Bone 81 (2015) 24–30

Contents lists available at ScienceDirect

Bone

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

Original Full Length Article

Altered trabecular bone morphology in adolescent and young adult athletes with menstrual dysfunction☆,☆☆,★

Deborah M. Mitchell [a,b,*], Padrig Tuck [a], Kathryn E. Ackerman [c,e], Natalia Cano Sokoloff [c], Ryan Woolley [c], Meghan Slattery [c], Hang Lee [d], Mary L. Bouxsein [a], Madhusmita Misra [b,c]

[a] Endocrine Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114, USA
[b] Pediatric Endocrine Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114, USA
[c] Neuroendocrine Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114, USA
[d] Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114, USA
[e] Division of Sports Medicine, Boston Children's Hospital, Boston, MA 02116, USA

ARTICLE INFO

Article history:
Received 31 March 2015
Revised 15 June 2015
Accepted 18 June 2015
Available online 27 June 2015

Keywords:
Bone density
Microarchitecture
Amenorrhea
Athlete

ABSTRACT

Context: Young amenorrheic athletes (AA) have lower bone mineral density (BMD) and an increased prevalence of fracture compared with eumenorrheic athletes (EA) and non-athletes. Trabecular morphology is a determinant of skeletal strength and may contribute to fracture risk.
Objectives: To determine the variation in trabecular morphology among AA, EA, and non-athletes and to determine the association of trabecular morphology with fracture among AA.
Design and setting: A cross-sectional study performed at an academic clinical research center.
Participants: 161 girls and young women aged 14–26 years (97 AA, 32 EA, and 32 non-athletes).
Main outcome measure: We measured volumetric BMD (vBMD) and skeletal microarchitecture using high-resolution peripheral quantitative computed tomography. We evaluated trabecular morphology (plate-like vs. rod-like), orientation, and connectivity by individual trabecula segmentation.
Results: At the non-weight-bearing distal radius, the groups did not differ for trabecular vBMD. However, plate-like trabecular bone volume fraction (pBV/TV) was lower in AA vs. EA ($p = 0.03$), as were plate number ($p = 0.03$) and connectivity ($p = 0.03$). At the weight-bearing distal tibia, trabecular vBMD was higher in athletes vs. non-athletes ($p = 0.05$ for AA and $p = 0.009$ for EA vs. non-athletes, respectively). pBV/TV was higher in athletes vs. non-athletes ($p = 0.04$ AA and $p = 0.005$ EA vs. non-athletes), as were axially-aligned trabeculae, plate number, and connectivity. Among AA, those with a history of recurrent stress fracture had lower pBV/TV, axially-aligned trabeculae, plate number, plate thickness, and connectivity at the distal radius.
Conclusions: Trabecular morphology and alignment differ among AA, EA, and non-athletes. These differences may be associated with increased fracture risk.

1. Introduction

Weight-bearing athletic activity during childhood and adolescence is a critical factor promoting bone growth and mineral accrual [1]. Increased bone accrual and greater peak bone mass in turn is protective against osteoporosis and fracture risk in later life [2]. However, excessive physical activity can lead to energy imbalance and functional hypothalamic oligo-amenorrhea [3]. Young female athletes are at particular risk; in one recent study, approximately 25% of female high school athletes had menstrual dysfunction [4].

This hypogonadal state seen with excessive exercise can counteract the beneficial effects of weight-bearing exercise, leading to lower bone mineral density (BMD) compared to eumenorrheic athletes, as measured by dual-energy x-ray absorptiometry (DXA). This deficit is particularly evident at the spine, a site composed primarily of trabecular bone [5]. More recently, high-resolution peripheral computed tomography (HR-pQCT) has enabled the investigation of volumetric BMD (vBMD) and skeletal microarchitecture in amenorrheic athletes. These studies have highlighted the competing effects of exercise and hypogonadism on skeletal properties. In particular, at the weight-bearing tibia, trabecular density is similar among athletes

☆ Support: This work was conducted with support from National Institutes of Health R01HD060827, K24HD071843, and by the Harvard Catalyst, the Harvard Clinical and Translational Science Center (NIH UL1 TR001102). We acknowledge funding for the HR-pQCT from a shared equipment grant (NIH/NCRR 1 S10 RR023405).
☆☆ Disclosure summary: No authors have any disclosures.
★ Clinical trials registration number: NCT00946192.
* Corresponding author at: Endocrine and Pediatric Endocrine Units, Massachusetts General Hospital, 50 Blossom Street, Boston, MA 02114, USA.
E-mail address: dmmitchell@mgh.harvard.edu (D.M. Mitchell).

http://dx.doi.org/10.1016/j.bone.2015.06.021
8756-3282/

and controls, while, at the non-weight-bearing radius, trabecular density is significantly lower in amenorrheic athletes compared to eumenorrheic athletes and non-athletes [6,7].

To further investigate the effects of activity and of hypogonadism on skeletal properties, we employed individual trabecula segmentation (ITS) analysis. This procedure classifies individual trabeculae as plate-like or rod-like and also quantitates axially-aligned trabeculae and trabecular connectivity. This distinction is clinically relevant, as osteoporosis due both to aging and hypogonadism specifically involves loss of plate-like trabeculae [8–10]. Importantly, experimentally-determined bone strength is highly correlated with plate-like bone volume fraction and the density of plate–plate junctions as determined by ITS [11]. In addition, an ITS-based model accurately predicts elastic modulus and yield strength of human trabecular bone [12]. ITS of data acquired by HR-pQCT in post-menopausal women has been shown to distinguish those with fracture from controls, those with hyperparathyroidism from controls, and those on chronic glucocorticoids from controls [13–16].

