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The pattern of trabecular bone microarchitecture in the distal femur of typically developing children and its effect on processing of magnetic resonance images

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Abstract

Introduction—Magnetic resonance imaging (MRI) is used to assess trabecular bone microarchitecture in humans; however, image processing can be labor intensive and time consuming. One aim of this study was to determine the pattern of trabecular bone microarchitecture in the distal femur of typically developing children. A second aim was to determine the proportion and location of magnetic resonance images that need to be processed to yield representative estimates of trabecular bone microarchitecture.

Materials and methods—Twenty-six high resolution magnetic resonance images were collected immediately above the growth plate in the distal femur of 6–12 year-old typically developing children ($n = 40$). Measures of trabecular bone microarchitecture [i.e., apparent trabecular bone volume to total volume (appBV/TV), trabecular number (appTb.N), trabecular thickness (appTb.Th) and trabecular separation (appTb.Sp)] in the lateral aspect of the distal femur were determined using the twenty most central images (20IM). The average values for appBV/TV, appTb.N, appTb.Th and appTb.Sp from 20IM were compared to the average values from 10 images (10IM), 5 images (5IM) and 3 images (3IM) equally dispersed throughout the total image set and one image (1IM) from the center of the total image set using linear regression analysis. The resulting mathematical models were cross-validated using the leave-one-out technique.

Results—Distance from the growth plate was strongly and inversely related to appBV/TV ($r^2 = 0.68$, $p < 0.001$) and appTb.N ($r^2 = 0.92$, $p < 0.001$) and was strongly and positively related to appTb.Sp ($r^2 = 0.86$, $p < 0.001$). The relationship between distance from the growth plate and

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appTb.Th was not linear ($r^2 = 0.06$, $p = 0.28$), but instead it was quadratic and statistically significant ($r^2 = 0.54$, $p < 0.001$). Trabecular bone microarchitecture estimates from 10IM, 5IM, 3IM and 1IM were not different from estimates from 20IM ($p > 0.05$). However, there was a progressive decrease in the strength of the relationships as a smaller proportion of images were used to predict estimates from 20IM ($r^2 = 0.98$ to 0.99 using 10IM, 0.94 to 0.96 using 5IM, 0.87 to 0.90 using 3IM and 0.66 to 0.72 using 1IM; all $p < 0.001$). Using the resulting mathematical models and the leave-one-out cross-validation analysis, measures of trabecular bone microarchitecture estimated from the 10IM and 5IM partial image sets agreed extremely well with estimates from 20IM.

Conclusions—The findings indicate that partial magnetic resonance image sets can be used to provide reasonable estimates of trabecular bone microarchitecture status in the distal femur of typically developing children. However, because the relative amount of trabecular bone in the distal femur decreases with distance from the growth plate due to a decrease in trabecular number, careful positioning of the region of interest and sampling from throughout the region of interest is necessary.

Keywords

magnetic resonance imaging; bone microarchitecture; children; pediatrics

1.1 Introduction

Trabecular bone microarchitecture is an important aspect of the skeleton and is an independent predictor of fracture risk [1]. This has led to the development of *in vivo* techniques to assess the trabecular bone microarchitecture using magnetic resonance imaging (MRI) and computed tomography. Magnetic resonance imaging is particularly attractive for the assessment of trabecular bone microarchitecture in children because it does not expose them to ionizing radiation. Despite the increased use of MRI to assess trabecular bone microarchitecture in children [2, 3] and adults [4–7], one of the limitations of the procedure is the amount of processing time required especially when a large number of images are collected and multiple sites are studied.

To reduce image collection and processing time, some investigators have used as little as one image to predict the tissue composition of a specific region of the body or the total body [8, 9]. However, this may be problematic in studies of children in whom bone is undergoing modeling and bone length is increasing [8, 10]. Studies examining the pattern of trabecular bone microarchitecture in children are needed to determine if fewer images can be used to evaluate trabecular bone microarchitecture or if the selection of images is dependent on the pattern of the bone microarchitecture. One aim of this study was to determine the pattern of trabecular bone microarchitecture in the distal femur of typically developing children. A second aim was to determine the proportion and location of magnetic resonance images that need to be processed to yield representative estimates of trabecular bone microarchitecture.

1.2 Materials and Methods

Forty seven children, ranging from age 6 to 12 years, and between the 5th and 95th age-based percentiles for height and weight were enrolled in the study. No participants were taking medications known to affect bone and all were without a prior fracture in the region of interest (i.e. distal femur). The participants were recruited from the Newark, DE community and the AI duPont Hospital for Children in Wilmington, DE. The Institutional Review Boards at the University of Delaware and the AI duPont Hospital for Children approved the study. Written consent was given by parents and written assent was given by children before testing.

