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Research article

Mapping the medullar adiposity of lumbar spine in MRI: A feasibility study

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ABSTRACT

Purpose: The bone medullar adiposity is a marker of bone quality to the point that there is a need to investigate the factors which influence or not the density and distribution of this fat in the spine, especially at the lumbar level. The purpose was to test the feasibility of a Dixon three-point technique and investigate the vertebral marrow fat distribution.

Material and methods: A sagittal sequence Iterative Decomposition of Water and Fat with Echo Asymmetry and Least-squares Estimation (IDEAL) IQ was performed on the lumbar spine of 46 subjects who were not suffering from any bone disease (21 women and 25 men, aged 18–77 years). Medulla adiposity was determined directly from the measurement of the fat fraction in each vertebral body (T12 to S1) obtained on the fat cartography automatically generated by the IDEAL sequence.

Results: Average vertebral fat fraction was 36.48% (SD 12.82), with a tendency to increase with age and to higher values among men. We observed a craniocaudal gradient of the fat fraction ($\beta = 1.37$; $p < 0{,}001$; SD 0.11) increasing with age in the lumbar spine from T12 to L5. Through multivariate analysis, this gradient was adjusted for sex, weight and height of the subjects.

Conclusion: This feasibility study shows the existence of a physiological craniocaudal gradient of vertebral medullar adiposity from T12 to L5. This gradient increases with age but it is independent of sex or BMI. The IDEAL sequence allows quick and reproducible measurement of the spine vertebral medullar adiposity.

1. Introduction

Bone marrow is composed of red marrow (generating haematopoietic cells) which "converts" with age into yellow marrow, containing a majority of adipocytes [1,2]. This medullar adiposity (yellow marrow) varies depending on age, sex, and anatomical site [1,3]. The relationship between bone and fat formation within the bone marrow is complex and remains an area of active investigation, including the effect of the body mass index (BMI) on it and on osteoporosis which is related to the bone mineral density. The literature records that bone marrow fat increase is related to a low bone mass during osteoporosis [1,3], which is characterized by a low bone mineral density [4,5,6,7].

It has already been demonstrated that medullar adiposity of vertebral bodies varied quantitatively between 2 adjacent vertebral bodies in postmenopausal female subjects [8,9] or in subjects with a medical history of prostate neoplasia treated with radiotherapy and hormonotherapy [10]. Effects of age and menopause were reported using IDEAL-IQ by Aoki et al [11]. However, no study has measured this medullar adiposity on all the vertebrae of the lumbar spine in a population without bone disease.

Magnetic resonance spectroscopy has proved its value in bone medullar triglycerides quantification [4,5,12,13], and it is considered as the gold standard for this method in MRI. Liney's study shows the existence of a difference in medullar fat fraction between L1 and L5 in 10 healthy subjects [13]. Nevertheless, the use of this method is limited by its acquisition time which limits the number of vertebrae that can be studied simultaneously.

The Ideal sequence (Iterative Decomposition of Water and Fat with Echo Asymmetry and Least-squares Estimation), which has become available recently in MRI, is based on fat and water separation. The main advantage of this sequence is that it permits measurements of fat in several vertebrae in a short time-frame. Its results agree closely with those of magnetic resonance spectroscopy in fat quantification [5,10,13,

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14]. Further, it s reliability has been proved in hepatic [15,16] and spine fat [16,17] analysis. We have studied the feasibility of an IDEAL sequence to quantify medullar adiposity of the lumbar spine in the general population.

2. Material and Methods

2.1. Population

This cross-sectional study was performed on a total of 46 subjects who had undergone an MRI of the lumbar spine with IDEAL-IQ sequence, as a part of a medical check-up in the context of a lumbar pain that occurred from January to March 2015.

Age, weight, height, sex and calculated body mass index (BMI) according to the Quetelet formula were collected for each subject. The menopause status was also recorded. This population had no past medical history of spine trauma, neoplasia, nor bone consistency or phosphocalcic metabolism modifying treatment e.g. steroids or calcium supplementation. These information were collected from the medical records and by phone calls. The absence of intercurrent bone damage was determined by two radiologists while reading the MRI scan. Each subject's data were anonymized. The institutional review board of our hospital approved the design of the study under the protocol ID: NCT 02887716.

