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Bone marrow fat content is correlated with hepatic fat content in paediatric non-alcoholic fatty liver disease

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Abstract

AIM—To investigate the relationship between bone marrow fat content and hepatic fat content in children with known or suspected non-alcoholic fatty liver disease (NAFLD).

MATERIALS AND METHODS—This was an institutional review board-approved, Health Insurance Portability and Accountability Act (HIPAA)-compliant, cross-sectional, prospective analysis of data collected between October 2010 to March 2013 in 125 children with known or suspected NAFLD. Written informed consent was obtained for same-day research magnetic resonance imaging (MRI) of the lumbar spine, liver, and abdominal adiposity. Lumbar spine bone marrow proton density fat fraction (PDFF) and hepatic PDFF were estimated using complex-based MRI (C-MRI) techniques and magnitude-based MRI (M-MRI), respectively. Visceral adipose tissue (VAT) and subcutaneous adipose tissue (SCAT) were quantified using high-resolution MRI. All images were acquired by two MRI technologists. Hepatic M-MRI images were analysed by an image analyst; all other images were analysed by a single investigator. The relationship between lumbar spine bone marrow PDFF and hepatic PDFF was assessed with and without adjusting for the presence of covariates using correlation and regression analysis.

RESULTS—Lumbar spine bone marrow PDFF was positively associated with hepatic PDFF in children with known or suspected NAFLD prior to adjusting for covariates ($r=0.33$, $p=0.0002$). Lumbar spine bone marrow PDFF was positively associated with hepatic PDFF in children with known or suspected NAFLD ($r=0.24$, $p=0.0079$) after adjusting for age, sex, body mass index z -score, VAT, and SCAT in a multivariable regression analysis.

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CONCLUSION—Bone marrow fat content is positively associated with hepatic fat content in children with known or suspected NAFLD. Further research is needed to confirm these results and understand their clinical and biological implications.

INTRODUCTION

Studies have demonstrated reduced bone mineral density (BMD) in obese children with non-alcoholic fatty liver disease (NAFLD); however, the pathophysiological connection between reduced BMD and NAFLD is not well understood [1–4]. Low BMD in children has been shown to persist into adulthood [5], and those who do not reach optimal bone mass during childhood are at higher risk for osteoporosis later in life [6]. Given the high prevalence of paediatric NAFLD, understanding how this condition affects BMD may have implications for preventing osteoporosis.

In adults, recent studies suggest that osteoporosis is associated with elevated bone marrow fat content [7], and that bone marrow fat content is positively associated with hepatic fat content [8]. Although these relationships have not been examined in children, the data from adults suggest that one potential factor related to osteoporosis in children with NAFLD is elevated bone marrow fat content. It was hypothesised that bone marrow fat content would be positively associated with hepatic fat content in children with known or suspected NAFLD.

The purpose of this study was to investigate the relationship between bone marrow fat content and hepatic fat content in children with known or suspected NAFLD. In addition, the influence of additional factors (age, sex, anthropometrics, and adiposity) on that relationship was explored. Proton density fat fraction (PDFF) is emerging as the standard quantitative magnetic resonance imaging (MRI) biomarker of tissue triglyceride concentration. Advanced MRI techniques were utilised to quantify bone marrow PDFF [9] and hepatic PDFF [10,11] as quantitative biomarkers of fat content in these organs. High-resolution MRI images were to measure abdominal adipose tissue compartments.

MATERIALS AND METHODS

Patients and research design

This single-centre, cross-sectional study was approved by the Institutional Review Board and is compliant with the Health Insurance Portability and Accountability Act. The study cohort comprised children aged 8–19 years who underwent research MRI examinations at ??? imaging center between October 2010 and March 2013 as part of prospective clinical studies. A paediatric hepatologist (initials withheld during submission) recruited the children from the institutional paediatric fatty liver and obesity clinics. All children had known NAFLD (based on prior biopsy) or suspected NAFLD (based on prior clinical ultrasound reports of fatty liver, obesity, otherwise unexplained transaminase elevations, or a first- or second-degree relative with NAFLD); none had contraindications to MRI, alcohol intake, or steatogenic medication use. The factors that led to suspicion of fatty liver disease were not recorded as this was outside the objective of this pilot observational study. Children aged 8–

17 years provided written informed assent with written informed consent by their parent(s) or guardian(s); those aged 18 and 19 years provided written informed consent.

