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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 myelomeningocele (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 16yrs. Differences in cross-sectional roundness along the length of the tibia diaphysis were observed across developmental stages (pre-pubertal, 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.

Keywords

bone morphology; spina bifida; mechanobiology; bone 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 1999–2007 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

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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) [3,4,5]. 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 [10,11,12]. 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 [15,16,17,18]. Because area moment of inertia increases with outer diameter to the fourth power, a small increase in outer 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 (I_{min}/I_{max}) 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, 1s 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 (Figure 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 standard t-tests or analysis of variance (ANOVA) that allows groups to be compared along an entire curve (e.g., at all points along the length of the diaphysis), accounting for spatial relationships between data points by adjusting the critical threshold. Significance is calculated at each normalized tibia slice, and regions of significance are identified adjusting for the multiple comparisons. One-way SPM ANOVA was used to compare the three developmental groups and the four ambulatory groups; two-tailed SPM t-tests were used in comparisons of two groups (MM vs. TD and paired post-hoc comparisons). The significance level was set at $p < 0.05$. While the SPM methodology accounts for the multiple comparisons of each slice in the dataset, Bonferroni adjustments were applied to adjust for the multiple group comparisons performed for post-hoc analysis.

3. Results

No significant differences were found between the TD and MM samples' demographics (Table 2). Additionally, no differences in SR were found by division of sex (male / female) or ethnicity (Hispanic / non-Hispanic) within the TD, the overall MM group, any of the developmental groups, or any of the ambulatory groups (excluding MM Non-Amb, in which there were no non-hispanic participants). All comparisons passed the SPM K2 test for normality, and non-parametric testing produced similar results. [26].

3.1 Differences in SR with Physical Development

In TD children, the SR differed among developmental groups over more than 80% of the diaphysis length ($p < 0.05$, Figure 2a). Specifically, the pre-pubescent group had a higher SR (rounder shape) over the proximal ~45% of the diaphysis when compared to the pubescent group and ~85% of the diaphysis when compared to the post-pubescent group ($p < 0.017$, black bars at bottom of Figure 2a). There were no significant differences between the pubescent and post-pubescent groups ($p < 0.017$).

In contrast, in children with MM, there were no significant differences among developmental groups ($p > 0.05$, Figure 2b). There were also no significant differences among developmental sub-groups within any MM ambulatory group.

3.2 Differences in SR Between MM and TD

In comparing children with MM to TD children of the same developmental stage, significant differences were found between groups in all developmental stages with more pronounced differences in the more developed groups ($p < 0.017$, Figure 3). Within pre-pubescents, the MM group had a significantly higher SR compared to the TD group in the distal ~40% of the diaphysis length (Figure 3a). Within both pubescents and post-pubescents, the MM

group showed a significantly higher SR compared to the TD group in >90% of the diaphysis length (Figure 3b,c).

3.3 Differences in SR Among Ambulatory Groups

Comparing ambulatory groups, the SR differed among groups over the entire diaphysis length (Figure 4). Pairwise posthoc comparisons showed that differences existed between nearly all ambulatory groups, with higher SR in the less ambulatory groups. The MM Ind group had a higher SR than the TD group across ~60% of the diaphysis length. The MM Assist and MM Non-Amb groups had a higher SR than the TD group across >90% of the diaphysis length. The MM Assist group had a higher SR than the MM Ind group across the central ~15% of the diaphysis length, and the MM Non-Amb group had a higher SR than the MM Ind group across the proximal ~60% of the diaphysis length. The MM Non-Amb group did not differ significantly from the MM Assist group.

4. Discussion

The results in this study indicate that ambulation is important throughout early physical development in order to more closely attain normal bone cross-sectional shape. Across much of the diaphysis, tibia cross-sectional shape is rounder in younger children during typical development, reflecting normal remodeling of the tibia from a circular to a triangular shape during growth. TD pre-pubescent children differed significantly from both the pubescent and post-pubescent groups, while the pubescent and post-pubescent groups did not differ from each other, suggesting that the majority of cross-sectional shape changes occur before puberty.

In contrast, tibia cross-sectional roundness is maintained in children with MM throughout childhood and adolescence compared to TD children. Pre-pubescent children with MM already differ from TD children. During puberty, there is very little change in the SR of children with MM, and differences compared to TD children become more pronounced with development. The same tests were performed with participants grouped by age instead of Tanner stage, and the results were very similar.

Our results also show that less ambulatory children with MM have rounder cross-sections than more ambulatory children with MM and TD children. Similar trends have been found with bone mass related to ambulation in this population [5]. These differences likely result from a lack of the loading needed to stimulate bone accretion, modeling, and remodeling. Without normal loading, the bone fails to develop, and an immature morphology and mechanical structure are retained. From a mechanobiological perspective, the results align with previous modeling studies which attribute non-circular cross-sections to combined cyclic intracortical and periosteal stresses [27]. In younger and less ambulatory children, the number of cycles of loading and load magnitudes would be lower than in TD children. This would cause less bone remodeling in regions perpendicular to load axes and adjacent to muscles, resulting in maintained circularity. Further investigation and additional shape characterization are needed to quantify the relative importance of intracortical and periosteal loading on this population.