The sample included 21 women and 25 men aged from 18 to 77 years. The mean age was 40 years, mean weight and height of 73.8 kg and 1.72 m (BMI: 22.88 $\pm$ 5.57 kg m^{-2}), respectively (Table 1). Seven women were post-menopausal (33%).

2.2. Technique

MRI was performed on a 1.5 T machine (Optima MR450w; GE Healthcare, Milwaukee, WI, USA). An IDEAL IQ Spoiled Gradient Echo sagittal sequence (TR: 14.4 ms, TE: 7.2 ms, field-of-view 40cm, matrix 256 $\times$ 256, slice thickness 4mm, 40 sagittal slices, acquisition time 1:48 min) was carried out. Water-only, fat-only, in-phase (water + fat), out-of-phase (water - fat), and cartography of medullar adiposity (fat fraction) images were generated automatically allowing direct measurement of fat percentage by selecting a region of interest (ROI). As the IDEAL-IQ sequence has been confirmed to be an accurate technique to quantify bone marrow fat, each ROI thus represented the average percentage of fat (vertebral fat fraction) [10,11,12,13]. Conventional Tl Fast Spin Echo sagittal sequence (TR: 579 ms, TE: 13.82 ms, time acquisition 1:59 min), and T2 Shot-Tau-Inversion-Recuperation sagittal sequence (TR: 3688 ms, T:57 ms, time acquisition 4:07 min), were assessed for medical purpose and taken into account in this study to guide the placement of the ROI and exclude focal vertebral lesion, such as vertebral angioma.

2.3. Measure

Fat fraction measurement was performed using the image processing software Osirix 5.9 (Pixmeo, Geneva, Switzerland). On the cartography generated by the IDEAL IQ sequence (Figure 1), a first observer manually drew and placed 15 ROIs to scan each vertebral body from right to left from T12 to S1 (on a set of 322 studied vertebrae). The ROIs were so selected as to exclude cortical bone, basivertebral veins, or vertebral focal lesions (Figure 2). The average of the 15 ROIs was then calculated to determine the average fat fraction per vertebral body. The initial observer repeated the measurements on a single ROI per vertebrae, from T12 to S1, onto the median sagittal slice. A second radiologist also placed on the same median sagittal slice an ROI for each vertebral body.

Table 1. Population description.

	Age (years)	Weight (kilograms)	Height (meters)	BMI*
Mean	40.43	73.8	1.72	24.88
SD**	15.27	19.42	0.097	5.57
Min	18	49	1.5	18.22
Max	77	150	1.9	48.98

* BMI: Body Mass Index ($kg.m^{-2}$).
** Standard Deviation.

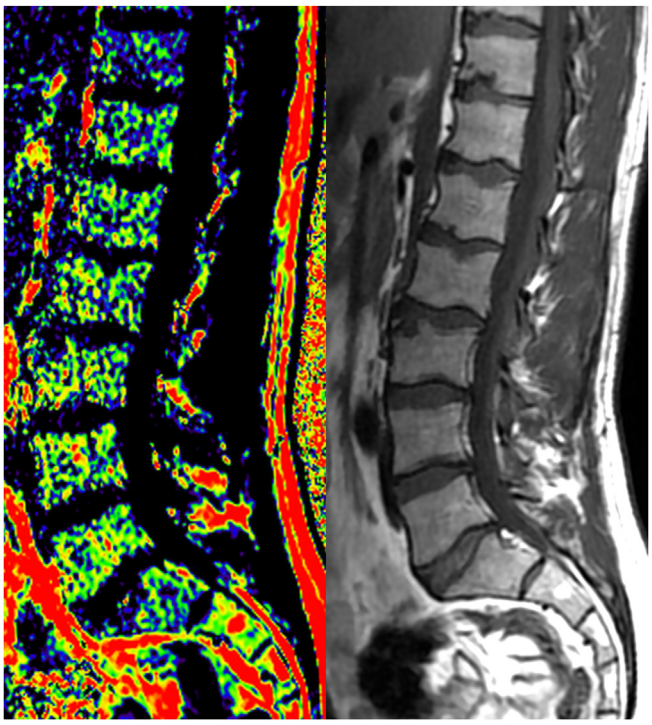

Figure 1. MRI Sagittal median slices of the lumbar spine: On the right, color-enhanced image representing the cartography of medullary adiposity, automatically generated from the IDEAL-IQ sequence: the brighter the color is, the higher the fat concentration is. On the left, a T1weighted slice at the same level on the same patient.

