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Gender and age groups interactions in the quantification of bone marrow fat content in lumbar spine using 3T MR spectroscopy: A multivariate analysis of covariance (Mancova)

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ABSTRACT

Introduction: There is an age-related conversion of red to yellow bone marrow in the axial skeleton, with a gender-related difference less well established. Our purpose was to clarify the variability of bone marrow fat fraction (FF) in the lumbar spine due to the interaction of gender and age groups.
Methods: 44 healthy volunteers (20 males, 30–65 years old and 24 females, 30–69 years old) underwent 3T magnetic resonance spectroscopy (MRS) and conventional MRI examination of the lumbar spine; single-voxel spectrum was acquired for each vertebral body (VB). After controlling body mass index (BMI), a two-way between-groups multivariate analysis of covariance (MANCOVA) assessed the gender and age group differences in FF quantification for each lumbar VB.
Results: There was a significant interaction between gender and age group, $p = .017$, with a large effect size (partial $\eta^2 = .330$). However the interaction explained only 33% of the observed variance. Main effects were not statistically significant. BMI was non-significantly related to FF quantification.
Conclusions: Young males showed a high FF content, which declined in the 4th decade, then increased the next 3 decades to reach a FF content just below the initial FF means. Females' FF were low in the 3rd decade, depicted an accelerated increase in the 4th decade, then a gradual increase the next 3 decades to reach a FF content similar to males' values. Our findings suggest that quantification of bone marrow FF using MRS might be used as a surrogate biomarker of bone marrow activity in clinical settings.

1. Introduction

Over the last two decades, magnetic resonance (MR) imaging has become the noninvasive imaging modality of choice in diagnosing bone marrow disorders [1]. Besides the ability to assess qualitatively the bone marrow composition based on signal intensity variations on MRI, it is possible nowadays to perform a quantitative measurement of the bone marrow by inferring the red (hematopoietic) and yellow (fatty) components; the MR spectroscopy (MRS) detects the water and fat signal contribution acquired from a small voxel [2]. At any age, a sustained increase in demand for blood cells can lead to resume hematopoiesis, and bone marrow cellularity shows dramatic changes in vertebral bodies (VBs) upon aging and various pathologic processes [3].

The gender-related difference in bone marrow content is less well established than the age-related difference, with some studies showing increased fat content in men [4,5] and others observing no variation [6]; also, the influence of body mass index (BMI) has not been evaluated in this context. There are some reports of fat concentration in some vertebral bodies of the lumbar spine [2], with most of these studies focusing on a single vertebral body [4,5,7]. An understanding of the normal variations in marrow cellularity of the whole lumbar spine is still missing in the medical literature and would be a useful tool for radiologist in the interpretation of lumbar spine pathology [3].

The aim of this study was to evaluate the influence of gender, age and body mass index (BMI) in the quantification of fat fraction (FF) in vertebral bodies (VBs) of the lumbar spine by using 3.0T single-voxel MRS in a sample of Mexican-Mestizo healthy volunteers.

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Table 1
Distribution of gender and age groups in 44 healthy volunteers.

Age groups	Gender		Total
	Male	Female	
30–39	6	3	9
40–49	5	4	9
50–59	4	7	11
60–69	5	10	15
Total	20	24	44

2. Subject and methods

2.1. Subjects

A cross-sectional study was performed on a consecutive sample of healthy volunteers at the MRI unit of Medica Sur Clinic & Foundation between August and December 2009. Interviews and medical examinations recorded information about gender, age and BMI (defined as the individual's body weight divided by the square of his or her height, unit of measure: kg/m^2). Exclusion criteria included histories of hematologic disease, liver disease, autoimmune disorders, infectious disease, recent bleeding episodes, cardiopulmonary disease, renal dysfunction, malignancy, acute trauma, smoking history and exposure to radiation. Race was established in each subject by self-report. Weight and height for calculation of BMI were evaluated on the same day as the screening examination. Written informed consent was obtained from all patients, the study received institutional ethical committee approval.

2.2. Descriptive statistics

The study was conducted in 20 males (mean age, 47.25 ± 11.41 years; range, 30–65 years) and 24 females (mean age, 54.42 ± 12.02 years; range, 30–69 years). Good quality spectra were acquired in all 44 cases for the 5 VBs in each patient. Age was grouped in four categories: 30–39, 40–49, 50–59 and 60–69 years old. BMI effect was controlled at the following value: 25.9545 kg/m^2 (in multivariate Mancova analysis, the chosen covariate is controlled at a central value representative of all groups). Table 1 depicts the gender and age groups distribution.

