Magnetic Resonance Materials in Physics, Biology and Medicine (2019) 32:591–597
https://doi.org/10.1007/s10334-019-00750-6

RESEARCH ARTICLE

^{1}H-MRS of femoral red and yellow bone marrow fat composition and water content in healthy young men and women at 3 T

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Received: 8 January 2019 / Revised: 16 April 2019 / Accepted: 23 April 2019 / Published online: 2 May 2019

Abstract

Objectives There is a discrepancy between studies suggesting that higher bone marrow fat saturation is associated with impaired health, and studies suggesting that erythropoiesis increases red bone marrow (RBM) fat saturation in young healthy individuals. Here, we seeked to elucidate these discrepancies by using long TE magnetic resonance spectroscopy (MRS) to study both yellow bone marrow (YBM) and RBM in the femur of healthy volunteers.

Materials and methods Thirty-three young healthy volunteers (17 females), age range 20–31 years, underwent long TE ^{1}H MRS at 3.0 T of RBM and YBM fat composition in the left femur. The water content of the bone marrow depots was measured using short TE MRS.

Results The female participants displayed a lower unsaturation in the sampled RBM volume (RBMV) than the males ($P<0.01$) without displaying a concomitant difference in YBM ($P=0.42$). They also showed a higher water content and broader spectral linewidths in RBM ($P=0.04$). The water content in RBM strongly associated with broader spectral linewidths ($R=0.887$, $P\ll0.01$) and inversely with RBMV fat unsaturation ($R=-0.365$, $P=0.04$).

Discussion These results partly support the notion that females display higher rate of erythropoiesis and lower fat unsaturation in RBM.

Keywords Red bone marrow · Yellow bone marrow · Proton magnetic resonance spectroscopy · Male · Female

Abbreviations

BMI	body mass index
YBM	Yellow bone marrow
RBM	Red bone marrow
RBMV	Red bone marrow volume
PRESS	Point-resolved spectroscopy sequence
VOI	Volume of interest
TE	Echo time
TR	Repetition time
NSA	Number of signal averages
Unsat	Unsaturation
ANOVA	Analysis of variance

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Introduction

There is increasing interest towards utilizing MRS to determine bone marrow fat composition, which may serve as a marker of bone and even metabolic health. Some studies suggest that bone marrow fat saturation is increased with risk of osteoporosis, obesity and diabetes mellitus [1–5]. In contrast, in vitro studies failed to find any association with bone marrow fat saturation and bone mineral density (an indicator of osteoporosis) [6, 7]. In fact, early studies suggested that saturated fat in bone marrow associated with the red bone marrow (RBM) fraction [8]. As the RBM fraction is highest in young and physically fit individuals [9], this does not support the notion that bone marrow fat saturation would convey or associate with risk of osteoporosis, obesity or diabetes mellitus.

Bone marrow comprises of RBM containing both hematopoietic and mesenchymal stem cells as the common precursors of blood cells, bone, cartilage and fat [10] and of adipocyte-rich yellow bone marrow (YBM). The relative proportion of RBM is highest at birth and is gradually replaced by YBM during aging, with distal bones losing RBM faster than central vertebrae and sternum [11]. Recently, Scheller et al. Showed in rodents that fat in RBM is more saturated than in YBM, and, using MRS, that humans also showed corresponding decreased fat saturation in distal bone marrow [7]. Similarly, another study showed decreased fat saturation in tibial bone marrow with age in young adults (age 15–27 years), coinciding with the known loss of RBM [12]. These recent studies complement previous observations suggesting that the higher saturation of RBM is due to haematopoieitic requirements [8].

Therefore, there seems to be a discrepancy between studies showing associations of increased marrow fat saturation with aging and impaired health [1–5] and those showing associations of increased marrow saturation with RBM and the young, physically fit phenotype [6–8, 12].

The regulation of bone marrow fat composition and its systemic impact are largely unknown. MRS, as a noninvasive method, is potentially a valuable tool for unraveling the role of bone marrow fat composition in pathology as well as normal physiology. However, the methodological difficulties and contradictory results of MRS compared to other methods need to be addressed, especially if fat composition is to be used as a diagnostic marker.