2.4. Statistical analysis

Data were analysed using STATA 12 (Statacorp LP, College Station, TX, USA). Quantitative data were described by using their mean, standard deviation (SD). Confidence intervals at 95% were estimated based on the exact binomial method.

Inter and intra-observer variability of the fat fraction was performed with the measurements done on a single median ROI. Inter- and intra-observer variability was analysed by calculating the intraclass correlation coefficient (ICC). Whole vertebrae and single-slice measurements were analysed using Pearson's correlation coefficient.

An analysis of variance (ANOVA) using the Bonferroni correction was used to analyse the vertebral fat fraction at the different vertebral levels. Effects of independent variables (such as age, sex, size, weight, BMI, menopausal status) on the dependent variables (vertebral adiposity measured by the fat fraction, and the vertebral fat gradient) were analysed using univariate and multivariate linear and polynomial mixed regression. $P < 0.05$ was considered as a significant value.

3. Results

3.1. Measure validity and reproducibility

Measure validity given by the first radiologist was based on the values, calculated for the 15 slices of each vertebral, which showed a

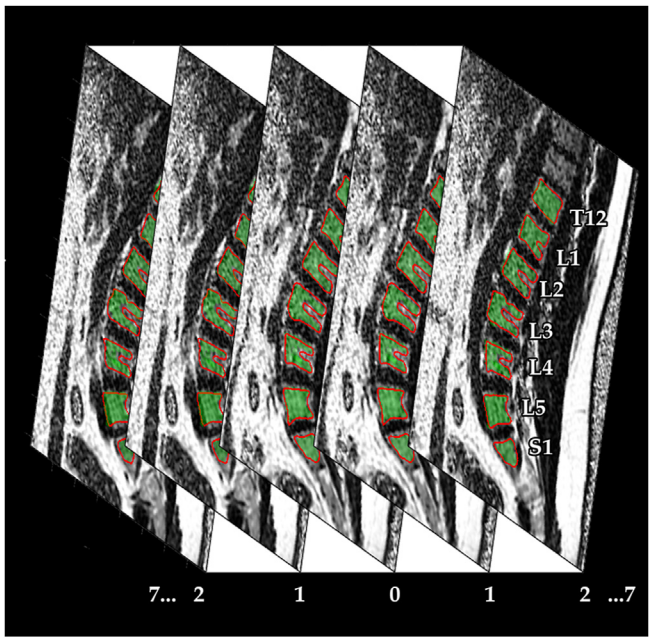

Figure 2. IDEAL sequence medullary adiposity cartography showing fat average at each vertebral level from T12 to SI, determined by regions of interest free-hand drawn, display here on 5 consecutives slices.

significant correlation with the value of the single measure of the midline slice, with a correlation coefficient of 0.997 ($p < 0.001$).

Measure reproducibility was given by the paired analysis of repeated midline ROI placement, the inter-observer ICC was 0.997 and the intra-observer ICC was 0.998.