Differences due to development in TD children were located more proximally (Fig 2a), while differences between TD and MM were located more distally (Fig 3a, Fig 4). The typical progression of bone shape change occurs more proximally, perhaps related to muscle attachments, though this change does not occur in children with MM. The proximal SR in children with MM starts off similar to TD in pre-pubescence, but diverges as children with MM fail to keep up with the changes observed in the TD group. In the pre-pubescent stage, children with MM already have rounder tibia cross-sections distally, perhaps due to pre-natal or early childhood loading, and therefore always differ in SR measured in the distal tibia compared to TD.

Bone deficits in people with MM contribute to an increased risk for fracture throughout their lives. Dosa et al. found the crude fracture rate to be 9/1000 per patient year on a sample including children, adolescents, and adults with MM [11]. Bone shape in particular affects bone resilience to fracture by modulating strength in particular loading directions. While an elliptical or triangular cross-section (low SR) will provide additional strength in common loading directions, it may weaken the structure to loads in other directions. Alternatively, a round cross-section (high SR) will provide equal strength in all loading directions. This means that less developed and less ambulatory children with MM have less adaptation in bone strength than more developed, more ambulatory children with MM, who all have less specialized bone structure than TD children. Less specialized bone shape would mean less resilience to loads created by ambulation. Further analysis is needed to determine if rounder cross-sections are more or less resilient to loads associated with non-ambulation tasks such as transfers. The ambulatory group results showed that even independently ambulatory children with MM have different bone shape than typically developing children. This suggests that the type of gait also likely contributes to shape differences. While children with sacral and low lumbar MM (higher functional level of MM) take a similar number of steps per day as TD children, and with a similar profile of low, medium, and high intensity walking [28], previous studies have found that children with all levels of MM exhibit kinematic [29,30,31] and kinetic [32] gait deviations compared to TD children. This suggests that for independently ambulatory children with MM, kinematic (and kinetic) deviations play a significant role in bone remodeling. Due to lack of innervation to lower leg muscles in children with MM, loading may be altered particularly in the distal region of the tibia where shape differences are most significant.

The relation of mobility to cross-sectional shape has also been described in patients with spinal cord injury (SCI). Biggin et al. describe significantly rounder tibia cross-sections in pediatric patients with SCI compared to controls, as well as significantly rounder tibia cross-sections in non-mobile SCI patients compared to mobile SCI patients [33]. While “roundness” was defined differently in this study and only a single cross-sectional slice was analyzed, it supports the positive relationship between mobility and normal bone remodeling during development.

The results of this study suggest that increasing ambulation level in children with MM could help in developing less round, possibly more fracture resilient bones, in addition to overall higher bone mass. Early studies suggest that interventional strategies could be employed to increase bone mass [34]; however more research is needed to validate the effectiveness of

interventions with respect to shape characteristics, different interventional strategies, and long term outcomes.

This study is not without limitations; while the smallest group used in the primary analyses was 12 (MM Non-Amb), some of the subgroups used to test interactions were smaller (e.g., 2 subjects in MM Non-Amb, Tanner stage 1). Our participant population was also predominantly Hispanic, so may not be representative of a more diverse population. While our analysis quantifies bone shape through $I_{\max}$ and $I_{\min}$, it does not include the directionality of this shape or how this would be related to the loading direction/strength.

5. Conclusion

Tibia cross-sectional morphology becomes less round with physical development in TD children. In children with MM, roundness is maintained throughout physical development. However, in children with MM who ambulate at higher levels, tibia cross-sectional morphology is less round than those who ambulate at lower levels. This suggests that intracortical and periosteal loads induced by the cyclic loading of gait play a crucial role in bone shape in children with MM. With abnormal or reduced gait, bone modeling fails to occur during adolescence, leaving bone cross-sections rounder and less specialized in directional loading strength. This effect is apparent even for independently ambulatory children with MM, but is more pronounced at lower ambulation levels.

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Highlights

- Tibia diaphyses become less round during typical development.
- Tibia diaphyses remain round through adolescence in Myelomeningocele development.
- Tibia diaphyses are less round in more ambulatory children with Myelomeningocele.

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

Fig. 2.
 Comparison of SR among developmental groups in a) typically developing children and b) children with Myelomeningocele. Post-hoc comparison indicates regions that are statistically different between two groups

Fig. 3.
Comparison of SR between children with MM and TD children within each developmental stage

Fig. 4.