Accurately assessing bone marrow fat composition using MRS can be challenging, especially when a large water peak is present [13]. Furthermore, differences in the obtainable linewidth may contribute to peak overlap between the water and unsaturated fat peaks. Accordingly, short echo time (TE) MRS of vertebral bone marrow, which displays relatively low fat content, has shown poor reproducibility for determining fat composition [14]. Long TE MRS can be utilized to suppress the intense water resonance, as J-coupling and T_2 effects lead to a relative increase in the intensity of the olefinic resonance compared to water, as shown in the liver [15] and bone marrow [12, 16].

Here we examined the bone marrow fat composition by using long TE MRS, which eliminates the confounding effects of the intense water resonance overlapping with the olefinic peak of fat. Furthermore, we utilize this method to detect differences in RBM and YBM fat composition in young men and women.

Materials and methods

Participant characteristics

Thirty-three young volunteers (female/male = 17/16), age range 20–31 years, consented to the protocol approved by the ethics board of Heinrich Heine University Düsseldorf and underwent measurements in a clinical 3-T magnet (Philips Achieva, Best, The Netherlands). Informed consent was obtained from all individual participants included in the study. All volunteers had measurements of RBM and YBM fat composition in the left femur. They had neither diabetes nor any overt cardiovascular or malignant diseases. The participants arrived for MRS measurements at 10 am, with the instructions to consume a light breakfast in the morning, and adhere to a stable dietary regime and restrain from strenuous physical activity for at least two days prior to the measurements.

^{1}H MRS of fat composition in bone marrow

Bone marrow spectra were acquired using a SENSE XL Torso coil (Philips Healthcare, Best, The Netherlands). Prior to acquisition, a $0.7 \times 0.7 \times 2.0$ cm^3 volume of interest (VOI) was placed within the bone marrow of the in the left femur, taking into account the chemical shift displacement artifact. T_2-weighted anatomical images were used for accurate positioning of the VOI. Short TE (= 29 ms) and long TE (= 200 ms) spectra were acquired using point-resolved spectroscopy sequence (PRESS), to measure water content and fat composition, respectively (TR = 4 s and NSA = 32).

Three VOIs were carefully positioned in the femur in order to measure YBM and RBM regions. The YBM region was identified in the diaphysis, i.e. central bone area, and had below 10% water content. Two VOIs were placed near the epiphysis, in regions determined to likely contain RBM, as indicated by a lower signal intensity in the T_2-weighted images (Fig. 2). In six of the volunteers, also the YBM in tibial bone was sampled using the same acquisition parameters. In three volunteers the acquisition protocol was repeated during the same day to determine measurement repeatability. Shimming was performed using the automatic pencil beam (PB-auto) second order shimming procedure. The RBM containing regions all had an observable water resonance in short TE spectra. The spectra from the two RBM regions were summed in post-processing. As the VOIs of RBM regions contained varying amounts of water, and by extension varying heterogeneous mixtures of RBM and YBM tissue, the RBM sampled by MRS here is referred to as RBM volume (RBMV).

All spectra were processed and analyzed using the AMARES algorithm in jMRUI v4.0 [17]. Single Gaussian lineshapes were used to fit fat resonances, while a Lorentzian linshape was used to fit the water resonance.

The unsaturation (Unsat) index of fat was calculated as the olefinic peak area relative to the summed area of three fat peaks in percentage [$=CH/(=CH+CH_2+CH_3)$]. The unsaturation index is not susceptible to broad linewidths, as the long TE completely suppresses the overlapping water resonance and other overlapping resonances are absent. Therefore, the unsaturation index can be used to compare fat depots displaying differences in linewidths, such as YBM and RBM. The linewidth marker was derived from the methylene line shape in the long TE spectra, while the water content of RBMV was calculated from the short TE spectra, as a percentage of total MRS signals [$H_2O/(H_2O+=CH+CH_2+CH_3)$]. In order to compare possible T_2 and J-coupling effects of estimating unsaturation from long TE spectra, we also analyzed the unsaturation using the short TE spectra of YBM.

