Bone 94 (2017) 90–97

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Full Length Article

Cortical bone deficit and fat infiltration of bone marrow and skeletal muscle in ambulatory children with mild spastic cerebral palsy

Daniel G. Whitney [a], Harshvardhan Singh [a], Freeman Miller [b], Mary F. Barbe [c], Jill M. Slade [d], Ryan T. Pohlig [e], Christopher M. Modlesky [a,*]

[a] Department of Kinesiology and Applied Physiology, University of Delaware, Newark, DE, United States
[b] Department of Orthopedics, Nemours AI duPont Hospital for Children, Wilmington, DE, United States
[c] Department of Anatomy and Cell Biology, Temple University School of Medicine, Philadelphia, PA, United States
[d] Department of Radiology, Michigan State University, East Lansing, MI, United States
[e] Biostatistics Core Facility, University of Delaware, Newark, DE, United States

ARTICLE INFO

Article history:
Received 30 July 2015
Revised 2 October 2016
Accepted 7 October 2016
Available online 11 October 2016

Keywords:
Bone structure
Bone strength
Cerebral palsy
Unloading
Fat depots

ABSTRACT

Introduction: Nonambulatory children with severe cerebral palsy (CP) have underdeveloped bone architecture, low bone strength and a high degree of fat infiltration in the lower extremity musculature. The present study aims to determine if such a profile exists in ambulatory children with mild CP and if excess fat infiltration extends into the bone marrow.
Materials and methods: Ambulatory children with mild spastic CP and typically developing children (4 to 11 years; 12/group) were compared. Magnetic resonance imaging was used to estimate cortical bone, bone marrow and total bone volume and width, bone strength [i.e., section modulus (Z) and polar moment of inertia (J)], and bone marrow fat concentration in the midtibia, and muscle volume, intermuscular, subfascial, and subcutaneous adipose tissue (AT) volume and intramuscular fat concentration in the midleg. Accelerometer-based activity monitors worn on the ankle were used to assess physical activity.
Results: There were no group differences in age, height, body mass, body mass percentile, BMI, BMI percentile or tibia length, but children with CP had lower height percentile (19th vs. 50th percentile) and total physical activity counts (44%) than controls (both $p < 0.05$). Children with CP also had lower cortical bone volume (30%), cortical bone width in the posterior (16%) and medial (32%) portions of the shaft, total bone width in the medial-lateral direction (15%), Z in the medial-lateral direction (34%), J (39%) and muscle volume (39%), and higher bone marrow fat concentration (82.1 ± 1.8% vs. 80.5 ± 1.9%), subfascial AT volume (3.3 fold) and intramuscular fat concentration (25.0 ± 8.0% vs. 16.1 ± 3.3%) than controls (all $p < 0.05$). When tibia length was statistically controlled, all group differences in bone architecture, bone strength, muscle volume and fat infiltration estimates, except posterior cortical bone width, were still present (all $p < 0.05$). Furthermore, a higher intermuscular AT volume in children with CP compared to controls emerged ($p < 0.05$).
Conclusions: Ambulatory children with mild spastic CP exhibit an underdeveloped bone architecture and low bone strength in the midtibia and a greater infiltration of fat in the bone marrow and surrounding musculature compared to typically developing children. Whether the deficit in the musculoskeletal system of children with CP is associated with higher chronic disease risk and whether the deficit can be mitigated requires further investigation.

1. Introduction

Cerebral palsy (CP) is a neurological condition that is associated with dysfunctional gait and progressive decrements in physical activity from childhood to adulthood [1]. Nonambulatory children with more severe spastic CP present with low bone mass and underdeveloped bone architecture [2–6], as well as small, weak [7] and qualitatively-compromised musculature, as indicated by a high degree of fat infiltration [8]. It is not surprising that this musculoskeletal phenotype is associated with a high incidence of low-energy fractures, primarily occurring in the lower limbs [9,10]. The latter complication may be due mainly to the lack of physical activity [4,8] and mechanical loading, which reduces the stimulus for periosteal and endocortical expansion in the lower extremities [4]. To date, it is unclear if the adverse musculoskeletal profile exhibited

Abbreviations: CP, cerebral palsy; Z_{ap}, section modulus in the anterior-posterior direction; Z_{ml}, section modulus in the medial-lateral direction; J, polar moment of inertia; AT, adipose tissue; GMFCS, gross motor function classification system; SI, signal intensity; *d*, Cohen's *d*.

* Corresponding author.
E-mail address: modlesky@udel.edu (C.M. Modlesky).

http://dx.doi.org/10.1016/j.bone.2016.10.005

in nonambulatory children with more severe CP is also present in ambulatory children with a milder form of the disorder.

In addition to possessing an underdeveloped musculoskeletal system, nonambulatory children with severe CP also have elevated adipose tissue (AT) surrounding bone and muscle [8]. Furthermore, human models of reduced mechanical loading show elevated levels of fat infiltration within the bone marrow cavity [11] and muscle [12], which are linked to osteoporosis [13–15], impaired glucose tolerance [12,16,17] and cardiometabolic disease [18]. The objective of the present study was to determine if ambulatory children with mild spastic CP have a deficit in bone architecture and elevated fat infiltration of the bone marrow in the midtibia and the surrounding leg musculature. We hypothesized that ambulatory children with mild CP vs. typically developing children would have a thinner shaft with a thinner cortex and lower estimates of strength in the midtibia. We also hypothesized that children with CP vs. typically developing children would have an elevated fat infiltration of the bone marrow in the midtibia and the surrounding leg musculature.

