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To cite this article: P E Menshchikov *et al* 2020 *J. Phys.: Conf. Ser.* **1461** 012098

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^1H MRS as a novel quantitative method for osteoporosis detection

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Abstract. Bone mineral density is an important parameter that determines strength of the bone. Decrease in bone mineral density (BMD) leads to dangerous skeletal diseases like osteopenia, osteoporosis and an increased risk of fractures, for instance compression vertebral fracture (CVF). Dual-energy x-ray absorptiometry (DXA) and quantitative CT (QCT) are commonly accepted methods for assessing of the BMD. Previously FF was shown to increase in adult patients with osteoporosis as compared to healthy volunteers. The aim of the study was to explore the relationship between FF and BMD in children. Correlation analysis revealed significant inverse correlation link ($p < 0.05$) between FF and BMD for all vertebrae of all patients (Fig.1C). The correlation suggests that the processes of increasing FF in the bone marrow and lowering the BMD are parallel in children. Therefore, ^1H MRS could be good alternative to QCT and DXA without radiation dose in osteoporosis detection. Revealed significant negative correlation between FF and BMD in children without osteoporosis suggests that the processes of increasing FF in the bone marrow and lowering the BMD are parallel. Therefore, ^1H MRS could be good alternative to QCT and DXA without radiation dose in osteoporosis detection.

1. Introduction

Osteoporosis is a metabolic disease of the skeleton which is characterized by decreased bone mineral density (BMD). This pathology increases the risk of fractures. By statistics, most often osteoporotic fractures occur in the wrist, vertebrae and the neck of femur. Such fractures have serious negative impacts on human's health and on the quality of life. In 2010, there were 27.5 million patients with osteoporosis in European Union; and by 2025 this number will increase to 33.9 million [1]. Such statistic data allow us to speak of osteoporosis as a serious and widespread disease. Currently, there are various methods for osteoporosis diagnostics. The most common techniques are dual-energy X-ray absorptiometry (DXA) and quantitative CT-densitometry (QCT). Their main disadvantage is some ionizing radiation exposed to a patient.

The localized proton magnetic resonance spectroscopy (^1H MRS) is a non-invasive and biologically safe technique that allows to estimate concentrations of low molecular compounds which are present in organs and tissues. Spectra from VOI localized in vertebra contains two signals - from water protons



($\delta_{\text{water}} = 4.67\text{ppm}$) and signal from bulk methylene ($-\text{CH}_2-$) protons of fat ($\delta_{\text{Fat}} = 1.20\text{ppm}$). The source of signals in the spectrum is red and yellow bone marrow. Red bone marrow (RBM) is represented by the myeloid tissue; yellow bone marrow (YBM) - mainly by the fat tissue [2]. Changes in the relative fat-water content, typically quantified as can LWR (lipid-to-water-ratio) [3] or FF (fat fraction) [4] could be noninvasive markers of bone health along with BMD, measured by DXA or QCT.

The purpose of this study is to determine a possible relationship between FF and BMD in healthy children's vertebrae. The revealed relationship will give a chance to consider ^1H MRS as dose-free alternative to QCT and DXA.

2. Materials and Methods

2.1. Patients and study protocol

Twenty patients aged 7-16 (average age 11.1 ± 2.1) participated in the study. All patients were hospitalized to the Clinical and Research Institute of Emergency Pediatric Surgery and Trauma (Moscow) with suspicion of compression vertebral fractures. Parents signed a written consent to participate in the study. The third and fourth lumbar vertebrae (L3 and L4) were chosen as a study area, because BMD is typically measured with QCT in this location.

The study protocol included: standard diagnostic MR images of the spine, two ^1H MRS spectra from lumbar vertebrae (L3, L4) and QCT of lumbar vertebrae (L3, L4).

^1H MRS spectra were acquired with STEAM pulse sequence without water suppression using Phillips Achieva 3.0 T and 8-channel Torso Coil with the following parameters: TE = 12.8 ms, TR = 3000 ms, the number of signals averaged (NSA) -32, acquisition time - 2.5 min. VOI with size $20 \times 15 \times 10$ mm was localized in the central part of L3, L4 vertebra (Fig. 1A). The MR spectra were processed in SpectraView program which was integrated into MRI scanner by approximating resonances from water and fat with Gauss lines. FF parameter was calculated using the obtained integral intensities of water and fat peaks for vertebrae L3 and L4 of each patient. The following formula was used for these calculations:

$$F = \frac{I_{\text{fat}}}{I_{\text{fat}} + I_{\text{water}}},$$

where I_{fat} – integral intensity of fat signal, I_{water} - integral intensity of water signal.