Analysis

Statistical analysis was performed using SPSS Statistics version 20.0.0 for Windows (SPSS Inc, Chicago, Illinois, USA). Sex differences were tested using one-way ANOVA. YBM to RBMV differences were tested using the paired *T* test. Associations between variables were analyzed by univariate correlation analyses using Pearson's product–moment correlation coefficient with partial correlations when adjusting for co-factors. The coefficient of variation (COV) was calculated for the repeated measurements. A *P* value below 0.05 was considered to indicate statistical significance.

Results

Utilizing a TE of 200 ms in ^{1}H MRS resulted in complete suppression of the water resonance in all bone marrow spectra, which enabled the accurate quantification of fat composition. Figure 1 shows typical short TE spectra from YBM and RBMV, showing the large difference in the intense water peak. Figure 2 shows a typical long TE spectrum from YBM and RBM along with illustration of the VOI positions.

The female participants displayed lower fat unsaturation in RBMV than the males (Table 1). They also had a higher water content and broader spectral linewidths in RBMV. In all persons, the spectral linewidth increased linearly with RBMV water content ($R=0.887$, $P\ll0.01$) (Fig. 3).

RBMV water content decreased with age in males ($R=-0.626$, $P=0.01$), but not in females ($R=-0.097$, $P=0.71$). RBMV fat unsaturation tended to associate inversely with RBMV water content in both females ($R=-0.314$, $P=0.12$) and males ($R=-0.417$, $P=0.11$), which was significant in both sexes combined ($R=-0.463$, $P<0.01$), even after adjusting for age and sex ($R=-0.365$, $P=0.04$).

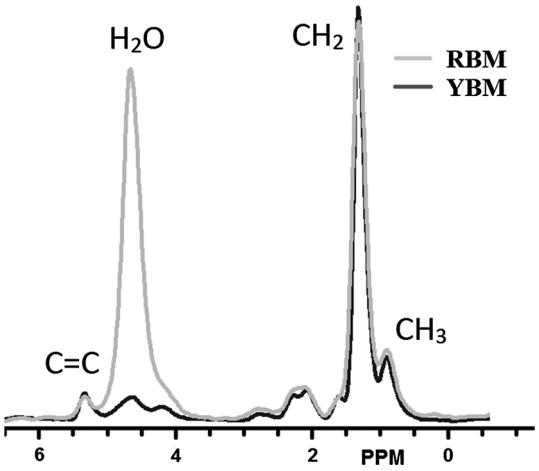

Fig. 1 Typical short TE spectra from yellow bone marrow (YBM) and red bone marrow (RBM). The water resonance is markedly more intense in RBM

The peripheral tibial YBM displayed higher fat unsaturation than YBM in the femur ($9.77\pm0.38\%$ vs. $7.73\pm1.94\%$, $P=0.03$, $N=6$), while the COV for repeated measurements was 1.6% for YBM and 2.7% for RBMV. Fat unsaturation in YBM as assessed from short TE spectra showed a strong linear association with that from long TE spectra with ($R=0.763$, $P\ll0.01$) (Fig. 4).

Discussion

We employed ^{1}H-MRS with long and short TE to study bone marrow fat composition and water content in the femur of young men and women. We found higher water content and lower fat unsaturation in the RBMV in women and an inverse association between RBMV unsaturation and water content. Although these results indicate that RBM is associated with lower fat unsaturation, we found no significant differences between RBMV and YBM.

Tavassoli et al. first suggested that erythropoiesis results in higher lipid saturation in RBM than in YBM at least in rabbits [8]. Later, Griffith et al. observed a trend towards a higher saturation in RBM compared to YBM in human biopsy samples, although this was not statistically significant [6]. Subsequently, Scheller et al. did confirm the previous findings in excised rat bone marrow, but in human bone marrow showed only that a distal gradient of fat unsaturation was present [7]. The present study now provides first in-vivo measurements of fat composition in both RBM and YBM of healthy humans.