Comparison of shape ratio among ambulatory groups

Table 1:

Participant Characteristics for Each Subgroup

	Ambulatory Groups				
Developmental Groups	MM				Typically Developing (TD)
	Non-Ambulatory (Non-Amb)	Ambulatory with Assistive Devices (Assist)	Ambulatory Independent (Ind)	All MM	
Tanner 1					
N	2	12	18	32	42
Age (years)	10.4 (0.7)	8.0 (1.3)	8.4 (1.7)	8.4 (1.6)	8.5 (1.8)
Male, N (%)	2(100%)	9 (75%)	12 (67%)	23 (72%)	26 (62%)
Hispanic, N (%)	2 (100%)	11 (92%)	17 (94%)	30 (94%)	39 (93%)
Height (cm)	114.3 (8.1)	118.5 (11.8)	125.9 (13.4)	122.5 (12.9)	131.3 (12.8)
Weight (kg)	26.7 (2.6)	29.6 (9.9)	32.7 (13.5)	31.2 (11.7)	32.7 (12.3)
BMI (kg/m ²)	20.4 (0.9)	20.0 (3.8)	19.8 (4.4)	19.9 (4.0)	18.5 (4.1)
Tanner 2–4					
N	5	9	8	22	41
Age (years)	13.6 (2.0)	12.3 (1.5)	11.3 (2.1)	12.2 (2.0)	11.8 (1.9)
Male, N (%)	5 (100%)	5 (56%)	3 (38%)	13 (59%)	24 (59%)
Hispanic, N (%)	5 (100%)	8 (89%)	8 (100%)	21 (95%)	38 (93%)
Height (cm)	138.4 (9.0)	141.4 (6.8)	139.1 (11.5)	139.9 (8.9)	151.2 (12.3)
Weight (kg)	64.8 (14.2)	41.0 (10.7)	36.7 (8.2)	44.8 (15.2)	49.9 (15.6)
BMI (kg/m ²)	33.9 (6.3)	20.3 (4.3)	18.8 (2.4)	22.8 (7.4)	21.4 (4.3)
Tanner 5					
N	5	7	11	23	41
Age (years)	13.9 (2.0)	14.7 (1.4)	14.1 (1.2)	14.2 (1.4)	14.8 (1.4)
Male, N (%)	3 (60%)	3 (43%)	4 (36%)	10 (43%)	20 (49%)
Hispanic, N (%)	5 (100%)	7 (100%)	9 (82%)	21 (91%)	34 (83%)
Height (cm)	143.7 (13.8)	144.4 (11.6)	158.9 (7.2)	151.2 (12.3)	163.2 (9.8)
Weight (kg)	57.3 (13.9)	62.8 (20.5)	67.3 (23.3)	63.7 (20.3)	58.3 (12.8)
BMI (kg/m ²)	27.5 (4.1)	29.7 (7.0)	26.6 (8.9)	27.7 (7.4)	21.8 (4.3)
all stages					
N	12	28	37	77	124
Age (years)	13.2 (2.2)	11.3 (3.2)	10.7 (3.0)	11.2 (3.0)	11.7 (3.1)
Male, N (%)	10 (83%)	17 (61%)	19 (51%)	46 (60%)	70 (56%)
Hispanic, N (%)	12 (100%)	26 (93%)	34 (92%)	72 (94%)	111 (90%)
Height (cm)	136.6 (14.8)	133.8 (16.3)	138.6 (18.2)	136.0 (16.9)	148.4 (17.6)
Weight (kg)	55.3 (18.3)	43.0 (19.0)	43.8 (22.2)	44.8 (20.6)	46.9 (17.2)
BMI (kg/m ²)	29.0 (6.8)	22.8 (6.3)	21.6 (6.6)	23.1 (6.9)	20.5 (4.5)

Continuous variables are reported as mean (SD). Categorical variables are reported as N (%). na = not applicable.

Table 2:

Demographic Comparisons between MM and TD Groups

	all MM	TD	p-value
N	77	124	
Age (years)	11.2 (3.0)	11.7 (3.1)	0.936
Male, N (%)	46 (60%)	70 (56%)	0.812
Hispanic, N (%)	72 (94%)	111 (90%)	0.917
Height (cm)	136.0 (16.9)	148.4 (17.6)	0.727
Weight (kg)	44.8 (20.6)	46.9 (17.2)	0.956
BMI (kg/m ²)	23.1 (6.9)	20.5 (4.5)	0.819
Pre-pubertal	32 (42%)	42 (34%)	0.543
Pubertal	22 (29%)	41 (33%)	
Post-pubertal	23 (30%)	41 (33%)	

Continuous variables are reported as mean (SD) and are compared using two-tailed t-tests. Categorical variables are reported as N (%) and compared using Fisher's Exact Test for 2×2 tests and Chi-Square for 2×3 tests.