted using SPSS 16.0 (SPSS Inc., Chicago, IL). Baseline population characteristics are expressed as median and range or mean and standard deviation (SD) for continuous variables, while discrete variables are expressed as the value and percentage frequency. Linear regression and residual analysis were performed to assess the relationships between bone mineral ratios and age. Knot (breakpoint) analysis was done by determining the two best-fit linear regression lines and their intercept using a program provided by David Matheson of SPSS. Clinical parameters were compared using chi-square, Mann–Whitney, or Fisher's exact tests. Primary analyses were performed on subjects with dominant handedness, including all subjects (referred to as Cohort 1), those under age 6 years, those 6 years of age or older, and the group of children excluding those with rheumatic conditions. Some analyses were also done on those with pure handedness (handedness scores of 0 % or 100 %) and on all children 6 years of age or older (Cohort 2). All reported *p* values are two-tailed and those less than 0.05 were considered to be statistically significant.

Results

Study subjects

One hundred fifty-eight subjects participated in this study, of whom almost half (n=78) were male (Table 1). Median age was 7.2 years (range, 1.5 to 17.0 years) with bone age being similar. Height and weight Z-scores were close to average for age while the spine BMD Z-score was −0.9 (SD, 1.3). Leukemia was the most common diagnosis (43 %), followed by rheumatic conditions (39 %), and nephrotic syndrome (18 %). The average time from initiation of glucocorticoid therapy until DXA scanning was 16 days (SD, 10 days).

Left hand dominance as defined for the main analysis was present in 10 (6.3 %) individuals (8 with handedness scores of 0 %, 2 with scores of 5.5 %), right hand dominance was present in 127 (80.4 %) subjects (90 with handedness scores of 100 %, 12 with scores of 94.4 %, and 25 with scores of 88.9 %), and mixed handedness was present in 21 (13.3 %; handedness scores ranging from 20 % to 83.3 %).

Limb BMC and BMD in relation to age

The initial analysis was done using subjects with dominant left or right handedness (Cohort 1; n=137; Table 1). Cohort 1 retained similar characteristics to the entire study population with no statistical differences for gender, age, bone age, disease category, height Z-score, weight Z-score, spine BMD Z-score, or days on glucocorticoids. Limb mineral was expressed as the ratio of the value in the dominant limb to the value of the nondominant limb (Fig. 1). Arm BMC and BMD ratios and leg BMC and BMD ratios were evaluated in relation to age by linear regression. The arm BMC ratio (Fig. 1a) and the leg BMD ratio (Fig. 1d) were significantly correlated with age. The relationship of arm BMC sidedness to age was: dominant:nondominant arm BMC ratio=0.00604×age [in years]+0.958 (r=0.294; p=0.0005). Leg BMD sidedness was related to age by the formula: dominant:nondominant leg BMD ratio=0.0017×age [in years]+0.993 (r=0.193; p=0.024). The relationships were not statistically significant for BMD sidedness in the arms (Fig. 1b; p=0.312) or BMC sidedness in the legs (Fig. 1c; p=0. 202). Since the primary intent of the study

Table 1 Subject characteristics

Parameter	All (N=158)	Cohort 1[a] (n=137)	Cohort 2[b] (n=94)
Male (%)	78 (49)	64 (47)	42 (45)
Age, years, median (range)	7.2 (1.5–17.0)	7.6 (1.5–17.0)	10.6 (6.1–17.0)
Bone age, years, median (range)	6.8 (1.9–17.0)	6.8 (1.9–17.0)	11.0 (4.6–17.0)
Diagnosis (%)			
Leukemia	68 (43)	58 (42)	36 (38)
Rheumatic conditions	61 (39)	56 (41)	45 (48)
Nephrotic syndrome	29 (18)	23 (17)	13 (14)
Height Z-score (SD)	+0.1 (1.0)	+0.1 (1.0)	0.0 (1.0)
Weight Z-score (SD)	+0.4 (1.2)	+0.2(1.2)	+0.1 (1.1)
Spine BMD Z-score (SD)	−0.9 (1.3)	−0.9 (1.3)	−0.7 (1.3)
Days on glucocorticoids (SD)	16 (10)	16 (10)	15 (10)