Research examinations included an advanced complex-based MRI (C-MRI) technique to measure lumbar spine bone marrow PDFF, and a magnitude-based MRI (M-MRI) technique to measure hepatic PDFF. These techniques acquire images with a low flip angle to minimise T1 weighting, with multiple echoes to permit measurement and correction of T2* decay, and are reconstructed using a multi-peak fat spectral model to correct for the multi-frequency interference effects of fat protons [12,13]. The source images are processed using algorithms that calculate PDFF, assuming monoexponential decay pixel by pixel, to generate parametric maps that display the spatial distribution of PDFF. As the C-MRI technique generates PDFF maps that range from 0 to 100% [9], C-MRI was chosen to measure lumbar spine bone marrow fat to accommodate the expected range of bone marrow PDFF from below to >50%. The lumbar spine was selected because this is a validated location for bone marrow fat quantification. Measuring the thoracic spine would have required patient and coil repositioning, thus adding considerable time to the examination. Although subsequent reports have validated C-MRI to measure hepatic PDFF in children, M-MRI was selected to measure hepatic PDFF because it was the most extensively validated method at the time study was initiated (2010) [10,11]. Additionally, high-resolution anatomical MRI was used to measure abdominal adipose tissue. If children had two or more examinations, only the first examination was included. Demographic and anthropometric data were collected.

MRI

Children were asked to fast for a minimum of 4 hours to reduce possible physiological confounding effects and scanned at 3 T (Signa HDx, GE Healthcare). They were positioned supine with an eight-channel torso phased-array coil centred over the abdomen. A dielectric pad was placed between the coil and the abdomen. MRI examinations were performed by two MRI technologists. Hepatic M-MRI images were analysed by an image analyst. A single investigator (initials withheld during submission) performed all other image analysis.

Lumbar spine bone marrow PDFF

The C-MRI technique has been previously described [9]. Images were centred on the lumbar spine and acquired in the sagittal plane with the parameters listed in Table 1. Images were processed online with an investigational IDEAL algorithm that generates water and fat images from complex source data using a region-growing approach to avoid water-fat swapping [9]. Similar to the algorithm used for M-MRI, the algorithm used for C-MRI corrected for the confounding effects of T2* decay [14] and multi-frequency interference of fat [15] using the same spectral model [18, 19, 20]. In addition, correction was made for the confounding effects of noise bias [13] and eddy currents [19]. One circular ROI was placed in the marrow of each of the five lumbar vertebral bodies on the parametric maps, while avoiding cortical bone and artefacts. ROI size was adjusted for each child to be as large as possible. The PDFF values at each ROI were recorded and averaged to generate a mean lumbar spine bone marrow PDFF for each child.

Hepatic PDFF

The M-MRI technique has been previously described [10,11]. Images were centred on the liver and acquired in the axial plane with the parameters listed in Table 1. Source images were processed online using a custom algorithm to generate PDFF maps as described previously [20]. Parametric maps were transferred offline for further analysis. A 1-cm radius circular region of interest (ROI) was placed in each of the nine hepatic segments on the parametric maps while avoiding liver edges, lesions, artefacts, and large blood vessels. The PDFF values at each ROI were recorded and averaged to generate a mean hepatic PDFF for each child.

Abdominal visceral adipose tissue (VAT) and subcutaneous adipose tissue (SCAT) T1-weighted, 3D spoiled gradient recalled, pulse sequence was used to measure VAT and SCAT. Based on body habitus, two or three stacks of images were acquired to cover the entire abdomen and pelvis in the axial plane using the parameters listed in Table 1. Images were transferred offline. Images at the following levels were selected: T12/L1, L1/L2, L2/L3, L3/L4, L4/L5, L5/S1. Images were segmented using a supervised pixel-intensity thresholding technique. (Slice-O-Matic software; Tomovision, Ontario, Canada). The average intervertebral level surface areas (mm²) of VAT and surface, deep, and total SCAT were obtained for each child. VAT was defined as the intra-abdominal adipose tissue measured within the parietal peritoneum excluding bowel, blood vessels, bone, spine, liver, and intramuscular fat. Although both deep and surface SCAT were segmented, the distinction did not have significant impact on the data. Thus, it was decided to treat deep and surface SCAT as total SCAT, defined as the adipose tissue measured from the abdominal muscle wall to the skin.

