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Bone marrow perfusion measured with dynamic contrast enhanced magnetic resonance imaging is correlated to body mass index in adults

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ABSTRACT

Bone marrow metabolism is complex and far from being fully understood. Novel aspects, such as the roles of bone marrow adiposity and vascularisation in bone metabolism currently attract attention. There is also a growing interest in the influence obesity might have on bone metabolism. Our objective was to determine the effect of BMI on bone marrow perfusion parameters using dynamic contrast-enhanced magnetic resonance imaging. This prospective monocentric study was approved by our local Ethics committee. Written consent was obtained. The right hip of 59 adults under 60 years old (mean age 37.5) was imaged with a dynamic 3D T1 spoiled gradient echo magnetic resonance imaging sequence. Mean BMI was 24.8 (+/−4.4). Perfusion parameters were measured in the acetabulum and femoral neck, in the greater trochanter, in the femoral head epiphysis and in the subcutaneous adipose tissue. Associations between perfusion parameters and BMI were studied using a linear mixed model adjusted for age and sex effects. Our results showed that as the BMI increased, the exchanges between blood and bone marrow appeared more important (increased K_{trans} and K_{ep} values, $p = 0.018$ and $p = 0.002$ respectively) and the intramedullary blood flow appeared increased (lower time to peak values, $p = 0.0002$). In the subcutaneous fat, as the BMI increased, the vascularization decreased (lower area under the curve and initial slope values, $p = 0.019$ and $p = 0.013$ respectively). These results suggest that there is a relation between bone marrow perfusion and BMI, and that subcutaneous fat and bone marrow fat have different microvascular behaviours. Researchers must be aware of the effect of BMI on bone marrow perfusion parameters when they build a MR research protocol and analyse their data. A better understanding of these findings may provide the basis for the management of obesity-related bone changes.

1. Introduction

In recent years there is a growing interest of researchers about bone marrow, especially bone marrow adiposity and bone marrow vascularization, and their possible involvement in bone metabolism [1,2]. Even if more and more data on bone marrow adiposity are gathered in the scientific literature, numerous questions on its physiological features remain. It is now well established that bone marrow fat is not a simple filling tissue, but a specific depot that is mainly present in yellow bone marrow and actively interacts with bone and hematopoietic cells [3]. This interplay between fat and the skeleton suggests a feedback system in which adipokines and other bone-derived molecules play a key role [4]. As these molecules transit through the blood vessels, we believe that a better knowledge of bone marrow microvascularization properties would certainly be helpful in the understanding of bone metabolism.

Among the pathophysiological processes that affect bone marrow, there is a specific interest in the relationship existing between bone metabolism and obesity [2,4,5]. Especially, the role of obesity on bone health, for example in osteoporosis in which the protective role of obesity has recently come into question following clinical and epidemiological studies [4]. Many factors (behavioural, morphological, physiological…) could modulate the bone-fat crosstalk but their role is

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insufficiently known [2,4]. A better understanding of this relationship could open new insights for the evaluation and management of patients with obesity related diseases.

Dynamic Contrast-Enhanced MRI (DCE-MRI) is a technique that can assess bone marrow perfusion in humans in safe and minimally invasive conditions [6]. It can be performed on most clinical magnetic resonance scanners using a conventional dose of gadolinium-based contrast media. It can assess changes in tissue contrast media concentration in vivo yielding qualitative and quantitative data in form of time-concentration curves and numerical parameters, respectively that are correlated with various aspects of tissular perfusion.

During a DCE-MRI acquisition, a time series of T1-weighted images are acquired with fast imaging techniques before, during and after the intravenous injection of a gadolinium-based contrast agent [6,7]. In each unit of volume explored with MRI (voxels), magnetic resonance signal intensity varies during the injection, as a reaction to the changing concentration of the contrast agent within the tissue. The resulting concentration-intensity curve is a reflection of these changes, and corresponds to a mix of vessels permeability, tissue perfusion and extravascular extra-cellular space [6]. Contrarily to conventional contrast-enhanced MR imaging, in which a single post-contrast acquisition is performed, in DCE-MRI, the analysis of this signal-intensity curve gives an insight into the microvascular properties of the tissue: parameters describe the progression of contrast agent concentration increase from baseline to the peak (initial slope, IS), the time needed to reach this peak (time to peak, TTP) and the total area under the curve (AUC) [6,7]. To go further in the description of tissular physiology, other parameters can be derived from a pharmacokinetic model. Most often, the model is two-compartimental, considering that the contrast agent may be either in the vessels (plasma space) or in the extravascular extracellular space (Ve) [6]. In the commonly used Tofts model [8], the exchanges between these two compartments are defined as bidirectional and symmetrical. The transfer constant (Ktrans) and the rate constant (Kep) describe these exchanges.