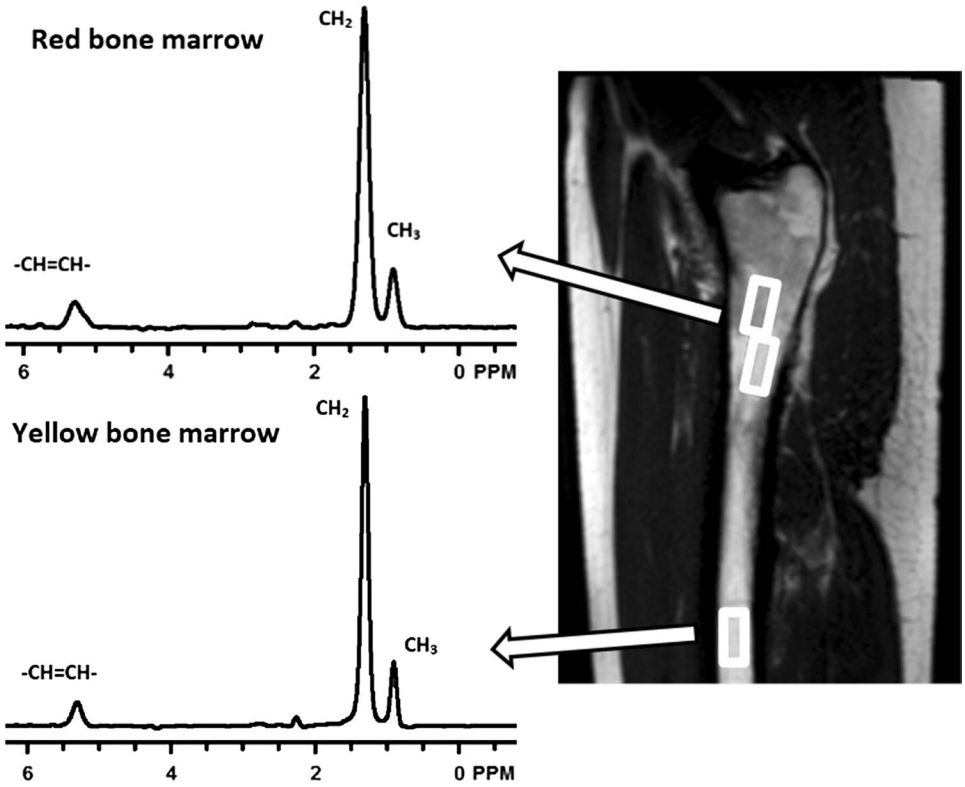

Fig. 2 Typical spectra from red and yellow bone marrow with the distinct fat resonances labelled (left). The localization of the volume of interest in red and yellow bone marrow is illustrated over a sagittal T_2-weighted MRI (right). Two spectra were acquired for red bone marrow and summed in post-processing

Table 1 Participant characteristics grouped by sex

	Female ($N=17$)	Male ($N=16$)	P value
Age (years)	23.7 ± 2.0 (21–28)	24.5 ± 3.5 (20–31)	0.43
BMI (kg/m^2)	21.4 ± 2.5 (18.4–27.3)	22.9 ± 2.3 (19.3–28.0)	0.10
YBM unsat (%)	8.43 ± 1.34 (6.29–11.26)	8.86 ± 1.66 (6.19–11.92)	0.42
YBM linewidth (Hz)	24.4 ± 5.5 (15.9–34.3)	22.1 ± 3.26 (17.4–28.4)	0.16
RBMV unsat (%)	7.83 ± 1.90 (4.62–11.2)	9.88 ± 1.17 (8.01–12.0)	**<u>< 0.01</u>**
RBMV linewidth (Hz)	39.3 ± 6.8 (25.3–48.8)	34.0 ± 6.2 8 (26.6–44.8)	**0.03**
RBMV H_2O (%)	43.6 ± 11.2 (23.6–62.2)	33.9 ± 14.5 (15.3–68.6)	**0.04**

Data are shown as mean ± SD (range) along with the P value of the ANOVA comparison for females with males

P values < 0.05 are in bold and P values < 0.005 in bold and underlined

All P values remained significant after controlling for false discovery rate

N number of participants, *BMI* body mass index, *YBM* yellow bone marrow, *RBMV* red bone marrow volume, *Unsat* olefinic to total lipid ratio