1.2.1 Anthropometrics

Anthropometrics were assessed without shoes and with minimal clothing. Height was measured to the nearest 0.1 cm using a stadiometer. Body mass was measured to the nearest 0.2 kg using a digital scale. Height, body mass, and BMI percentiles were determined using normative graphs published by the Center for Disease Control [11].

1.2.2 Tanner Staging

Sexual maturity was determined by a physician assistant using the Tanner staging technique [12]. Signs of pubic hair growth and testicular/penis development were assessed in boys and signs of pubic hair and breast development were assessed in girls. The rating system ranges from 1 to 5, with 1 indicating no signs of sexual development, 2 indicating early sexual development and 5 indicating full development.

1.2.3 Magnetic Resonance Imaging

Magnetic resonance images of the nondominant distal femur were collected with a GE 1.5 Tesla MRI (Milwaukee, WI). A phased array coil (USA Instruments; Aurora, OH) was secured to the lateral portion of the nondominant distal femur using a VacFIX system (PAR Scientific A/S; Sivlandvaenge, Denmark). Children were immobilized from the waist down using the BodyFIX (Medical Intelligence, Inc., Schwabmunchen, GER), as previously described [2]. After participants were immobilized, the distal femur was identified using a three-plane localizer. Then, 26 high resolution axial images were collected from the metaphysis, immediately above the growth plate using a 3D fast gradient echo sequence with a partial echo acquisition (echo time = 4.5 ms; repetition time = 30 ms; 30° flip angle; 13.89 kHz bandwidth), a 9 cm field of view and an imaging matrix of 512 × 384. The reconstructed voxel size was 175 × 175 × 700 μm³. Scan time was approximately 7 minutes. Distance from the growth plate was determined by multiplying image thickness (700 μm) by image number.

The lateral half of the 20 most central images of the distal femur (20IM; images 4 – 23) were analyzed using custom software created with Interactive Data Language (IDL; Research Systems, Inc, Boulder, CO). The lateral half was chosen for analysis because the coil placement on the lateral aspect of the bone resulted in a greater signal to noise ratio on the lateral than the medial half of the bone. The first three and last three images were not analyzed because their radio frequency excitations were different from the more central

images. The analysis software was patterned after the procedure described by Majumdar et al. [5] and has been used previously [2, 3]. A summary of the collection and analysis procedures is presented in Figure 1.

The average values for apparent trabecular bone volume to total bone volume (appBV/TV), trabecular number (appTb.N), trabecular thickness (appTb.Th) and trabecular separation (appTb.Sp) for the entire set of images analyzed (20IM) were compared against average values taken from partial image sets in which 10 images (10IM; every other image), 5 images (5IM; images 4, 9, 14, 19, 23), and 3 images (3IM; images 4, 14, 23), and values taken from a single image located at the middle of the image set (1IM; image 14) were used. A single investigator analyzed all images to ensure consistency. The reproducibility of the assessment of procedure was determined in typically developing children and in children with cerebral palsy ($n = 6/\text{group}$) with coefficients of variation ranging from 2 to 3 % and intraclass correlation 94 % [2].

1.2.4 Statistical analysis

Data were analyzed using SPSS (Version 17.0, Chicago, IL). Descriptive statistics for all variables were conducted to screen for outliers and to assess normality. Height, body mass and BMI percentiles were compared to their respective 50th age-based percentile using a one-sample t-test. Linear regression analysis was used to determine the relationship between measures of trabecular bone microarchitecture (i.e., appBV/TV, appTb.N, appTb.Th and appTb.Sp) and distance from the growth plate in the distal femur. If the relationships were not linear, alternate models were explored. Analysis of variance with repeated measures was used to determine if measures of trabecular bone microarchitecture from the partial image sets (10IM, 5IM, 3IM and 1IM) were different from 20IM. Linear regression analysis was also used to determine the relationships between estimates of trabecular bone microarchitecture using the partial image sets vs. 20IM. The resulting mathematical models were cross-validated using the same sample of typically developing children and the leave-one-out technique [13]. Alpha level was set at $p = 0.05$. A Bonferroni correction was employed for multiple comparisons.