2.3. MR imaging

Conventional MR evaluations of the lumbar spine were performed prior to spectroscopy acquisition using a 3.0T GE Signa HDxt scanner (General Electric Healthcare, Waukesha, WI) with an 8-channel spine coil. The spine imaging protocol included standard clinical parameters of sagittal T1-weighted (T1w) and T2-weighted (T2w) images, axial T1w and T2w, and coronal T2w images.

2.4. MRS acquisition and data analysis

In all cases, the lumbar spine was examined at five locations with spectra acquired in all five VBs (L1–L5) using point-resolved spectroscopy (PRESS), 16 acquisitions were averaged with 0repetition time/echo time of 1500/30 ms and 62.5 kHz bandwidth. A single voxel (2 cm × 2 cm × 2 cm) was positioned within the trabecular bone at the center of each particular VB (cases in which was not possible to exclude compact bone a smallest voxel was used 1.5 cm × 2 cm × 2 cm); outer volume saturation bands were used to eliminate unwanted signal contamination from outside the voxel. These saturation bands typically covered the cerebrospinal fluid (CSF) and adjacent vertebral discs. Automatic voxel shimming was carried out to achieve good magnetic field homogeneity of the chosen voxel. MRS data were processed with the software SAGE Dev2007.1 (General Electric Healthcare, Waukesha, WI). Raw data were zero-filled to 2k and apodized using a 30 Hz Gaussian filter. The data was Fourier transformed, phase corrected, and baseline corrected. Marquardt curve fitting was performed using a Lorentzian function to calculate the area under the fat and water peaks. Spectra were referenced to peak water at δ 4.7 ppm [8]. The fat fraction (FF) percentage was defined as: FF = FA/(FA + WA) × 100, where FA is the area under the fat peak and WA is the area under the water peak. Two radiologists blinded to the MRI results reviewed MRS data. Fig. 1 shows typical spectra obtained from a young adult and elderly subjects.

2.5. Statistical analysis

Sample size was determined based on the software G*Power v 3.1.3 [9], for Ancova analysis; considering a priori effect size $f^2(V) = .35$ (medium size effect), α err prob = .05 and Power (1 − β err prob) = .95, with 2 independent variables (gender and age groups); a sample size of 40 was recommended, our sample included 44 subjects.

A two-way between-groups multivariate analysis of covariance (Mancova) [10] was performed to investigate gender and age group differences in FF quantification of the lumbar spine. Five dependent variables were used: the FF percent in L1, L2, L3, L4 and L5 VBs. The independent variables were the gender and age groups. Scores of the BMI measured before the MRI studies were used as a covariate to control for individual differences.

Preliminary assumption testing was conducted to check for normality, linearity, univariate and multivariate outliers, homogeneity of variance covariance matrices, and multicollinearity, with no serious violations noted. The effect size assessment (proportion of the variance in the dependent variable that can be explained by the independent variable) of each one of the results was obtained by using the partial eta squared (η^2) proposed by Cohen [11], where .01–.06 = small effect; .06–.14 = moderate effect and a value more than .14 = large effect.

All analyses were carried out using the IBM® SPSS® Statistics software (version 21.0.0. IBM Corporation; Armonk, NY). General presentation of the manuscript was prepared in accordance with the guidelines set by the International Committee of Medical Journal Editors [12]. Statistical significance was indicated by $p < .05$ (two-tailed).

3. Results

3.1. Interactions, main effects and effect sizes

The assumption of homogeneity of variance-covariance matrices was interpreted as non-significant (Box's M value = 57.514, $p = .003$), assuming the covariance matrices between the groups were equal (for this specific multivariate analysis, values > .001 are considered that they do not violate the assumption of homogeneity of variance-covariance matrices) [13]. The homogeneity of variance at each VB was also non-significant ($p > .05$). After adjusting for BMI, there was a significant interaction effect between gender and age groups on the combined dependent variables, Fisher's F (15, 86 degrees of freedom, df) 3.246, $p = .017$; Wilks' Lambda .492; with a large effect size (partial $\eta^2 = .330$). Neither of the main effects were statistically significant, gender: $F(5, 31) = 2.216$, $p = .078$, age groups: $F(15, 86) = .431$, $p = .966$; this fact means, that, it is only the combined effect of these variables, which is significant, not the individual effects. The covariate, BMI, was non-significantly related to FF quantification: $F(5, 31) = .540$, $p = .745$. Table 2 presents a summary of the multivariate assessment. Bonferroni's adjustment