Using DCE-MRI, previous studies have shown that bone marrow perfusion decreases with age [9], and that an increasing bone marrow fat content corresponds to a decreased perfusion [10,11]. Thus, the distribution pattern of red and yellow bone marrow significantly influences bone marrow perfusion [11]. Women also have higher bone marrow perfusion than men [9]. In their DCE study of vertebral and pelvic bone marrow in 43 females, Breault et al. showed that Ktrans and Kep values were inversely correlated with age and fat fraction. AUC and Ve also decreased as fat fraction increased [10].

However, to the best of our knowledge, the relationship between bone marrow perfusion and BMI has never been studied. Indeed, among the consequences of obesity on bone, changes in bone marrow perfusion might exist. As BMI increases, changing interactions between fat and bone might involve modifications in bone marrow vascularization, possibly to convey fat- and bone-derived molecules. If such microvascular modifications exist, they might constitute a bias in further clinical studies.

We hypothesize bone perfusion is influenced by BMI. Therefore, our objective was to determine the effect of BMI on bone marrow perfusion parameters using DCE-MRI.

2. Materials and methods

This prospective monocentric study was approved by our local Ethics committee as an observational study. Oral and written information was delivered before the examination and written consent was obtained.

2.1. Population

Sixty adults under sixty years old were included in this study. The subjects were referred to our imaging department for an MRI examination of the lumbar spine or the pelvis. They were addressed for weak clinical suspicion of axial spondyloarthritis, but eventually did not fulfil the 2009 ASAS (assessment of spondyloarthritis international society) classification criteria. In order to avoid potential pathological changes of the bone marrow, we applied many non-inclusion criteria. The patients were not included if they reported: neoplastic, inflammatory, hematologic or rheumatologic diseases; osteoporosis or osteopenia; hyperparathyroidism, current acute or chronic inflammatory syndromes; history of hip osteoarthritis or osteonecrosis; current hip pain. Also we did not include patients with hip orthopaedic hardware, as it induces artefacts, or chronic renal failure, because gadolinium-based contrast agents were used. Finally, the patients were not included if their hip joint and bones showed any abnormality on MR images.

Clinical data collected were: age, gender and body mass index.

2.2. MRI protocol

Patients were examined on a 3 Teslas MR scan (Ingenia, Philips Healthcare, The Netherlands). The hips were imaged with a coronal T1 spin echo sequence and short tau inversion recovery sequences acquired in axial and coronal planes. Three variable flip angles sequences (3°, 10° and 17°) were acquired before injection. A previously described dynamic 3D T1 spoiled gradient echo covered the right hip [12]. Its main features were as follows: 94 axial slices covered a field of view of 228 × 130 × 169 mm. Time of repetition, time of echo, flip angle and bandwidth per pixel were 4.5 and 2.1 ms, 10° and 389 Hz respectively. Acquisition and reconstruction matrix were 64 × 66 and 128 × 128 respectively. Temporal resolution was 13.5 s. Five baseline scans were acquired. At the beginning of the sixth scan, 0.1 mmol/kg of gadoteric acid (DOTAREM, Guerbet, France) were injected through a peripheral catheter positioned in an antecubital vein, with an automatic injector, at a rate of 2.5 ml/s followed by 20cm^3 of saline flush. Twenty dynamic scans were collected. Total DCE examination time was 9 min.

2.3. Post-processing

A senior musculoskeletal radiologist (J.F.B.), blinded to clinical data, analyzed DCE images with the open-source software Osirix [13] and DCE tool software (Kyung Sung, Body MRI research group, Stanford University, CA, USA), according to the methodology used in a previous feasibility study [12] and in a recent study [14]. Arterial Input Function was measured manually in the femoral artery and T1 maps were calculated. Tofts model was applied. As shown in Fig. 1, eight regions of interest (ROI) of 10 mm^2 were drawn on DCE native images in areas of red and yellow bone marrow, identified by their aspect on T1-weighted images: acetabulum and femoral neck (red bone marrow), greater trochanter (extra-articular yellow bone marrow) and five in the femoral head epiphysis (yellow bone marrow; one in the center, four in the subchondral bone marrow). One ROI was positioned in the subcutaneous adipose tissue more than 1 cm away from the skin surface, to avoid chemical shift artefacts that were identified in our preliminary study [12]. For each ROI, semi-quantitative and pharmacokinetic parameters were calculated: initial slope (IS), area under the curve (AUC), time to peak (TTP), transfer constant (K_{trans}), rate constant (K_{ep}) and extra-vascular extra-cellular space volume (V_e).

2.4. Statistical analysis

Quantitative variables are expressed as mean (+/− standard deviation). Normality of distributions was checked graphically and using the Shapiro-Wilk test. Skewed distributed variables (IS, AUC, K_{trans}, K_{ep} and V_e) were log-transformed before analysis. Qualitative variables are expressed as number (percentage).

Associations between each perfusion parameter and body mass index were studied using a linear mixed model in order to take into account the correlation between the repeated measures within subjects