[a] Cohort 1 was comprised of subjects with dominant left or right handedness

[b] Cohort 2 was comprised of subjects over age 6 years

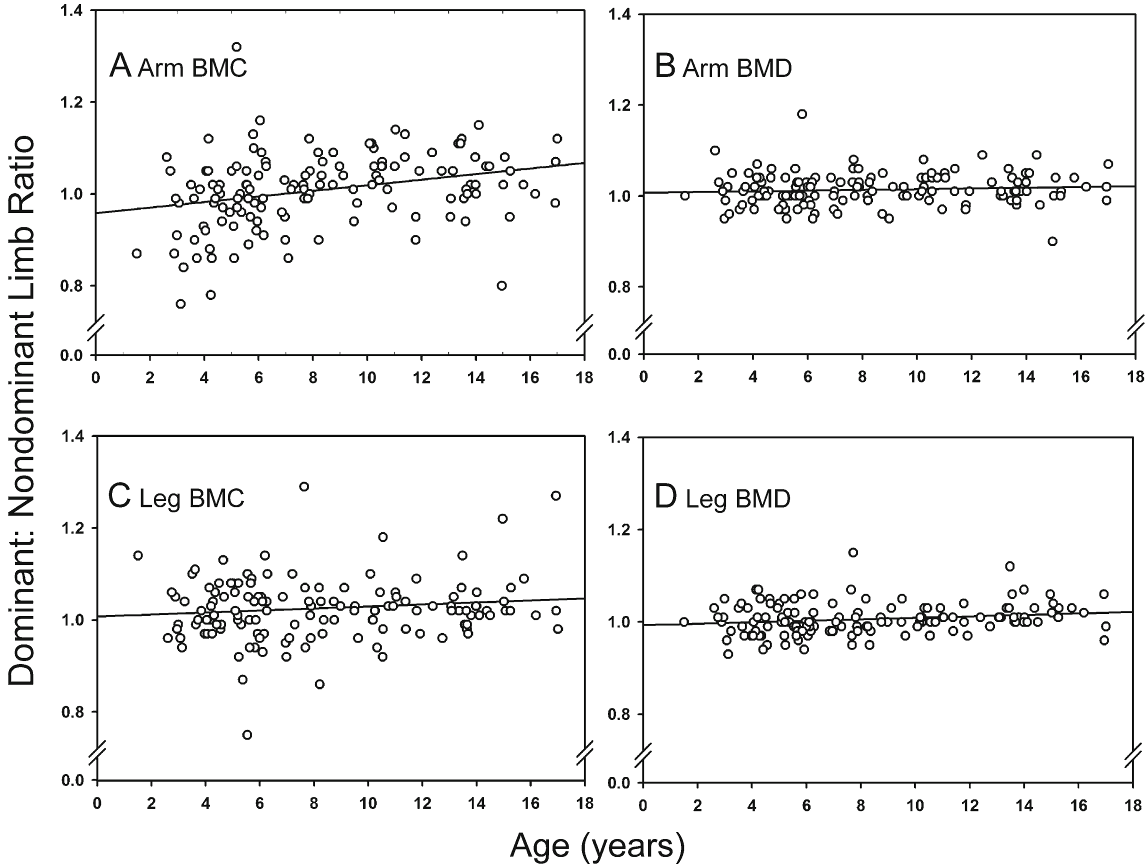

Fig. 1 Ratios of dominant to nondominant limb mineral for subjects with left or right hand dominance. (**a**) Arm BMC ratio. (**b**) Arm BMD ratio. (**c**) Leg BMC ratio. (**d**) Leg BMD ratio. The slopes were significant for arm BMC (r=0.294; p=0.0005) and leg BMD (r=0.193; p=0.024)

was to investigate arm mineral lateralization in relation to handedness, and since the arm BMC relationship was stronger than the leg BMD sidedness, further analysis was carried out on arm BMC ratios.