We observed that the femur region identified to include RBM, here denoted RBMV, displayed lower fat unsaturation, higher water content and broader spectral linewidths in women than in men. The fat unsaturation in RBMV decreased with increasing water content in both women and men. The water content of bone marrow is an indicator of RBM content and a higher water content translates to a larger RBM fraction in the sampled volume. Therefore, the higher water content—as observed in RBMV of women—is indicative of higher RBM content, supporting previous in vivo MRS studies that found higher water content in the bone marrow of women [18–20]. The spectral linewidth of RBMV increased linearly with the water content, indicating that RBM tissue induces line broadening by magnetic susceptibility effects. This can be attributed to tissue heterogeneity and/or iron deposits in RBM [21].

The lower fat unsaturation in RBMV in women and the decrease in fat unsaturation with increasing water content are in line with the notion that erythropoiesis increases fat saturation in RBM [7, 8]. However, we did not observe differences in fat composition in direct comparison between sampled YBM and RBMV. This indicates

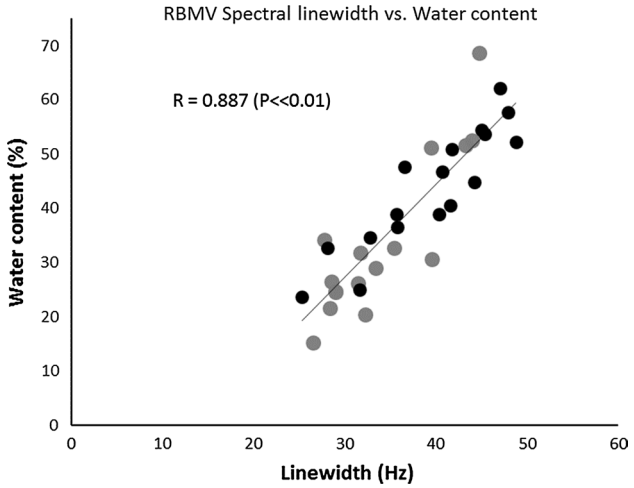

Fig. 3 Scatter plot of water content (*y*-axis, %) vs spectral linewidth (*x*-axis, Hz) in the sampled red bone marrow volume (RBMV). Black circles denote females and grey circles males ($R = 0.887$, $P \ll 0.01$)

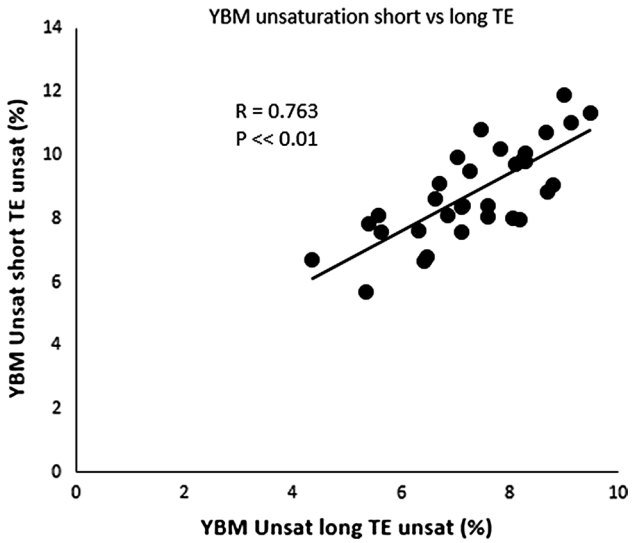

Fig. 4 Scatter plot of YBM fat unsaturation derived from short TE (*y*-axis, %) vs long TE (*x*-axis, Hz) ($R = 0.763$, $P \ll 0.01$)

that the association between YBM to RBM conversion and expressed fat composition is more complex than the relatively crude fat unsaturation index can capture. Also YBM fat unsaturation seems to relate insulin sensitivity adding another factor that may influence YBM/RBM comparison [22]. In addition, the sampled RBMV regions seemed to display large intra-individual variation in fat unsaturation, without a corresponding variation in water content (data not shown). The reason for the large intra-individual variation in RBMV fat unsaturation was not immediately apparent, but may be due to the heterogeneous mixture of RBM and YBM in the sampled volume. We therefore chose to sum the two RBMV spectra to obtain an average estimate for each individual.