3.2. Medullar adiposity of the spine

The average fat fraction was 36.48% (SD 12.82); its measurement ranged from 14.69% to 72.81%. The largest difference in fat fraction for the same subject was 12.8% between L1 and L5. Table 2 shows the fat fraction average of each pair of adjacent vertebra in the studied population. In the entire whole population (n = 46), fat fraction average varied from 31.71% (SD 11.75) at T12 to 39.91% (SD 13.98) at L5. It increased from one vertebra to next toward the lower part of the spine, and it decreased to 38.93% (SD 13.92) at S1 (Figure 3). Fat fraction average on all vertebrae was significantly more important ($p < 0,001$) for men (39.47% SD 12.19) than for women (35.92% SD 13.85). It was also significantly higher for post-menopausal women (44.54% SD 17.02; versus 29.55% SD 7.81 for pre-menopausal; $p < 0.001$). No significant link was found with other independent variables such as BMI ($p = 0.919$), height ($p = 0.112$), weight ($p = 0.111$). Using a robust variance estimator, in a mixed multivariate regression model, the vertebral fat fraction was adjusted for sex ($p = 0.149$), weight ($p = 0.244$), height ($p = 0.819$), BMI ($p = 0.291$) and menopausal status ($p = 0.856$) and age. This study showed an independent effect of age on fat average by vertebral level ($p = 0.003$; $\beta = 0.52$; SD 0.18). As age increases, the average percentage of fat found by vertebral level was more important.

Table 2. Average fat fraction per vertebral body.

Vertebra	Average fat fraction in % (95% CI)	Gradient* in %	p-value
T12	31.71 (14.70–57.08)		Reference
L1	33.24 (15.86–59.45)	1.53	0.522
L2	35.36 (17.99–59.16)	2.12	0.141
L3	37.47 (19.13–63.84)	2.11	0.025
L4	38.75 (19.35–66.76)	1.28	0.007
L5	39.91 (19.47–72.82)	1.16	0.002
S1	38.93 (16.98–68.67)	-0.98	0.006

* The gradient is calculated making the difference between the average fat fraction of the considered vertebra and the average fat fraction of the superior vertebra. Comparison is done with T12 as a reference for this gradient. 95% CI: 95% confidence interval.

3.3. Fat fraction gradient

The hypothesis of the presence of a gradient of distribution of vertebral fat percentage has been tested using a robust variance estimator within a mixed model. We demonstrated the presence of a fat fraction craniocaudal gradient. This gradient was estimated at an average of 1.37% ($p < 0.001$; SD 0.25) between T12 and L5. It did not follow a linear distribution ($p < 0.001$) but it can be studied using a polynomial law ($R2 = 0.52$). Furthermore, a mean fat fraction reduction of 7.2% between L5 and S1 in 31 of 46 subjects ($p < 0,05$) was observed. This gradient was adjusted for age ($p = 0.040$), sex ($p = 0.052$), weight ($p = 0.141$), height ($p = 0.638$), BMI ($p = 0.181$) and menopausal status ($p = 0.657$). BMI (as well as weight and height) did not have significant specific effect on fat distribution on the spine.

Once the fat percentage values per vertebra were divided into two population subgroups (>40 years old (n = 25) and <40 years old (n = 21)), a significant difference between fat fraction averages of each vertebra between the groups ($p < 0.001$) became apparent. The averages were calculated with a mean difference of 14.24% (IC95% 12.85–15.63). Gradient amplitude was significantly higher ($p < 0.001$) in subjects over 40 years old (10.59% SD 1.09) than in subjects under 40 years old (7.06% SD 1.16) (Figure 4). In subjects over 40 years old, the fat fraction average value per vertebra varied from 38.33% to 48.92% from T12 to L5, whereas it varied from 25.84% to 32 .91% in the other group.

4. Discussion

The IDEAL IQ sequence is a multi-echo technique (Dixon 3 points). It supports the T2* effect, corrects B0 magnetic field inhomogeneity, reduces T1 bias due to a short repetition time and a low flip angle and it analyses fat in a multi-spectral way [16].

Using the IDEAL IQ sequence allows a quick and reproducible measure of vertebral medullar adiposity on a large number of vertebral bodies. Although MR spectroscopy is thought to be the most accurate method for quantifying fat-water content, its limitations of long scan time and resolution to be used in a clinical setting persist. Therefore, IDEAL-IQ may represent an interesting alternative to study the fat fraction, because this sequence was confirmed to be an accurate technique to quantify bone marrow fat because of the close similarity of its results with those of MR spectroscopy [5,10,11,12,13,14]. The analytical method used in our study based on a single ROI placed within the vertebral body on the median sagittal plane shows close intra- and inter-observer correlation.