BMD (mg/cm^3) of lumbar vertebra L3 and L4 was determined using quantitative CT densitometry using Philips Brilliance16 CT scanner. Field of view (FOV) included only vertebra L3 and L4 (Figure 2). Basic parameters for the registration of CT images: tube voltage - 120 kV; slice thickness - 3mm; exposure depended on patient's weight and varied in the range of 25-50 mAS. To calculate BMD software Extended Brilliance Workspace was used.

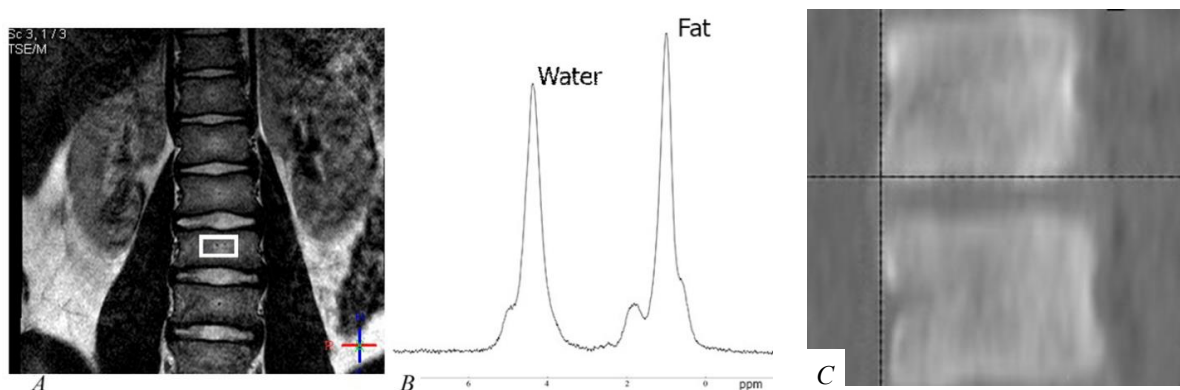


Fig. 1. VOI localization for ^1H MRS examination (A). Typical spectrum of vertebra (B). Field of view at CT densitometry (C)

3. Results

For the first time, a significant ($p=.001$) reverse inverse correlation link between FF and BMD parameters calculated for vertebrae L3 and L4 (Fig. 3) was revealed.

Patients were divided into two groups depending on the severity of their compression vertebral fractures revealed at MRI examination. Patients with one or two injured vertebrae were assigned to the group with mild compression vertebral fracture (mild CVF), patients with more than two injured vertebrae were assigned to the group with severe compression vertebral fracture (severe CVF). First group - 8 patients; second group - 12 patients.

The intergroup analysis revealed a statistically significant increase in FF ($p < .005$) in severe CVF group comparing to mild CVF group as well as a statistically significant decrease ($p < .005$) in BMD in severe CVF group comparing to mild CVF group.