Knot analysis of arm BMC in relation to age

Residual analysis of the linear regression results for arm BMC ratios in relation to age had a funnel appearance for the unstandardized residuals and studentized residuals (Fig. 2). The graphs showed greater variability at younger ages, indicating that a single line was not the optimal description of the relationship [31]. The graphical appearance of arm BMC vs. age (Fig. 1a) suggested that two slopes might be present, with the BMC ratio increasing in younger children and then stabilizing across older ages, so knot (breakpoint) analysis was carried out (Fig. 3). Knot analysis revealed two lines with a knot at 6.0 years (95 % CI, 4.5–7.5 years). The formula for the first line was: dominant:nondominant arm BMC ratio=0.029×age [in years]+0.850 (r=0.323; p=0.017). The 95 % CI on the slope was 0.005 to 0.052 per year. For the second line, after age six, the formula was: dominant:nondominant arm BMC ratio=0.002×age [in years]+1.002. The 95 % CI on the slope was −0.002 to 0.007 per year, not significantly different from 0 (r=0.108; p=0.332). The slopes for the two lines were significantly different (p=0.027). Residual analysis of the linear regression results for both lines showed equal variances across the full age ranges.

When subjects with pure left or right handedness (scores of 0 % or 100 %) were assessed, the knot and slopes for the two lines were similar to the results for Cohort 1, with a knot at 5.8 years (95 % CI, 4.3–7.4 years), the slope for the first line at 0.040 per year (95 % CI, 0.009 to 0.071; r=0.396; p=0.014), and the slope for the second line not significantly different from 0 (95 % CI, −0.005 to 0.006; p=0.886) but different from the slope of the first line (p=0.011). The knot was not different from the knot for Cohort 1 (p=0.853), and the slopes of the two lines were not different from the corresponding slopes for Cohort 1 (for first line slopes, p=0.568; for second line slopes, p=0.610).

Subjects with dominant handedness (Cohort 1) were divided into two groups based on the knot point: 6 years of age or younger (n=64) and over 6 years (n=94). The median age for the young group was 4.6 years (range, 1.5–

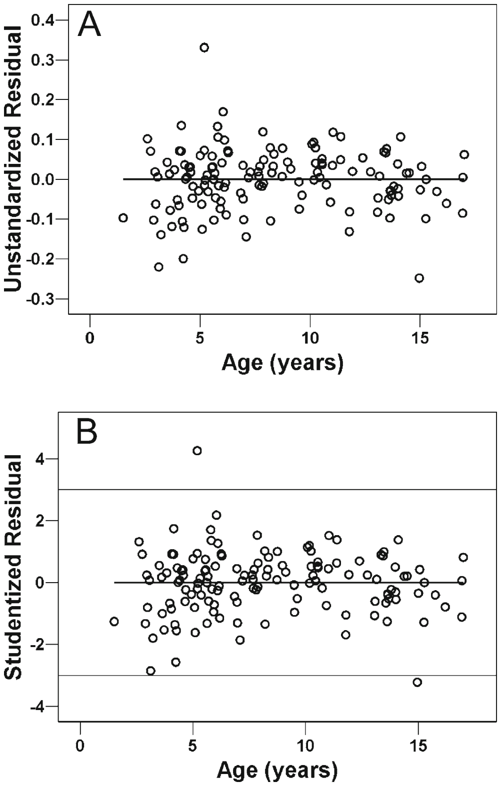

Fig. 2 Residual graphs for dominant to nondominant arm BMC ratios for subjects with left or right hand dominance. (**a**) Unstandardized residuals vs. age. (**b**) Studentized residuals vs. age. Plots show funnel patterns with more spread at lower ages

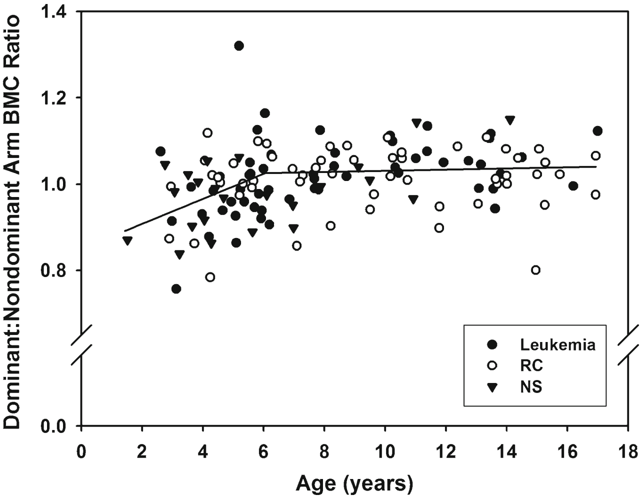

Fig. 3 Knot (breakpoint) analysis of dominant to nondominant arm BMC ratios revealed two lines with a knot at 6.0 years (95 % CI, 4.5–7.5 years). The slope for the first line was 0.029/year (95 % CI, 0.005 to 0.052; r=0.323; p=0.017). The slope for the second line was not different from 0 (95 % CI, −0.002 to 0.007; r=0.108; p=0.332). The slopes for the two lines were significantly different (p=0.027). *Solid circles* are children with leukemia, *open circles* are children with rheumatic conditions, and *solid triangles* are children with nephrotic syndrome