Our results contribute to the knowledge of vertebral bone medullar adiposity knowledge among patients without any bone disease. Consistent with previous studies [10,12], there is a significant increase of vertebral medullar adiposity with age (uni- and multivariate) as well as gender (univariate). He et al. [18] also found significant sex differences for the fat fraction values in a normal bone density group ($p < 0.001$), with higher values for males ($p < 0.001$). The lack of power of the study may explain the absence of a proper effect of sex on the adiposity of the spine ($p = 0.149$) or on the fat fraction gradient ($p = 0.052$) during the multivariate analysis.

Previous studies have investigated the association between bone marrow fat and menopausal status or osteoporosis [19,20]. Griffith et al. found that the vertebral marrow fat fraction shiwed a significant increase among osteoporotic subjects (67.8 ± 8.5%) compared with healthy subjects (59.2 ± 10.0%) [19], and similar results were found by the same team in another study in men [7]. Kim et al. used a T2*-corrected 6-echo

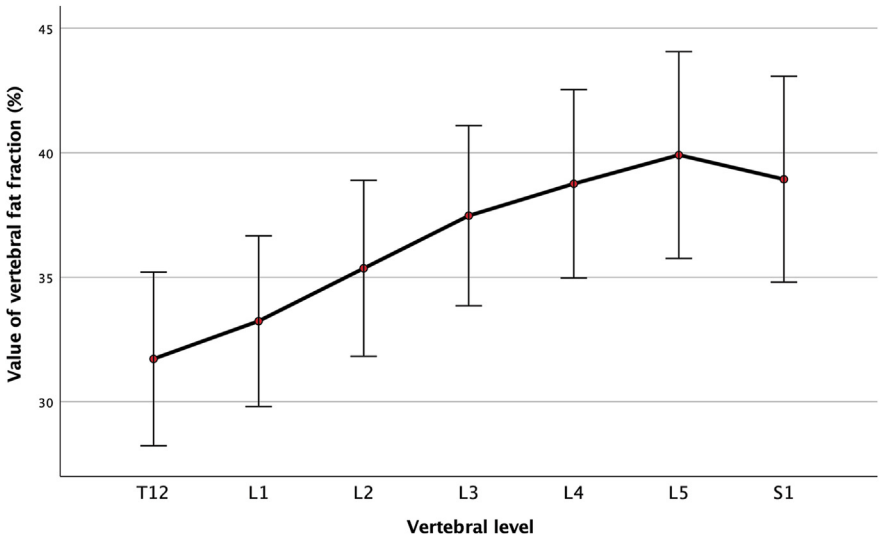

Figure 3. Graphic showing average fat fraction and 95% confidence interval by vertebral body depending on the vertebral level.