1.3 Results

To minimize the potential effects of sexual maturity, only children with a Tanner stage of I or II were included in the study. Height ($51 \% \pm 25 \%$), body mass ($51 \% \pm 26 \%$), and BMI ($52 \% \pm 30 \%$) of the 40 children included in the final analysis were not different from the 50th percentile for age based norms ($p > 0.05$). To demonstrate the pattern of trabecular bone microarchitecture in the distal femur, scatter plots of the distance from the growth plate vs. measures of trabecular bone microarchitecture are reported in Figure 2. Distance from the growth plate was strongly and inversely related to appBV/TV ($r^2 = 0.68$, $p < 0.001$) and appTb.N ($r^2 = 0.92$, $p < 0.001$) and was strongly and positively related to appTb.Sp ($r^2 = 0.86$, $p < 0.001$). The relationship between distance from the growth plate and appTb.Th was not linear ($r^2 = 0.06$, $p = 0.28$), but instead it was quadratic and statistically significant ($r^2 = 0.54$, $p < 0.001$).

A comparison of trabecular bone microarchitecture measures from partial image sets and 20IM is presented in Table 1. There were no significant differences between trabecular bone microarchitecture measures from 10IM, 5IM, 3IM or 1IM vs. 20IM ($p > 0.05$). Scatter plots demonstrating the relationship between estimates of trabecular bone microarchitecture from partial image sets vs. 20IM are shown in Figures 3–6. Trabecular bone microarchitecture estimates from all partial image sets were positively and strongly related to estimates from 20IM. However, there was a progressive decrease in the strength of the relationships as a smaller proportion of images were used to predict estimates from 20IM ($r^2 = 0.98$ to 0.99 using 10IM, 0.94 to 0.96 using 5IM, 0.87 to 0.90 using 3IM and 0.66 to 0.72 using 1IM; all $p < 0.001$). Using the resulting regression models presented in Table 2, and the leave-one-out crossvalidation analysis, measures of trabecular bone microarchitecture estimated from partial image sets agreed extremely well when 10IM and 5IM were used as indicated by a very high degree of variance explained ($r^2 = 0.98$ to 0.99 for 10IM and 0.93 to 0.96 for 5IM; all $p < 0.001$), low SEEs (0.4 to 1.2 % for 10IM and 1.0 to 2.0 % for 5IM), and a lack of significant or meaningful differences ($p > 0.95$). A similar pattern was observed for 3IM and 1IM, although the variances explained were lower ($r^2 > 0.85$ for 3 IM and > 0.62 for 1IM; all $p < 0.001$) and the SEEs were higher (1.4 to 3.2 % for 3IM and 2.2 to 5.4 % for 1IM).

1.4 Discussion

To our knowledge, this is the first study to examine the pattern of trabecular bone microarchitecture in typically developing children. We found that appBV/TV and appTb.N decreased, and appTb.Sp increased with an increase in distance from the growth plate and toward the femoral diaphysis in typically developing children. This pattern is consistent with the decrease in trabecular bone density with increased distance from the growth plate in the proximal tibia of children with cerebral palsy previously reported [8] and in the distal radius of typically developing children [10]. On the other hand, it is inconsistent with the increase in appTb.N and the decrease in appTb.Sp with increased distance from the growth line toward the femoral diaphysis in adults [4]. The decrease in appBV/TV and appTb.N observed in the present study of children may be related to the uncoupled resorption of trabecular bone that occurs above the growth plate in the distal femur to accommodate the longitudinal growth of the bone [14].

Another novel finding in the present study was the strong agreement between trabecular bone microarchitecture estimates from partial image sets and total image sets. Although the relationships progressively weakened as the number of images used to predict the total decreased, the relationships were still moderately strong even when only a single image was used. The findings are consistent with studies of other tissues. For example, moderate to strong correlations between muscle area and adipose tissue area from a single image collected at different places within the abdomen and total body muscle volume and total body adipose tissue volume have been reported in adults [9]. Furthermore, a strong relationship between trabecular bone density from a single image in the metaphysis of the proximal tibia vs. the average trabecular bone density from images representing the entire metaphysis ($r^2 = 0.89$, $p < 0.001$) has been reported in children with cerebral palsy [8].

The advantage of using fewer magnetic resonance images to assess trabecular bone microarchitecture is a substantial reduction in processing time. In the current study, analyzing five vs. 20 images reduced processing time from approximately 30 minutes to approximately 7.5 minutes per participant. This is a particular benefit when many subjects and multiple bone sites are evaluated. The benefit may be extended to image collection if protocols are developed that cover the same region with fewer images and a reduced scan time. In this study, scan time was approximately 7 minutes. Reducing scan time to less than 4 minutes would not only reduce testing time, but it would also make it easier for participants to complete the exam and increase the success rate of image collection. Although images were successfully collected from all participants in this study, magnetic resonance image collection can be difficult in younger children and in children with movement disorders or intellectual disabilities [2, 15, 16]. Developing protocols for MRI scanners with higher field strength should be explored. There is evidence that images from 3.0 vs. 1.5 Tesla MRI scanners can be collected in a shorter time while yielding estimates of trabecular bone microarchitecture that are more strongly correlated with estimates from micro-computed tomography [17].

