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Children with myelomeningocele do not exhibit normal remodeling of tibia roundness with physical development

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ABSTRACT

Skeletal loading through daily movement is an important factor in the normal development of bones. This loading is affected by the neurological and muscle deficits that result from myelominingocele (MM). While children with MM have been shown to have atypical gait, decreased bone accrual, and increased fracture risk, it is still unclear what morphological bone differences exist and to what extent they relate to physical developmental and ambulation level. This study analyzed computed tomography images of the tibia from 77 children with MM and 124 typically developing (TD) children between the ages of 6 and 16 years. Differences in cross-sectional roundness along the length of the tibia diaphysis were observed across developmental stages (prepubertal, pubertal, post-pubertal) and ambulation level (MM non-ambulatory, MM assistive devices, MM independent, and TD). The results showed that tibia cross-sectional morphology becomes less round with development in TD children ($p < 0.017$). In children with MM, however, roundness is maintained throughout adolescence ($p > 0.017$), with greater roundness in less ambulatory children ($p < 0.0083$). These in vivo results align with mechanobiological modeling studies suggesting that intracortical loads (caused by joint loading) as well as periosteal loads (imposed by surrounding muscles) are critical in promoting non-circular cross-sectional bone shape remodeling.

1. Introduction

Spina bifida is a neurologic birth defect caused when the spinal column fails to close properly in utero. The birth-prevalence rate of spina bifida in the US from 1999 to 2007 was 3.17 per 10,000 live births [1]. Myelomeningocele (MM) is the most common (78% [2]) and severe form of spina bifida, where the spinal cord protrudes from the vertebrae resulting in spinal cord damage. Children with MM experience various levels of neurological and muscle deficits which affect walking ability. Altered gait patterns may lead to atypical or insufficient lower extremity loading, decreased bone accrual, and increased fracture risk. Ambulation level in myelomeningocele is positively associated with bone mass and mineral density (BMD) [3–5]. Comparatively, in typically developing (TD) adolescents, BMD is positively associated with Gross Motor Score at 18-months [6], and high levels of physical activity at 17 years, but not medium or low levels of physical activity [7]. Differences in tibia cross-sectional geometry have also been observed in children with spina bifida paralysis shortly after birth, suggesting that genetics, prenatal loading, and/or non-ambulatory loading contribute to bone shape as well [8]. The mechanical environment during ontogeny is known to influence skeletal morphology through bone modeling and remodeling [9]. Altered skeletal loading may therefore lead to abnormal bone morphology in children with MM.

For people with MM and others with paralysis, the risk of fracture, particularly in the lower extremities, is higher than in those without paralysis [10–12]. To better understand the bone characteristics that influence fracture risk, bone material properties and shape should be evaluated. Bone material properties are commonly studied through the assessment of bone mass or BMD [13], while bone shape is often overlooked despite being equally important for structural integrity [14]. Principles of structural engineering state that distribution of material away from the centroid in a cross-section makes beams more resistant to bending and torsional loads (e.g., I-beams). In long bones such as the tibia, bone formation occurs away from the bending axis, increasing strength [15–18]. Because area moment of inertia increases with outer diameter to the fourth power, a small increase in outer

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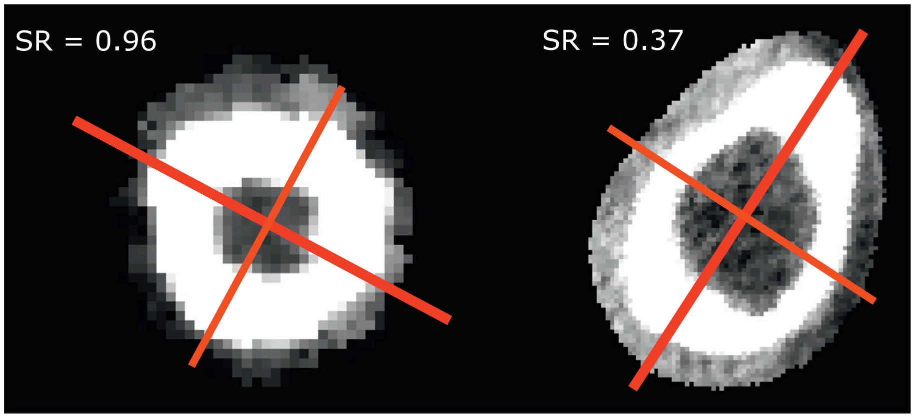

Fig. 1. Sample cross-sectional tibia slices with corresponding Shape Ratio (SR).

diameter yields a large increase in bending strength [19]. A round cross-section would represent equal strength in all directions while a non-round cross-section (e.g., oval or triangular) represents greater strength in particular loading directions. The ratio of minimum to maximum area moment of inertia (Imin/Imax) gives insight into the cross-sectional "roundness" of bone as a metric for structurally-important shape. In MM, strength may fail to develop preferentially in directions of typical loading due to lack of or differences in load exposure.