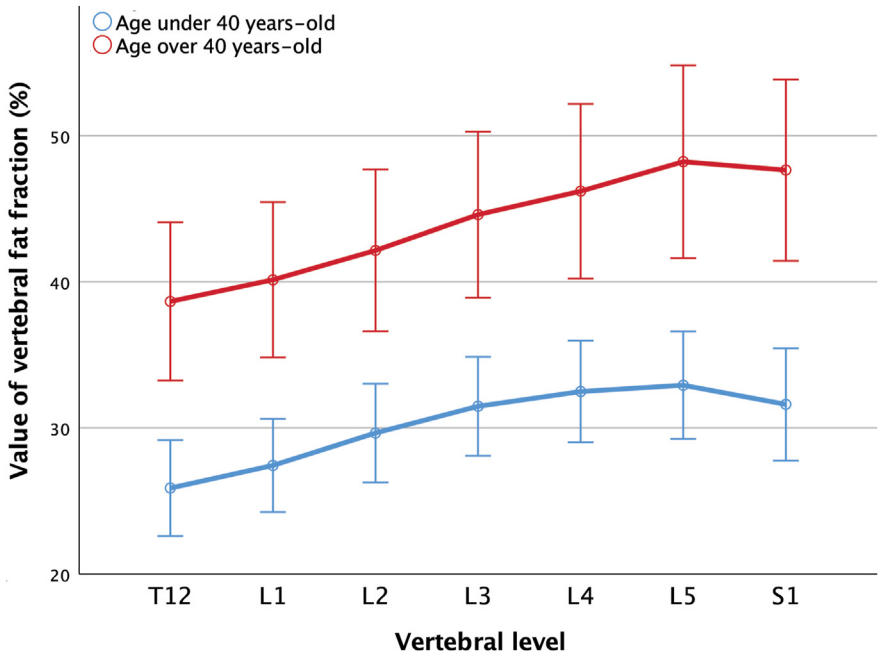

Figure 4. Graphic showing average vertebral fat fraction and 95% confidence interval depending on level and age subgroups (under and over 40 years-old).

Dixon VIBE imaging and found sex-, age-, and menopause-related differences in the associations between the fat fraction, R2*, and bone mineral density. Our study did not show a proper effect of menopause on the fat fraction in the multivariate analysis, probably because of a lack of data on patients of the same age and different menopausal statuses. The seven post-menopausal women in the population were more than 50 years old, and there were no pre-menopausal women beyond this age. Furthermore, we did not study bone mineral density to characterize their precise osteopenia or porotic status.

This study also shows that the craniocaudal gradient from T12 to L5 is estimated on average at 1,37%. Martin [10], using an IDEAL sequence, noted the existence of a craniocaudal gradient from T10 to S2 (with an increase in the fat fraction at an average of 2.7% per vertebrae) in five subjects suffering from prostatic neoplasia treated with hormonotherapy and radiotherapy. However, the small number of subjects included, and the consequences of a treatment associating radiotherapy with hormonotherapy on the bone marrow do not allow extending these results to the rest of the population. Li [8,9] also observed this gradient extending from L1 to L4 in postmenopausal women. Liney [13] found a fat fraction difference between L1 and L4 (L4 < L1) in 10 healthy subjects within a population aged from 8 to 57 years old.

The cause of this craniocaudal gradient is unknown. Liney [13] suggests that it simply reflects the centripetal medullar conversion (from the appendicular skeleton to the axial skeleton). But this gradient could also be an indirect consequence of the increase of mechanical stress on the axial skeleton from T12 to L5. Sex and BMI do not affect this gradient which is more important with age.

The existence of this physiological gradient indicates that vertebral fat fraction measures based only on one or two vertebrae must be interpreted with caution, because the variability of this fat fraction average from L1 to L5 is 6.3% and can reach more than 12% in some subjects.

Also, it is necessary to perform a larger study randomized on age since we observed a significant difference of vertebral bone medullar fat fraction between patients older and younger than 40 years (mean difference of 14.24%). This also confirms the results of Aoki et al. that the rate of increase in fat fraction per decade is about 6.4% [11].

It seems necessary to determine the method of vertebral fat fraction measurement. Two studies [21,22] compared the vertebral fat measure method using the IDEAL sequence to bone densitometry using dual-energy X-ray absorptiometry. These studies showed a significant difference in fat fraction between healthy patients and osteopenic patients. Our study confirms findings from prior studies [10,12] of fat distribution in healthy patients but one of the potential limitations of this study is that this population with back pain is prone to be less physically active. To compensate for the limitation of the study, it would be interesting to work on a larger population comparing sedentary and sporting volunteers to determine the effect of physical activity on medullar adiposity variation.

In conclusion, the exploration of the medullar adiposity of the spine by the IDEAL-IQ sequence is reproducible and fast, and its measurement may be based on a single ROI placed within the vertebral body on a median sagittal slice. In healthy subjects, medullar adiposity of the lumbar spine tends to be higher in men and to increase with age. A physiological craniocaudal gradient of vertebral bone medullar adiposity in the spine from T12 to L5 does exist. This gradient and the vertebral fat fraction both increase significantly with age but are independent of other covariates in this study, including BMI and sex.

Declarations

Author contribution statement

D. Ben Salem: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

A. Saraux: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.

N. Demany Performed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

J. Ognard: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

J. Mesrar: Performed the experiments; Contributed reagents, materials, analysis tools or data.

S. Aho: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

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Data availability statement

Data will be made available on request.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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