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Rapid Communication

Differential associations between appendicular and axial marrow adipose tissue with bone microarchitecture in adolescents and young adults with obesity

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ABSTRACT

Marrow adipose tissue (MAT) in humans is distributed differentially across age and skeletal site. We have shown impaired microarchitecture and reduced bone strength at appendicular sites in conditions associated with high MAT of the axial skeleton in adults (including conditions of over- and undernutrition). Data are lacking regarding differences in MAT content of the appendicular versus the axial skeleton, and its relationship with bone microarchitecture and strength. Furthermore, data are conspicuously lacking in adolescents, a time when hematopoietic marrow is progressively converted to fatty marrow. The purpose of our study was to examine differential associations between appendicular (distal tibia) and axial (lumbar spine) MAT and bone microarchitecture and strength estimates of the distal tibia in adolescents with obesity. We hypothesized that compared to MAT of the axial skeleton (lumbar spine), MAT of the appendicular skeleton (distal tibia) would show stronger associations with bone microarchitecture and strength estimates of the appendicular skeleton (distal tibia). We evaluated 32 adolescents and young adults (27 females) with obesity; with a mean age of 17.8 ± 2.1 years and median body mass index (BMI) of 41.34 kg/m^2, who underwent dual energy X-ray absorptiometry (DXA) for total fat mass, proton MR spectroscopy (1H-MRS) of the distal tibia and 4th lumbar vertebra for MAT, high resolution peripheral quantitative computed tomography (HR-pQCT) of the distal tibia for volumetric bone mineral density (vBMD) and microarchitecture, and micro finite element analysis (FEA) for distal tibial strength estimates. Linear correlations between bone parameters and MAT were determined using the Spearman or Pearson methods, depending on data distribution. Lumbar spine MAT was inversely associated with age ($r = -0.36$; $p = 0.037$). Total and trabecular vBMD and trabecular number at the distal tibia were inversely associated with MAT at the distal tibia ($r = -0.39$, $p = 0.025$; $r = -0.51$, $p = 0.003$; $r = -0.42$, $p = 0.015$ respectively) but not with lumbar spine MAT ($r = -0.19$, $p = 0.27$; $r = -0.18$, $p = 0.3$; $r = 0.005$, $p = 0.97$ respectively). In adolescents and young adults with obesity, the associations between MAT and appendicular bone parameters differ depending on the site of MAT assessment i.e. axial vs. appendicular. Studies evaluating these endpoints in adolescents and young adults with obesity should take the site of MAT assessment into consideration.

1. Introduction

Bone strength is determined not only by bone mineral density (BMD) and bone microarchitecture but also by its microenvironment, such as marrow adipose tissue (MAT) [1]. The distribution of MAT varies by age and skeletal site [2]. At birth, most of the marrow cavity is filled with red marrow which is a site of hematopoiesis. During childhood and adolescence, red marrow is progressively replaced by yellow or fatty marrow, and in the long bones this process begins in the epiphyses, followed by the diaphyses, the distal metaphyses and the

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proximal metaphyses. In contrast, red marrow may persist in the axial skeleton (pelvis and spine) well into adulthood [2]. MAT maturation reaches equilibrium in adulthood and may constitute up to 70% of the composition of bone marrow [3]. However, bone marrow is a dynamic organ and MAT content and composition can change in response to hormonal stimuli, and over- and undernutrition [4,5].

In translational studies, we have identified two different types of MAT; constitutive MAT (cMAT), which remains relatively stable to different hormonal and nutritional changes and is more prominent in the distal tibia, and regulated MAT (rMAT), which is more dynamic and responds to hormonal and nutritional changes and is found in the proximal tibia, femur and lumbar vertebra [6]. In humans, the different properties of distal and proximal MAT are highlighted by the varied degree of unsaturation of marrow adipocytes between the distal tibia and proximal femur suggesting MAT composition varies by site [6]. Hence, it is crucial to consider the age, and the site (appendicular vs. axial) when assessing the effects of MAT on bone health.

Most studies assessing MAT content in humans have quantified MAT in the axial skeleton (lumbar spine and proximal femurs) and assessed its relationship with bone microarchitecture at appendicular sites (distal radius and distal tibia) [1,4,7,8]. To our knowledge, there are no data in humans evaluating the effect of MAT on bone parameters at the same site.

The purpose of our study was to examine differential associations between appendicular (distal tibia) and axial (lumbar spine) MAT and bone microarchitecture and strength estimates of the distal tibia in adolescents with obesity. We hypothesized that bone microarchitecture and strength estimates of the appendicular skeleton (distal tibia) would have stronger associations with MAT of the appendicular skeleton (distal tibia) as compared to MAT of the axial skeleton (lumbar spine).