6.0 years) and the older group had a median age of 10.6 years (range, 6.1–17.0 years). The two age groups did not differ in gender, disease category, height Z-score, weight Z-score, spine BMD Z-score, or days on glucocorticoids. The dominant to nondominant arm BMC ratio was 0.97 (SD, 0.10) for the young group compared to 1.03 (SD, 0.08) for those over 6 years of age (p=0.00006). Similar dominant to nondominant arm BMC ratio differences between age groups were present when rheumatic conditions were excluded so that only subjects with leukemia and nephrotic syndrome were analyzed (0.97±0.09 for 6 years of age (n=48) or under vs. 1.04±0.06 for those over 6 years (n=49), p=0.00009).

Arm BMC sidedness in relation to handedness

To explore the relationship of BMC sidedness to handedness after stabilization of the dominant to nondominant arm BMC ratio, further analysis was done on all subjects over age 6.0 years (Cohort 2, n=94; Table 1). This cohort included those with left hand dominance (n=9), mixed handedness (n=11), and right hand dominance (n=74). These groups did not statistically differ for gender, age, bone age, diagnosis, height Z-score, weight Z-score, spine BMD Z-score, or days on glucocorticoids. For these three groups, right to left arm BMC ratios were assessed (note that this is different from the dominant to nondominant ratios previously presented; Fig. 4). For the left handers, the ratio was 0.98 (SD, 0.08); for those with mixed handedness, the ratio was 1.05 (SD, 0.09); and for right handers, it was 1.03 (SD, 0.07). The ratio for left handers differed from that of right-handed subjects (p=0.036), while the ratio for mixed handers did not differ from that of left handers (p=0.152) or right handers (p=0.565).

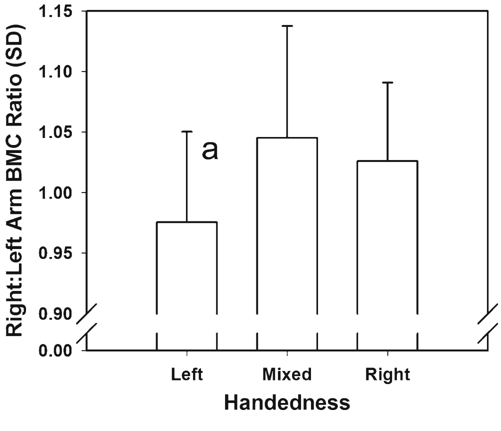

Fig. 4 Right to left arm BMC ratios for left-handed (n=9), mixed-handed (n=11), and right-handed (n=74) children over age 6.0 years of age. The ratio for left handers differed from that of right handers (p=0.036) while the ratios for mixed-handers did not differ from left-handers (p=0.152) or right-handers (p=0.565). *a* p=0.036 compared to right handed subjects

Discussion

The temporal profile we observed for the development of arm BMC sidedness is consistent with mechanical stimulation of the skeleton in response to asymmetrical muscle use as handedness becomes manifest in early childhood. In our patient group, BMC sidedness increased up to age 6.0 years (95 % CI, 4.5–7.5 years) and then remained stable with a dominant to nondominant ratio similar to that reported in adults and normal children over age eight [2–4]. Bone in this pre-pubertal growth phase appears to be highly responsive to mechanical loading, as active bone apposition is more sensitive to mechanical stimulation [12, 13, 15, 17]. The skeletal loading is provided by rising muscle mass and strength, which is enhanced by physical activity [4, 5, 12, 13, 15–17, 32]. It is likely that as the dominant arm develops greater muscle mass and strength than the nondominant arm due to a higher level of use, this serves as the stimulus for greater bone growth and BMC accumulation on the dominant side.

Overt hand preference starts to become apparent around 18 months to 2 years of age, and the proportion of children showing clear hand dominance then gradually increases so that most children around age four to five show a preference [18, 20]. During the crawling phase of infants, even in those with overt side preference, both upper limbs are likely exposed to similar levels of mechanical stimulation [8]. Only after walking begins in the second year is there the opportunity for substantial selective use of the preferred arm [8]. Some time would be required after this to stimulate the muscles and then bones of the dominant side, consistent with our observation of increasing sidedness of arm BMC from 2 years to 6 years.

