Joint Bone Spine xxx (2014) xxx–xxx

Available online at
SciVerse ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en

Review

Bone marrow fat

Pierre Hardouin[a,b,c,*], Vittorio Pansini[a,d,e,f], Bernard Cortet[a,d,e,g]

[a] Université Lille Nord-de-France, 59000 Lille, France
[b] Université du Littoral Côte-d'Opale PMOI, boulevard Napoléon, BP 120, 62327 Boulogne-sur-Mer, France
[c] PMOI EA 4490, 62327 Boulogne-sur-Mer, France
[d] PMOI EA 4490, 59000 Lille, France
[e] Université droit et santé Lille 2, 59000 Lille, France
[f] Service d'imagerie musculo-squeletique, CHRU, 59000 Lille, France
[g] Service de rhumatologie, CHRU, 59000 Lille, France

ARTICLE INFO

Article history:
Accepted 6 January 2014
Available online xxx

Keywords:
Bone marrow
Adipocyte
Osteoblast
Fat
Osteoporosis
Anorexia nervosa

ABSTRACT

Bone marrow fat (BMF) results from an accumulation of fat cells within the bone marrow. Fat is not a simple filling tissue but is now considered as an actor within bone microenvironment. BMF is not comparable to other fat depots, as in subcutaneous or visceral tissues. Recent studies on bone marrow adipocytes have shown that they do not appear only as storage cells, but also as cells secreting adipokines, like leptin and adiponectin. Moreover bone marrow adipocytes share the same precursor with osteoblasts, the mesenchymal stem cell. It is now well established that high BMF is associated with weak bone mass in osteoporosis, especially during aging and anorexia nervosa. But numerous questions remain discussed: what is the precise phenotype of bone marrow adipocytes? What is the real function of BMF, and how does bone marrow adipocyte act on its environment? Is the increase of BMF during osteoporosis responsible for bone loss? Is BMF involved in other diseases? How to measure BMF in humans? A better understanding of BMF could allow to obtain new diagnostic tools for osteoporosis management, and could open major therapeutic perspectives.

The organ "bone" is not only composed of bone tissue, but also includes bone marrow, which is located between bone trabeculae of spongious bone, and inside the diaphysis of long bones. Bone marrow is called "red marrow" when it is mainly filled with haematopoietic cells, and "yellow marrow" when it contains a majority of adipocytes. The existence of fat inside bones is known since hundred years, but it is much more recently that bone marrow fat (BMF) aroused the interest of researchers, as illustrated by the increasing number of publications over the last fifteen years in the database "PubMed" (Fig. 1). Indeed BMF does not appear any more as a simple filling tissue, but is considered from now as an actor within bone microenvironment. Due to these recent works, BMF is known better and better and its involvement in bone physiopathology is more and more argued. However numerous questions remain debated.

1. Bone Marrow Fat (BMF): main characteristics

BMF results from an accumulation of fat cells within bone marrow. These adipocytes contain a big lipid vacuole of triglycerides made of fatty acids, which can be saturated, mono or polyunsaturated.

1.1. Variations with age

At birth, bone cavities are mainly filled with red hematopoietic marrow. Then occurs during childhood a "conversion" of the red marrow which is gradually replaced by yellow, fat marrow. This conversion of bone marrow begins in terminal phalanges after birth, then goes forward by a centripetal evolution up to the axial skeleton [1]. So, at the age of 25, red marrow is limited to the axial skeleton, ribs and breastbone. A "reconversion" can be observed in conditions of hypoxia, such as in smokers or in patients with obstructive sleep apnoea. Although large individual variations are found, it exists globally a positive correlation between BMF and age [2,3].

* Corresponding author.
E-mail address: pierre.hardouin@univ-littoral.fr (P. Hardouin).

doi:10.1016/j.jbspin.2014.02.013
1297-319X/

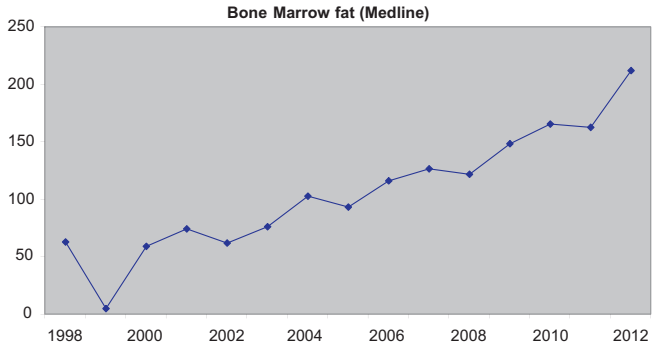

Fig. 1. Annual number of publications referenced in the PubMed database between 1998 and 2012 with keywords "bone marrow fat".

1.2. Location and quantity

In adults, yellow bone marrow is mainly located in the appendical skeleton. Its volume is approximately estimated at 7% of total fat [3] and so 2,6 kg in an adult, which represents a storage of about 23,000 calories [4]. However important variations are found, not only with age as previously seen, but also according to gender (BMF is higher in men than in women) and to anatomical location (BMF is higher in long bones diaphysis than in axial skeleton) [1,5,6]. In a given long bone, yellow marrow is preferentially located in the diaphysis and in the epiphyses, whereas red marrow is mainly localized in the metaphysis [1]. Moreover, quantitative modifications of BMF can be observed in several diseases, especially in osteoporosis [5–7].