Statistical analysis

Demographic and MRI-based characteristics of the cohort were summarised descriptively. Body mass index (BMI) *z*-score was computed for all children using their height, weight, age, gender, and reference parameters provided by the Center for Disease Control and Prevention [21]. Relationships between the adiposity measures were examined using pairwise Spearman's correlations. Averages for each anatomical structure were computed for use in the analyses. Pearson's correlation coefficient between average lumbar spine bone marrow PDFF and average hepatic PDFF was computed for all children and for boys and girls separately. A stepwise linear regression procedure with the Akaike information criterion (AIC) was used to select an optimal model for predicting average lumbar spine bone marrow PDFF. M-MRI hepatic PDFF, age, sex, BMI *z*-score, average VAT surface area, average total SCAT surface area, and the average VAT surface area to average total SCAT surface area ratio were assessed as predictors for that model. Age and sex interaction was evaluated. Finally, the relationship between lumbar spine bone marrow PDFF and hepatic PDFF was assessed after adjusting for the presence of other factors (covariates in the final model selected with AIC as criterion) using partial correlation analysis.

RESULTS

The research cohort included 125 children (82 boys, 43 girls) ranging in age from 8 to 19 years (mean 13.9 ± 2.4 [$\pm$ standard deviation, SD]) and in BMI z -score from -2.2 to 2.1 (mean 1.84 ± 0.81 SD). Cohort characteristics are summarised in Table 2. Representative children are shown in Fig. 1. As illustrated in these children, there was a positive correlation between bone marrow fat content and hepatic fat content. The positive correlation between lumbar spine bone marrow PDFF and hepatic PDFF was significant overall ($r=0.33$, $p=0.0002$). Both sex and sex–age interaction were significant in a multivariable regression modelling lumbar spine bone marrow PDFF as a function of hepatic PDFF and other covariates, suggesting that analysing boys and girls separately might be of additional interest. The positive correlation between lumbar spine bone marrow PDFF and hepatic PDFF was significant in boys ($r=0.32$, $p=0.0038$), but not in girls ($r=0.24$, $p=0.1312$; Fig. 2).

After adjusting for all other covariates in the model, the partial correlation between lumbar spine bone marrow PDFF and hepatic PDFF was found to be still significant overall ($r=0.24$, $p=0.0079$) and in boys ($r=0.25$, $p=0.023$), but not in girls ($r=0.22$, $p=0.1707$; Fig. 2).

DISCUSSION

The present study demonstrates a positive association between lumbar spine bone marrow PDFF and hepatic PDFF after adjusting for age, sex, BMI z -score, VAT, and SCAT in children with known or suspected NAFLD.

These findings suggest that there is a quantitative relationship between bone marrow fat content and hepatic fat content overall and in boys independent of other fat deposits. There was a positive, but not statistically significant, correlation between bone marrow fat content and hepatic fat content in girls. This result is important for two reasons. First, it advances our understanding of the association between paediatric NAFLD and low BMD. Second, this study extends results from adults to the paediatric population.

Classically, bone marrow adipocytes were hypothesised to passively fill empty space in the marrow [24]; however, recent evidence points to an active metabolic role for bone marrow adipocytes as well as important functions in bone modelling [23,24]. Furthermore, bone marrow fat is thought to inhibit osteoblast differentiation and enhance osteoclast differentiation, reducing overall bone strength [7, 25]. In adults, *in vivo* studies have suggested that osteoporosis is associated with elevated bone marrow fat content [7], and that bone marrow fat content is positively associated with hepatic fat content [8]. This evidence suggests that elevated hepatic fat content may be a potential risk factor for poor bone health.

The present study attempts to extend these results to the paediatric population by investigating the biological association between bone marrow fat content and hepatic fat content using advanced MRI techniques. Pardee *et al.*³ have shown that obese children with NAFLD have significantly lower BMD than obese children without liver disease. Importantly, the present data demonstrate a novel quantitative relationship between paediatric bone marrow fat content and hepatic fat content. This relationship remained significant independent of BMI z -score, VAT, and SCAT. As elevated bone marrow fat is

thought to be associated with osteoporosis [7], the study suggests that there may be a unique metabolic contribution from the liver to bone health independent of BMI z-score and abdominal adiposity measurements.

The present results show a positive relationship between bone marrow fat content and hepatic fat content that was significant in boys, but not significant in girls, with known or suspected NAFLD. This raises the question whether this relationship is stronger in boys than in girls. One possibility is that there are biological differences in fatty liver and bone marrow fat in boys and girls; however, because there were fewer girls than boys, there was less power to detect a significant relationship in girls. In addition, the positive correlation coefficients in boys and girls were similar. Thus the non-significant result in girls is more likely to represent the difference in sample sizes than a genuine difference between boys and girls (Fig. 2). The present results should be interpreted with caution, and further research is needed to explore this relationship.

