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

N.Y. Yu [a], T. Wolfson [d], M.S. Middleton [a], G. Hamilton [a], A. Gamst [d], J.E. Angeles [b], J.B. Schwimmer [a,b,c], C.B. Sirlin [a,*]

[a] *Liver Imaging Group, Department of Radiology, University of California, San Diego School of Medicine, San Diego, CA, USA*

[b] *Division of Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, University of California, San Diego School of Medicine, San Diego, CA, USA*

[c] *Department of Gastroenterology, Rady Children's Hospital San Diego, San Diego, CA, USA*

[d] *Computational and Applied Statistics Laboratory, San Diego Supercomputer Center, University of California, San Diego, La Jolla, CA, USA*

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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.

* Guarantor and correspondent: C.B. Sirlin, Liver Imaging Group, Department of Radiology, 408 West Dickinson Street, San Diego, CA 92103-8226, USA. Tel.: +1 (619) 471 0776; fax: +1 (619) 471 0503.
E-mail address: csirlin@ucsd.edu (C.B. Sirlin).

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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 the University of California, San Diego Liver Imaging Center between October 2010 and March 2013 as part of prospective clinical studies. A paediatric hepatologist (J.S.) 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, Aurora, OH, USA). 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.

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