We hypothesized that young amenorrheic athletes would have compromised trabecular properties at the radius as compared to eumenorrheic athletes and non-athletes in conjunction with their hypogonadal status. We further hypothesized that this distinction would not be evident at the tibia, where increased mechanical loading associated with weight-bearing physical activity would counter the effects of hypogonadism. Finally, we hypothesized that among amenorrheic athletes, trabecular morphology would be altered in those with a history of recurrent fracture.

2. Methods

2.1. Study design and setting

This was an observational cross-sectional study comparing measures of bone density and microarchitecture across three groups: amenorrheic athletes (AA), eumenorrheic athletes (EA), and non-athletes. Study procedures were conducted at a Clinical Research Center of a tertiary care hospital. This study was approved by the Institutional Review Board of Partners HealthCare. Informed consent was obtained from all subjects ≥ 18 years and from the parents of subjects < 18 years. Informed assent was obtained from subjects <18 years.

2.2. Study participants

Subject recruitment and eligibility has been previously described [6]. Briefly, subjects were recruited from local pediatrics and sports medicine practices as well as from local high schools and colleges. Targeted advertisements for the AA group sought athletes and dancers with oligoamenorrhea, and subjects were informed in recruitment material that research participation would include bone density testing and nutritional and hormonal evaluation. Enrolled subjects were girls and young women ages 14–26 years with a bone age of at least 14 years. Subjects had a body mass index (BMI) between the 10th–90th percentiles for age, or weight ≥ 85% of ideal body weight. Three subjects in the AA group did not meet weight criteria due to low weight but were enrolled in the study as exceptions due to small skeletal frame, history of stable weight, and absence of eating disorder symptoms as determined by the study psychologist.

Subjects were excluded if they used a medication potentially affecting bone metabolism, including estrogen, progesterone, anabolic steroids, systemic glucocorticoids within the previous 3 months, phenytoin, or phenobarbitone. Subjects were also excluded if they had an illness potentially affecting bone metabolism, including hypo or hyperthyroidism, diabetes mellitus, Cushing's syndrome, cancer, renal disease, celiac disease, and inflammatory bowel disease, as well as conditions which may lead to amenorrhea including pregnancy, polycystic ovarian syndrome, thyroid dysfunction and primary ovarian insufficiency. Subjects were further classified by athlete and menstrual status as detailed below.

2.2.1. Athletes

Athletes participated in at least 4 h of aerobic weight-bearing activity or ran at least 20 miles per week for at least 6 months of the preceding year. Rowers, swimmers and gymnasts were excluded due to proposed differing effects of this type of weight-bearing and impact on bone density vs. leg-dominant activities [17,18]. Non-athletes participated in fewer than 2 h/week of weight-bearing exercise and in no organized team sports.

2.2.2. Menstrual status

Amenorrhea was defined as absence of menses for at least three months within a ≥six month period of oligoamenorrhea, or absence of menarche at ≥16 years with a bone age of ≥14 years. Six AA had primary amenorrhea, and causes other than functional hypothalamic amenorrhea were ruled out in these participants. Eumenorrhea was defined as at least nine menses in the previous 12 months. All non-athletes were required to be eumenorrheic.

2.3. Study procedures

All subjects underwent a screening visit including a structured history, a physical exam including anthropometric measurements, and a bone age x-ray. Blood samples were obtained to rule out exclusion criteria. DXA (Hologic 4500, Hologic Inc., Waltham, MA) was used to measure bone mineral content and density at the hip and spine as well as body composition parameters, and Z-scores were generated from race-specific normative databases.

2.4. HR-pQCT and micro-finite element analysis (μFEA)

Total volumetric density, compartment-specific densities, and microarchitecture of the distal radius and tibia were assessed using HR-pQCT (XtremeCT, Scanco Medical AG, Brüttisellen, Switzerland) as previously described [6,7]. Scans consisting of 110 CT slices were acquired with an isotropic voxel size of 82 μm. The non-dominant arm or leg was scanned unless there was a prior fracture at that region in which case the contralateral side was scanned. 2D scout views were obtained and used to locate the distal CT slice at 9.5 mm and 22.5 mm from the radius and tibia endplate respectively. We used semi-automated software to segment cortical and trabecular regions, and compartment-specific areas and volumetric bone densities as well as microarchitectural features of trabecular and cortical bone were determined.

μFEA was performed to estimate the biomechanical properties of the bone in the setting of simulated axial compression, as previously described [19]. Briefly, following image segmentation, each bone voxel of the HR-pQCT distal radius and tibia images was converted to hexahedral finite elements having linear–elastic and isotropic material behavior, with a Young's modulus and Poisson's ratio of 10 GPa and 0.3, respectively. Failure load was estimated by scaling the resultant load from a 1% apparent compressive strain until 2% of all elements reached an effective strain >7000 μstrain.

Same-day reproducibility for repeated measurements is 0.2 to 1.4% for density values, 0.3 to 8.6% for trabecular microarchitecture parameters, 0.6 to 2.4% for cortical microarchitecture parameters, 7.3 to 20.2% for cortical porosity measurements, and 2.1 to 3.0% for μFEA measures.

HR-pQCT and μFEA analyses of an earlier smaller subset of this cohort have previously been reported [6,7,20].

2.5. Individual trabecula segmentation

The trabecular bone compartment was extracted from each HR-pQCT image and the entire compartment underwent ITS-based