2. Materials and methods

2.1. Participants and study design

Ambulatory children with mild spastic CP and between the ages of 4 and 11 years were recruited from the AI duPont Hospital for Children in Wilmington, DE and other pediatric hospitals in the Mid-Atlantic region of the U.S. Typically developing children that matched children with CP for age, sex and race were recruited from the Newark and Wilmington, DE areas using flyers and word of mouth. Additional inclusion criteria for controls included falling between the 5th and 95th percentile for height and body mass, no history of chronic medication use, no previous fracture in the nondominant lower extremity and no current or previous regular participation in an activity that involved high loading of the skeleton, such as artistic gymnastics. Participants were recruited from April 2012 through May 2016 and testing was conducted from November 2012 to May 2016. The Institutional Review Boards at the AI duPont Hospital for Children and the University of Delaware approved the study procedures. Prior to testing, written consent and assent was obtained by the parents and the participants, respectively.

2.2. Anthropometrics

Height and body mass were measured while the child was in a t-shirt and shorts. Height was measured to the nearest 0.1 cm using a stadiometer (Seca 217; Seca GmbH & Co. KG., Hamburg, GER). Body mass was measured to the nearest 0.2 kg using a digital scale (Detecto 6550, Cardinal Scale, Webb City, MO). Height, body mass and BMI percentile were calculated from the normative graphs published by the Centers for Disease Control and Prevention [19].

2.3. Tanner staging

Sexual maturity was assessed by a physician assistant using the Tanner staging technique [20]. The technique is based on a 5-point scale, with I indicating no development and V indicating full development. Pubic hair and breast development were assessed in girls. Pubic hair and testicular/penile development were assessed in boys.

2.4. Gross motor function

Gross motor function of children with CP was assessed by a physician assistant using the gross motor function classification system (GMFCS) [21]. Children who were GMFCS I or II were included in the study. In short, a child with the ability of walking indoors and outdoors and gross motor skills of running and jumping, but limited ability of speed, balance and coordination was classified as GMFCS level I. Limitations of walking on uneven surfaces and inclines and minimal gross motor skills of running and jumping was classified as GMFCS level II.

2.5. Physical activity

Physical activity was estimated using accelerometer-based activity monitors (Actical; Respironics Inc., Bend, OR). The activity monitors contain an omnidirectional accelerometer that is most sensitive to movements in the vertical plane when worn on the ankle and is sensitive to movements in the 0.5 to 3 Hz frequency range [22]. Physical activity counts were registered in 15 second epochs. Each participant wore two monitors on the lateral aspect of the ankle on the more affected side in children with CP and on the nondominant side in controls. Monitors were worn continuously (i.e., 24 h per day) for four days (three week days and one weekend day). Participants and participant parents were instructed to take the monitors off only when swimming at a depth >0.91 m and during bathing/showering. This was confirmed by reviewing activity logs kept by the children with assistance from their parent and by visually examining the graphical output generated using software provided by the manufacturer. If participants did not wear the monitors on any of the days, they were asked to re-wear the monitors to make up for the lost day(s). The total physical activity counts per day averaged from the two monitors are reported. The reliability of the total physical activity counts was assessed in 8 ambulatory children with mild CP and 8 typically developing children between 4 and 11 years of age who wore the monitors for four days on two separate occasions approximately one month apart. The intraclass correlation was 0.935 for children with CP and 0.913 for typically developing children indicating excellent reliability.

2.6. Magnetic resonance imaging

Magnetic resonance imaging (MRI; GE, 1.5 T, Milwaukee, WI) was used to assess bone architecture and the degree of fat infiltration in the bone marrow at the level of the middle-third of the tibia (i.e., midtibia) and in the surrounding leg musculature (i.e., midleg). The more affected limb in children with CP and the nondominant limb in controls were tested. Children were immobilized from the waist down using the BodyFIX (Medical Intelligence, Inc., Schwabműnchen, GER), as previously described [3]. A three plane localizer was used to identify the region of interest. Axial images were collected from the tibia plateau to the malleolar articular surface (0.5 cm thick separated by 0.5 cm of spacing) using a semiflex long bone array coil (ScanMed, Omaha, NE) and two different sequences. The first sequence (fast spin echo, TR = 650, TE = 14, FOV = 12, NEX = 3, BW = 15.63, frequency = 512, phase = 256) yielded T1-weighted images. The second sequence (IDEAL: fast-spin-echo, TR = 600, TE = min full, FOV = 12, NEX = 2, BW = 31.25, frequency = 320, phase = 224) yielded fat and water images.

All image collection was overseen by the senior author (CMM). Images at the level of the midtibia were processed blindly by the same technician using software developed with Interactive Data Language (Research Systems, Inc., Boulder, CO) and procedures previously described for the midthigh [8]. A general visual description of the image processing procedure used to quantify bone architecture and strength of the midtibia and the fat infiltration of the bone marrow and surrounding musculature is provided in Fig. 1. A more specific description follows. Using an automated procedure, the T1-weighted images at the level of the middle-third of the tibia were filtered using a median filter and voxels were segmented and assigned to cortical bone, bone marrow, muscle and AT using a fuzzy clustering algorithm [23] and their volumes (cm^3) were calculated. Widths (cm) of the cortical bone in the anterior, posterior, medial and lateral portions, widths of the bone marrow cavity and total bone in the anterior-posterior and medial-lateral directions and estimates of bone strength [i.e., polar moment of