2. Methods

We evaluated cross-sectional data from 32 adolescents and young adults between the ages of 14–21 years with obesity from an ongoing trial at Massachusetts General Hospital. Subjects had a BMI > 35 kg/m^2 and did not have any known condition that would affect bone health. Our study was IRB approved and HIPAA compliant. Written informed consent/assent was obtained. A previously published subset of 14 healthy adolescents of normal weight, who had undergone proton MR Spectroscopy (1H-MRS) of the L4 vertebral body for MAT quantification using identical methods and equipment as in the present study, were used as a control group to compare the amount of L4 MAT between adolescents of normal weight and with obesity [9].

2.1. Experimental protocol

A detailed history was obtained, with attention to the use of medications and/or conditions that affect bone health. Participants were weighed on a calibrated electronic scale wearing a hospital gown, and height was measured in triplicate on a stadiometer. BMI was calculated using the formula: weight (kg) / height^2 (m^2).

2.2. Proton MR spectroscopy (1H-MRS)

Single voxel 1H-MRS was used for assessment of MAT of the L4 vertebral body and the distal tibia using a 3.0 T MR imaging system (Siemens Trio, Siemens Medical Systems, Erlangen, Germany) (Fig. 1). Single-voxel 1H MRS data was acquired using point-resolved spatially localized spectroscopy (PRESS) pulse sequence without water suppression with the following parameters: TE of 30 ms, TR of 3000 ms, 8 acquisitions,1024 data points, and receiver bandwidth of 2000 Hz. Automated procedures for optimization of gradient shimming and transmit and receive gain were used. MAT is reported as the quotient of the lipid peak to the water peak.

2.3. Dual-energy X-ray absorptiometry (DXA)

DXA was used to assess total fat mass. The same scanner (Hologic 4500 A, Waltham, MA) was used for all subjects.

2.4. High resolution quantitative computed tomography (HR-pQCT)

HR-pQCT was used to assess bone size parameters, volumetric BMD (vBMD), and trabecular bone microarchitecture at the distal tibia (Xtreme CT; Scanco Medical AG, Brüttisellen, Switzerland) with an isotropic voxel size of 82 μm^3. Measurements were performed at the non-dominant leg unless there was a prior fracture at that site. 2D scout views were obtained to locate distal CT slice site at 22.5 mm from the tibial endplate.

2.5. Micro-finite element analysis (FEA)

FEA was performed to estimate the biomechanical properties of bone in the setting of simulated axial compression. Failure load and stiffness (kN) were estimated by scaling the resultant load from a 1% apparent compressive strain until 2% of all elements reached an effective strain > 7000 μstrain, per previously published methods [10].

2.6. Statistical analysis

Statistical analysis was performed using JMP software (SAS Institute, Carey, NC). Normally distributed data are reported as means ± standard deviation (mean ± SD). In the case of non-normally distributed data, the median and interquartile range are reported. Pearson or Spearman correlations (depending on the distribution of the data) were used to determine univariate associations of MAT with clinical and bone parameters. Analyses were controlled for sex using standard least squares regression modeling. To adjust for multiple comparisons we used false discovery rate correction of < 0.05 for estimating q-values for assessing statistical significance [11].

3. Results

3.1. Subject characteristics

Table 1 shows the clinical characteristics of study participants. Participants (27 female and 5 male) had a mean age of 17.8 ± 2.1 years and a median BMI of 41.34 (38.31–45.60) kg/m^2. None of the participants exercised for > 2 h per week in the preceding year and none had a history of diabetes or hypothyroidism. We present their body composition including the MAT content at the distal tibia and lumbar spine in Table 1.

MAT content of L4 was lower compared to normal-weight controls of similar age: mean age 18.6 ± 1.6 (normal weight) vs 17.8 ± 2.1 years (obese), $p = 0.2$; L4 MAT 0.53 ± 0.27 (normal weight) vs 0.37 ± 0.17 (obese), $p = 0.02$.

3.2. Correlations of MAT at the distal tibia and L4 with age and body composition

MAT at the distal tibia was not associated with age, but we found a negative correlation of lumbar spine MAT with age ($r = -0.36$; $p = 0.037$), which remained significant after controlling for sex, but lost significance after false discovery rate correction. We found no correlation of axial and appendicular MAT with BMI or total fat mass (Table 2).

3.3. Correlations of MAT at tibia and L4 spine with bone vBMD, microarchitecture and strength estimates at the distal tibia

Distal tibial MAT correlated negatively with distal tibial total and