The fact that this dominant to nondominant profile was observed for arm BMC but not arm BMD indicates that the observed sidedness relates to increasing bone size with unchanged BMD rather than an effect on density. This is consistent with data in children showing that bone volume and BMC increase with age in direct proportion to increasing muscular strength, while volumetric BMD remains relatively stable [12, 32]. In a similar manner, vigorous exercise of the arms has the greatest effect on increasing total mineral and bone size, rather than increasing volumetric density [6].

Very limited assessment of handedness was undertaken in most studies examining effects of handedness on arm mineral laterality in adults. Many studies, for example, simply asked which hand was dominant or which was used for writing [4, 7, 23]. We employed a more detailed assessment, allowing us to classify individuals as left-handed, mixed-handed, or right-handed [20, 21]. The validity of this approach was confirmed by the fact that the results using this definition of dominance were statistically identical to those found using individuals with pure left or right handedness. Further, when we examined children and adolescents over 6 years of age, when the ratio of dominant to nondominant arm BMC is stable, we found that the right to left arm BMC ratio was lower among left handers than right handers, again confirming the utility of our definition.

This lower right to left arm BMC ratio in left handers reflects lesser use of the right hand, as would be anticipated. Children with mixed handedness, however, showed the same right to left ratio as right handers. This likely results from the fact that although these children used each of their hands preferentially in certain activities, they likely used the right hand for the most intense activities, a necessity thrust upon them by the facts that most tools and domestic devices are designed for right-handed use and that cultural constraints sometimes favor using the right hand [8, 18].

There is an alternative possibility to muscle use causing the relative increase in arm BMC on the dominant side, which is that lateralization of arm mineral is genetically determined so that it develops independently of the level of muscle stimulation [18, 33]. One gene associated with handedness has been identified, and handedness has been associated with a large number of anatomical, physiological, and behavioral characteristics in many body systems that have nothing to do with use of the limbs, including skeletal manifestations such as hyperkyphosis [18, 33, 34]. It is possible that lateralization of bone mineral is genetically linked to handedness and is not a consequence of arm use and muscle stimulation of bone.

We found that the intercept at age 0 years for the line relating the dominant to nondominant arm BMC ratio to age was 0.85 (95 % CI, 0.74 to 0.95). This suggests that there is a lower BMC value in the dominant limb at birth, but caution needs to be exercised in interpreting this extrapolated value as our data set does not extend below age 2 years. There is limited literature for comparison, but a study of archeological samples similarly found lower right to left ratios (as a surrogate for dominant to non-dominant ratios) for several humerus measurements in those under 1 year of age [8]. The ratios for those over 1 year of age were greater than 1.0 and the differences were statistically significant. Taken together, these findings suggest that the dominant arm at birth has smaller size and lower BMC than the nondominant arm. Further studies are needed to explore this intriguing finding.

The principle limitation to our study is that the children we studied were not randomly chosen from a normal population. The study subjects were children with underlying diseases who had several weeks of exposure to glucocorticoids and some of whom had exposure to other bone-toxic medications [24–26]. Individuals with impaired limb function were excluded from the study and there is no reason to expect that the underlying conditions or drugs would selectively alter the dominant to nondominant BMC ratio at younger ages. Although some children in the study had rheumatic conditions, the dominant to nondominant arm BMC ratios were unchanged when these subjects were excluded. A related limitation is that our study was cross-sectional. It will be of interest to monitor our children prospectively to see if individuals follow the same pattern we have observed by cross-sectional analysis. The most definitive data would come from a prospective study of randomly selected healthy children, and such data will be necessary before concluding that the observed temporal profile is the normal bone mineral accrual pattern.

In conclusion, we have found that in our subjects the ratio of dominant to nondominant arm BMC increases from age 2 years to 6 years, after which it is stable. Beyond age six, arm BMC is higher on the left in left handers and higher on the right in right handers, while individuals with mixed handedness also have higher BMC on the right. This study provides insight into the temporal emergence of relatively greater mineral in the dominant arm and provides guidance for forearm densitometry in children.

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Conflicts of interest None.

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