The objective of this study was to understand how tibia cross-sectional shape changes with physical development and how this process differs in children with MM due to atypical and/or reduced ambulation. We hypothesized that tibia cross-sections would become less round with development, but children with MM would retain rounder tibia cross-sections than TD children. We further hypothesized that rounder tibia cross-sections would be found in less ambulatory children with MM.

2. Methods

This study included 77 children with MM and 124 TD children. Exclusion criteria for all participants were metal in tibias bilaterally, current use of glucocorticoids or other medications affecting bone, chronic conditions other than hydrocephalus (for the MM group only) and asthma. Controls were recruited as a sample of convenience; the MM participants were recruited from local spina bifida clinics. Computed tomography (CT) images were collected along the length of the tibias for all participants using a standard clinical scanner (Philips Gemini GXL, Philips Medical Systems Inc., Cleveland, OH) with the participant lying supine. The tibia was chosen as the site of interest for this study because of its high fracture rate in the spina bifida population [11, 12] as well as the ability to scan the entire bone using CT due to its distance from vital organs. Contiguous 1 mm slices were acquired from the knee to ankle joints at 90 kVp, 32 mA, 1 s rotation time, and matrix resolution of 512 × 512 pixels (see [5] for more details). The Institutional Review Board at Children's Hospital Los Angeles approved the study protocol, and all participants and their parents provided written assent and consent.

Images of the right tibias were segmented and isolated in OsiriX software (v5.8.5) [20] from the most proximal slice where the intercondyloid eminence was visible to the most distal slice where the medial malleolus was visible. Using ImageJ (1.50i) [21] with the BoneJ plugin (v1.4.1) [22] the bone was aligned to its long axis using the moments of inertia function, thresholded to a minimum of 206 HU to capture cortical and trabecular bone [5], then maximum (I_{max}) and minimum (I_{min}) area moment of inertia were calculated. Custom MATLAB (R2013b, Mathworks Inc., Natick, MA) programming was performed to calculate a measure of bone roundness (Shape Ratio, SR):

$$SR = {I_{min}}/{I_{max.}}$$

An SR value of 1 indicates a circular shape, and the degree of circularity decreases as SR changes from 1 towards 0 (Fig. 1). The SR value was calculated for each cross-sectional slice along the length of the tibia. These values were filtered (5-sample moving average) and linearly interpolated to 200 longitudinal slices to account for differences in tibia lengths. Similar to Horenstein et al. [5], the proximal and distal 20% were removed in order to exclude the epiphyses. The central 60% represents the estimated diaphysis region [5]. All analyses were performed on this diaphysis region, and were presented in plots as 100% normalized diaphysis length.

For analysis, participants were divided by physical developmental status and ambulation level for comparisons of SR. The developmental groupings in both TD children and children with MM were pre-pubertal, pubertal, and post-pubertal based on Tanner stages, where stage 1 was considered pre-pubertal, stages 2–4 were considered pubertal, and stage 5 was considered post-pubertal [23,24]. The ambulatory level groupings were non-ambulatory children with MM (MM Non-Amb), children with MM requiring assistive devices to walk (MM Assist), independently ambulatory children with MM (MM Ind), and TD children. Ambulatory groups were defined based on their Functional Mobility Scale (FMS) scores, which were from self/parent-reported walking ability for home (short), school (medium), and community (long) distances [25]. For grouping from FMS scores, "non-ambulatory" was defined as crawling or using a wheelchair (score of 1) at all distances, "ambulatory with assistive devices" was defined as walking with a walker or crutches for one or more distances (2 or higher) without qualifying for "ambulatory independent", and "ambulatory independent" was defined as walking independently (5 or 6) for home and school distances.

Participant characteristics for all ambulatory and developmental groupings are shown in Table 1. Comparisons in SR were made with divisions by sex (male/female) as well as ethnicity (Hispanic/non-Hispanic).

Comparisons of SR along the tibia diaphysis were performed in MM and TD based on developmental stage as well as ambulatory status. All comparisons were performed using one-dimensional statistical parametric mapping (SPM) [26]. Essentially, SPM is an extension of