1.3. Microscopic aspect

Bone marrow adipocytes are not grouped in lobules as in the other fat depots, but they are scattered within the hematopoietic tissue. Mean diameter of these adipocytes is around 50 μ, which is lower than the diameter of subcutaneous or visceral adipocytes [8,9], but great variations are found in literature according to the location. In usual optic microscopy of undecalcified bone, the technical preparation of the sample removes the lipid content, then the shapes of adipocytes appear as cellular "ghosts" (Fig. 2). Bone marrow adipocytes can be also studied with confocal microscopy or on frozen slides or by microtomography after labelling with osmium.

1.4. In vivo imaging

Measurement of BMF can be made by X-rays quantitative tomography but the geometrical resolution of this method is weak and a preferential loss of photons with low energy leads to underestimation of the quantity of fat in long bones [10]. Magnetic resonance imaging (MRI) is the best method to distinguish yellow fat marrow from haematopoietic red marrow.

Yellow marrow appears in hypersignal in T1-weighted sequences having intermediate to elevated signal on spin-echo T2 images and on T2 fast spin-echo images and low signal on sequences with fat saturation. Yellow bone marrow does not enhance significantly after gadolinium injection. Red bone marrow shows intermediate signal on T1 or on T2 images, generally more elevated than muscular or yellow bone marrow signal. On fat-suppressed images red bone marrow shows intermediate to elevated signal, thus constantly higher than yellow bone marrow. In any case the difference of signal between the two types of bone marrow (red and yellow) is less evident on T2 images than on T1 or on STIR ones. Red bone marrow shows generally a mild enhancement after injection of gadolinium.

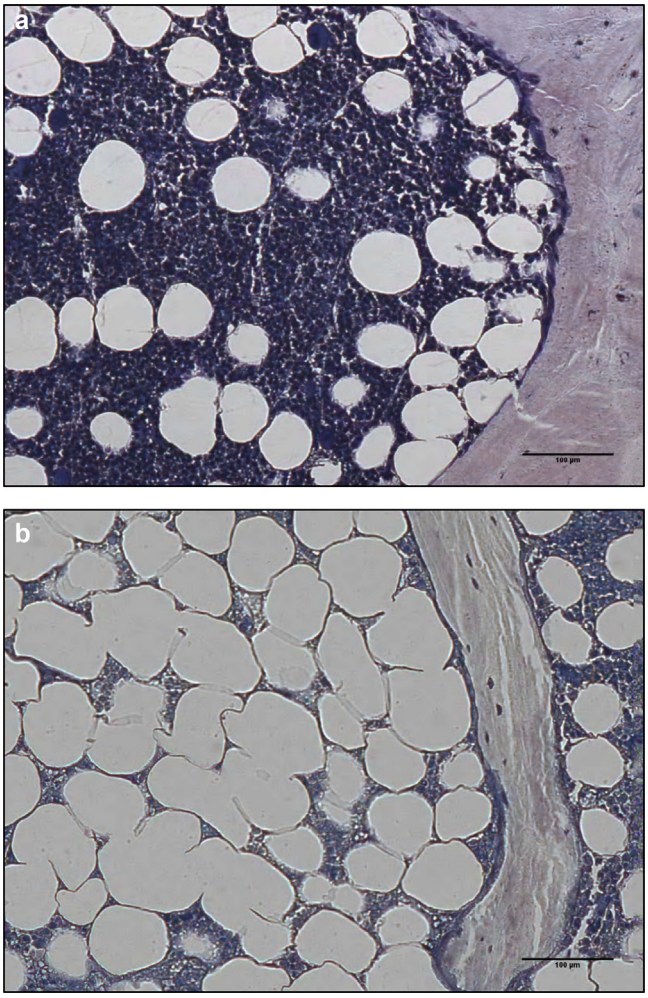

Fig. 2. Microscopic aspect of bone marrow fat on iliac crest biopsy in osteoporosis. Undecalcified microscopy, May Grünwald Giemsa staining (bar = 100 μ): a: osteoporotic woman, 56 years old; weak amount of marrow adiposity; mean adipocyte diameter = 51,5 μ; adipocytes number = 108/mm^2: b: osteoporotic woman, 68 years old; important amount of adiposity; mean adipocyte diameter = 61,9 μ; adipocytes number = 170/mm^2.

Altough MRI permits to depict precisely yellow and red bone barrow, it provides no quantification of these two components. Proton magnetic resonance spectroscopy (^{1}H MRS) allows to quantify BMF compared to water quantity with a good reproducibility [11,12]. The obtained spectra show water and fat peaks that allows to estimate the rate of BMF (Fig. 3). The percentage of fat fraction linearly increases with age, less fast in women than in men [13], ranging from 20.5% for the second and third decades of life to 49.4% for the eighth and ninth decades [14]. MRI thus confirms the increase of BMF in elderly patients but also in osteoporotic patients.

2. Recent data on BMF

2.1. BMF is a specific fat depot

It is now established that BMF constitutes a specific fat location, which is not comparable to subcutaneous and abdominal fat depots. BMF differs because of its location inside bones, which leads to interactions with the bone microenvironment, because of a more scattered distribution of fat cells, and because of its composition in fatty acids [15]. BMF is not correlated with weight, body mass index or body fat [6,16,17]. BMF is even increased in anorexia nervosa, contrasting with the meagreness of these patients [8,18], which

Please cite this article in press as: Hardouin P, et al. Bone marrow fat. Joint Bone Spine (2014), doi:10.1016/j.jbspin.2014.02.013