The present study had some limitations. The cross-sectional nature of this study limits the ability to demonstrate causation. This study was conducted at a single institution, which may limit generalisability, but the large and diverse cohort supports the validity of the present results in children who have known or suspected NAFLD. The present research participants did not have biopsy-confirmed NAFLD; however, a previously validated M-MRI technique [10] was used, which has been shown to correlate well with histological assessment in children with NAFLD [11]. In addition, three different MRI techniques were used to assess biological associations. At the time of recruitment, rapid fat and water separation techniques that could cover the whole abdomen and pelvis rapidly were not available at the authors' institution. It is possible that the study measurements could be made more efficiently with the even more advanced fat-water separation techniques that have emerged in recent years. In addition, it is recognised that the known process of progressive fatty replacement of haematopoietic bone marrow with aging could potentially weaken the present data. Although haematopoietic bone marrow of the axial skeleton and lumbar spine have been shown to predominantly persist with minimal fatty conversion before age 20 [26], the present results should be interpreted with caution and further research is needed. Finally, this is a preliminary observational study in the absence of a normal control group, and the relationship between bone marrow fat content and hepatic fat content is likely to be complex and multifactorial. Future studies are needed to investigate the pathophysiological mechanism of this relationship.

In conclusion, the present study suggests that bone marrow fat content is positively associated with hepatic fat content independent of age, sex, BMI z-score, VAT, and SCAT in children with known or suspected NAFLD, which may carry implications both for metabolic research and clinical management of children with NAFLD. As elevated bone marrow fat is thought to be associated with low BMD, this study may help explain and support further studies to validate and further understand the association between paediatric NAFLD and low BMD.

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Highlights

- Bone marrow PDFF is positively correlated with hepatic PDFF in pediatric NAFLD.
- The correlation is independent of age, sex, BMI z-score, VAT, and SCAT.
- Our understanding of the association between NAFLD and low BMD is advanced.
- This study may contribute to preventing osteoporosis later in life.

Figure 1.

Examples of MRI from two children. Child A is a 13-year-old girl with a BMI z -score: 2.2, lumbar spine bone marrow PDFF: 18.1%, and hepatic PDFF: 3.7%. Child B is an 11-year-old girl with a BMI z -score: 2.18, Lumbar spine bone marrow PDFF: 50.7%, and hepatic PDFF: 20.9%.

Figure 2. Non-adjusted (left) and adjusted (right) correlations between lumbar spine bone marrow PDFF and hepatic PDFF in all children.

Table 1

MRI acquisition parameters

Parameter	C-MRI lumbar PDFF	M-MRI hepatic PDFF	Abdominal adiposity
Plane	Sagittal	Axial	Axial
Dimension	3D	2D	3D
Repetition time (ms)	8	240	2.4
Echo time (ms)	1.14, 2.06, 2.98, 3.90, 4.82, 5.74	1.15, 2.30, 3.45, 4.61, 5.76, 6.91	1.02
Flip angle	3	10	10
Section thickness (mm)	8	8	10
Gaps (mm)	8	8	10
Frequency	256	224	256
Phase	160	128	224
Parallel imaging type	Autocalibrating Reconstruction for Cartesian imaging (ARC)	Array Spatial Sensitivity Encoding Technique (ASSET)	N/A
Parallel imaging acceleration	2×	1.25	N/A
Band width (kHz)	125	143	125

* C-MRI was acquired in two echo trains with fly-back readouts and with echo spacing.

C-MRI, complex-based magnetic resonance imaging, PDFF, proton density fat fraction; M-MRI, magnitude-based magnetic resonance imaging; 3D, three-dimensional; 2D, two-dimensional.

Table 2

Patient characteristics

Variable	Mean $\pm$ SD (range)
Age (years)	13.9 $\pm$ 2.4 (8–19)
Height (cm)	164.1 $\pm$ 13.4 (125–246)
Weight (kg)	81.8 $\pm$ 24.2 (22.5–161.5)
BMI z-score	1.84 $\pm$ 0.81 (–2.16–3.13)
VAT (mm ²) [*]	7114 $\pm$ 3437(707–24810)
Total SCAT (mm ²) [*]	29540 $\pm$ 13178(2983–68970)
VAT/total SCAT ratio	0.252 $\pm$ 0.086 (0.075–0.464)
M-MRI hepatic PDFF (%)	12.0 $\pm$ 9.1 (1.3–34.8)
C-MRI lumbar spine bone marrow PDFF (%)	35.1 $\pm$ 10.7(16.2–65.4)

^{*} Average intervertebral level surface area of six predetermined intervertebral locations

BMI, body mass index; VAT, visceral adipose tissue; SCAT, subcutaneous adipose tissue; C-MRI, complex-based magnetic resonance imaging, PDFF, proton density fat fraction; M-MRI, magnitude-based magnetic resonance imaging