We used a long TE MRS approach to eliminate the issue of the water resonance overlapping with the olefinic resonance. Previous studies have provided incompatible results regarding the composition of bone marrow fat and health indices. The higher saturation of RBM and higher saturation of central bone depots would indicate that higher bone marrow saturation is associated with improved bone health. All studies reporting contrasting data, i.e. associations of increased marrow fat saturation with aging and impaired health, used short TE MRS to measure bone marrow in the vertebra [1–5]. Vertebral marrow has a higher water content, indicating presence of RBM, with higher water content proven a reliable indicator of bone health [23]. The variation in water resonance intensity at 4.7 ppm is therefore a concern when estimating fat unsaturation from the olefinic resonance at 5.3 ppm. We found that RBM is also associated with broader spectral linewidths that will further hamper resolving the nearby resonances of water and olefinic fat in short TE spectra. As both the intensity of the water resonance and spectral linewidth increase with RBM content, the estimation of unsaturation becomes biased. The use of long TE MRS overcomes this problem, as no water resonance is present and the olefinic resonance is well resolved.

Long TE MRS however represents a trade-off, as it introduces T_2 weighting that can potentially impact the fat composition indices. We tested this by comparing the fat unsaturation index obtained from YBM using short TE and long TE. As YBM lacks a significant water resonance, the results should be comparable. The two fat unsaturation indices showed strong a linear correlation, indicating that long TE spectra produce good estimates of the underlying true fat composition. We also observed using long TE that tibial YBM was more unsaturated than femoral YBM, reproducing the results that Scheller et al. obtained using short TE MRS [7]. Furthermore we have recently validated the long TE MRS approach in subcutaneous adipose tissue using Gas Chromatography analysis of biopsies [24].

During placement of the MRS voxel, the chemical shift artifact was taken into account and fitted within the bone marrow in all participants. Also, changes in T_2 of fat do not seem to result in changes in long TE determined unsaturation, as previously shown using oils measured at different temperatures [25]. Our results are, however, restricted to femurs of healthy young volunteers, which may differ from the traditionally used vertebral bone marrow in elderly patients.

In summary, we found using long TE MRS that fat composition in RBMV is more saturated in young women than in young men. We also observed that RBMV fat unsaturation was inversely associated with RBMV water content. These results support the notion that erythropoiesis is linked to

higher fat saturation in bone marrow. We also found that higher RBM water content is related to broader spectral linewidths that may hamper fat composition estimation from short TE spectra. Long TE at 3 Tesla can overcome this challenge of short TE MRS.

Acknowledgements We thank Andrea Nagel, Nicole Achterath, Sofiya Gancheva, Kai Tinnes, Agnieszka Sutkowski and Martin Röhling (Institute for Clinical Diabetology, German Diabetes Center, Düsseldorf) for their excellent help with the studies. Additionally, the authors appreciate the voluntary contribution of all study volunteers. This work was supported by grants of the Deutsche Diabetes Gesellschaft (DDG), by the Ministry of Culture and Science of the State of North Rhine-Westphalia and the German Federal Ministry of Health, and in part by a grant from the Federal Ministry of Education and Research (BMBF) to the German Center for Diabetes Research.

Author contributions JL, AB, JS, KM and MR conceived and designed the study. AB acquired the data and contributed to the analysis and interpretation of the data and reviewed and edited the manuscript. JL analyzed and interpreted the data and drafted the manuscript. KB, MA, JS, KM, JH and MR contributed to the discussion, and reviewed and edited the manuscript. All authors gave final approval of this version to be published.

Compliance with ethical standards

Conflict of interest The authors have no potential conflicts of interest relevant to this article.

Ethical approval The study protocol was approved by the ethics board of Heinrich Heine University Düsseldorf and adhered to the ethics guidelines of the Declaration of Helsinki.

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