The mathematical models developed in the present study were cross-validated using the leave-one out technique suggesting that partial image sets can be used to predict measures of trabecular bone microarchitecture in the distal femur of typically developing children. However, the model used needs to be considered carefully because the variance explained (r^2) decreases and the SEE increases as the number of images used to predict measures of trabecular bone microarchitecture decreases. Based on the explained variance and the SEE values observed in the current study, it would seem reasonable to use 10IM and 5IM and the mathematical models presented to predict measures in trabecular bone microarchitecture in the distal femur. For comparison, studies in which dual-energy X-ray absorptiometry-based mathematical models were developed and used to predict muscle mass from MRI in children, the SEE relative to average muscle mass was 4.7 % for the total body [18] and 6.9 % for the mid thigh [19], which is considerably higher than the 0.4 to 2 % SEE values reported for measures of trabecular bone microarchitecture in the present study of children. Whether the mathematical models developed in the present study can be used with confidence in longitudinal studies is unknown. Lee et al. [8] reported that the relationship between 6-month measures of change in trabecular bone density from a single image vs. an average of the entire metaphysis was much weaker ($r^2 = 0.36$, $p < 0.05$) than the relationship between absolute measures at a single time point. Studies that examine the relationships between changes in trabecular bone microarchitecture measures from partial image sets vs. change from total image sets are needed in typically developing children and in other populations.

It must be emphasized that the partial image sets in this study were created by equally sampling 3–10 images throughout the total image set or a single image from the center of the total image set. Because appBV/TV and appTb.N decline, appTb.Sp increases and appTb.Th demonstrates a quadratic relationship with distance from the growth plate, sampling images from the distal end or the proximal end of the total image set will underestimate or overestimate the average from the total sample. This shows the importance

of sampling technique used to predict average values for the entire sample. It also demonstrates the importance of region of interest placement when collecting magnetic resonance images (or images using another technique, such as computed tomography).

The distal femur was chosen for evaluation in the present study because it has been used as an assessment site in previous MRI studies of children [2, 3]. Moreover, there are clinical populations that have severely compromised trabecular bone microarchitecture and a high fracture rate in the distal femur. For example, appBV/TV, appTb.N and appTb.Th are lower and appTb.Sp is higher in nonambulatory children with cerebral palsy vs. typically developing children [2]. This is consistent with the high rate of fracture in the distal femur of children with cerebral palsy [20]. A similar pattern is reported in individuals with complete spinal cord injury [21–23]. Whether the mathematical models developed in the present study can be applied to clinical populations with compromised trabecular bone microarchitecture requires further investigation.

In conclusion, the findings indicate that partial magnetic resonance image sets can be used to provide reasonable estimates of trabecular bone microarchitecture status in the distal femur of children. However, because the relative amount of trabecular bone in the distal femur decreases with distance from the growth plate due to a decrease in trabecular number, careful positioning of the region of interest and sampling from throughout the region of interest is necessary. Furthermore, follow up studies are needed to determine the applicability of the models in longitudinal studies and in other population groups.

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Abbreviations

appBV/TV	apparent bone volume to total volume
appTb.N	apparent trabecular number
appTb.Th	apparent trabecular thickness
appTb.Sp	apparent trabecular separation

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Highlights

- Relative amount of trabecular bone decreased with distance from the growth plate in children
- Trabecular number decreased with distance from the growth plate
- Partial magnetic resonance image sets accurately estimated trabecular bone microarchitecture
- Mathematical models using partial image sets were cross-validated
- Careful positioning needed for accurate trabecular bone microarchitecture estimates

Figure 1.

A visual depiction of the procedure used to assess trabecular bone microarchitecture in the distal femur. Coronal (A) and sagittal (B) scout images show the region of interest in the distal femur where 26 magnetic resonance images were collected immediately above the growth plate. The 20 most central raw images (C) were filtered using low-pass filter-based correction algorithm and then reversed in gray scale to optimize visualization (D). The lateral aspect of the trabecular bone in the distal femur was masked by identifying the trochlear groove (large arrow), extending perpendicular to the posterior portion of the bone (medium arrow) and then following the boundary between the trabecular bone from the cortical shell (small arrows). In each image, eight samples were taken from the cortical shell (E) and the three samples with the highest signal intensity were used to separate the region of interest into bone and marrow phases (binarized; F). As described by Majumdar et al. [5], measures of trabecular bone microarchitecture were calculated for each of the twenty binarized images and the averages are reported.