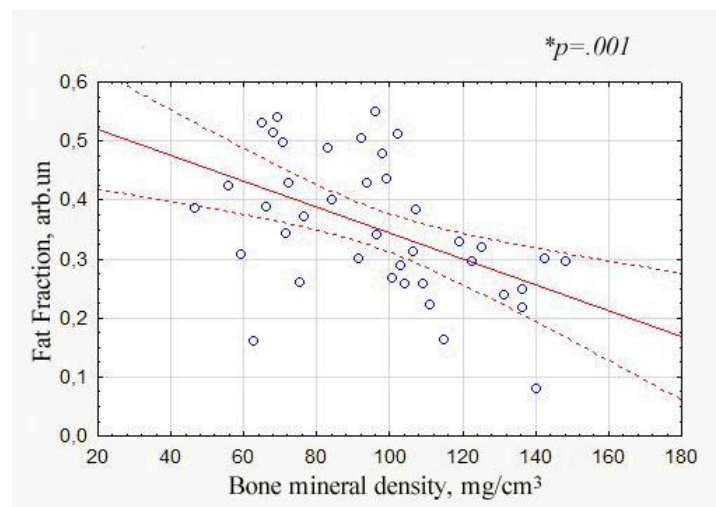


Fig.2. Correlation link between FF and BMD. Correlation coefficient $R = -0.51$

4. Discussion

In present study for the first time correlation between FF and BMD was revealed on the base of ^1H MRS and QCT findings, respectively, in healthy vertebrae of children. The main result of this work is a significant negative correlation ($R = -0.51$, $p = .001$) between FF and BMD indicating simultaneous processes of BMD decrease and fat accumulation in healthy vertebra. A similar significant correlation between these parameters measured in the lumbar vertebra bodies was also found in people of middle and old age [5, 6]. An negative correlation between FF and BMD averaged for L1-L3 lumbar vertebrae was found not only in healthy women (mean age 57 ± 4) but also in patients with diabetes mellitus type 2 (mean age 59 ± 4) [6]. In elderly men [7] and women [8] (mean age 73), a significant increase in the fat content was found in groups with osteoporosis and osteopenia relative to patients with normal BMD; and a strong correlation was found between the fat content in vertebral bodies and T- criterion ($r = -0.320$, $P < .003$ in [7], $r = -0.356$, $P < .001$ in [8]). Thus, this correlation indicates that there is a definite association between fat and BMD levels for all age groups.

BMD measurements are made not only in vertebrae but also quite often in the neck of femur (especially in women with age-related high risk of fracture of this bone). The fat content determining with ^1H MRS in women over 60 years old is significantly increased in patients with osteoporosis and osteopenia comparing to the controls.

Results of in vivo studies and previous histological findings [9-10] showing age-related replacement of bone tissue with the yellow bone marrow in vertebrae, confirm parallel decreasing in BMD and increasing in fat content in the bone marrow independently of age. Various mechanisms are proposed to explain a negative correlation between FF and BMD. It is assumed fat in bone marrow is not only the material for filling cavities in bone matrix [11]. Adipocytes and osteoblasts originate from a common

progenitor - mesenchymal stem/stromal cells. In vitro studies using bone marrow-derived mesenchymal stem/stromal cells found agents inducing adipocyte differentiation. Likewise, agents inducing osteoblast differentiation inhibited adipogenesis [12]. The secretion of fatty acids by bone marrow adipocytes could have a lipotoxic effect on differentiation, function and survival of osteoblasts [13].

Due to an inverse correlation between FF and BMD, we can use changes in fat content in the vertebra bone marrow measured with ^1H MRS for assessing bone mineral density. A significant advantage of such technique is the absence of ionizing radiation on a patient. That is why we can use it for screening even children. Assessment of vertebrae strength in children is an important task since during childhood bone mass and bone mineral density that reach the peak values between 20 - 30 years. After this, BMD level starts going down. Some disruptions to the process in childhood may not allow achieving maximal peak values. It can lead to substantially increasing the risk of age-related osteoporosis in adult age. In addition, it leads to less strength in bones what is the cause of more severe traumas. Therefore, it is very important to identify such disorders as early as possible. With early diagnostics, children's lifestyle and nutrition can be changed to achieve BMD peak value.

Our findings demonstrate that severe compression vertebral fractures are associated with higher FF values and lower BMD values, while mild compression vertebral fractures are associated with lower FF values and higher BMD values. This also indirectly indicates a parallelism in the processes of fat content increasing and BMD decreasing mentioned above. A similar relationship between BMD level and severity of vertebral fracture was also found in adult patients examined with DXA. A negative correlation between FF measured with ^1H MRS and biomechanical strength of vertebrae was found in in-vitro studies [4] in elderly people (mean age 58 ± 12). Biomechanical strength is a parameter characterizing vertebrae resistance to uniaxial mechanical loadings of compression and stretching. It also proves the negative correlation between bone strength and fat content in the bone marrow. Likewise, a positive correlation between BMD and vertebrae biomechanical strength was revealed [4]. Findings of the present study and findings [4] demonstrate FF and BMD values are important parameters for evaluating vertebrae strength.

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