Figure 2.

Scatter plots show the relationships between proximal distance from the growth plate in the distal femur and A) apparent trabecular bone volume to total bone volume, B) apparent trabecular number, C) apparent trabecular thickness and D) apparent trabecular separation in typically developing children.

Figure 3.

Scatter plots show the relationships between estimates of apparent trabecular bone volume to total bone volume (appBV/TV) from a total image set in the distal femur (i.e., 20 images, 20IM) and estimates from A) 10 images (10IM), B) 5 images (5IM), C) 3 images (3IM), and D) 1 image (1IM).

Figure 4.

Scatter plots show the relationships between estimates of apparent trabecular bone number (appTb.N) from a total image set in the distal femur (i.e., 20 images, 20IM) and estimates from A) 10 images (10IM), B) 5 images (5IM), C) 3 images (3IM), and 1 image (1IM).

Figure 5.

Scatter plots show the relationships between estimates of apparent trabecular bone thickness (appTb.Th) from a total image set in the distal femur (i.e., 20 images, 20IM) and estimates from A) 10 images (10IM), B) 5 images (5IM), C) 3 images (3IM), and 1 image (1IM).

Figure 6.

Scatter plots show the relationships between estimates of apparent trabecular bone separation (appTb.Sp) from a total image set in the distal femur (i.e., 20 images, 20IM) and estimates from A) 10 images (10IM), B) 5 images (5IM), C) 3 images (3IM), and D) 1 image (1IM).

Table 1

Measures of trabecular bone microarchitecture in 40 typically developing children

	20IM	10IM	5IM	3IM	1IM
appBV/TV	0.322 ± 0.028	0.323 ± 0.029	0.321 ± 0.030	0.319 ± 0.030	0.322 ± 0.035
appTb.N	1.676 ± 0.064	1.678 ± 0.062	1.672 ± 0.067	1.670 ± 0.067	1.668 ± 0.081
appTb.Th	0.192 ± 0.013	0.192 ± 0.014	0.192 ± 0.014	0.191 ± 0.014	0.193 ± 0.016
appTb.Sp	0.406 ± 0.029	0.405 ± 0.029	0.408 ± 0.032	0.410 ± 0.033	0.408 ± 0.038

appBV/TV = apparent trabecular bone volume fraction; appTb.N = apparent trabecular number; appTb.Th = apparent trabecular thickness; appTb.Sp = apparent trabecular separation; IM = number of images processed. Values are means ± SD.

Table 2

Mathematical models for predicting measures of trabecular bone microarchitecture from magnetic resonance imaging in the distal femur of typically developing children ($n = 40$) using partial image sets

Predicted variable	Model	r^2	SEE
appBV/TV 20IM	appBV/TV 10IM * 0.973 + 0.008	0.982	0.0038
	appBV/TV 5IM * 0.927 + 0.025	0.950	0.0064
	appBV/TV 3IM * 0.871 + 0.044	0.866	0.0104
	appBV/TV 1IM * 0.658 + 0.110	0.630	0.0173
appTb.N 20IM	appTb.N 10IM (1/mm) * 1.018 – 0.032	0.987	0.0074
	appTb.N 5IM (1/mm) * 0.923 + 0.133	0.930	0.0172
	appTb.N 5IM (1/mm) * 0.889 + 0.192	0.866	0.0237
	appTb.N 5IM (1/mm) * 0.664 + 0.568	0.674	0.0370
appTb.Th 20IM	appTb.Th 10IM (mm) * 0.961 + 0.007	0.982	0.0018
	appTb.Th 5IM (mm) * 0.960 + 0.008	0.957	0.0028
	appTb.Th 3IM (mm) * 0.909 + 0.019	0.886	0.0045
	appTb.Th 1IM (mm) * 0.689 + 0.059	0.689	0.0075
appTb.Sp 20IM	appTb.Sp 10IM (mm) * 1.000 + 0.001	0.984	0.0037
	appTb.Sp 5IM (mm) * 0.895 + 0.041	0.937	0.0075
	appTb.Sp 3IM (mm) * 0.836 + 0.064	0.857	0.0112
	appTb.Sp 1IM (mm) * 0.625 + 0.151	0.629	0.0181

appBV/TV = apparent trabecular bone volume to total bone volume ; appTb.N = apparent trabecular number; appTb.Th = apparent trabecular thickness; appTb.Sp = apparent trabecular separation; IM = number of images processed; SEE = standard error of estimate. All models are statistically significant, $p < .001$.