# Bone–Fat Interaction

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**KEYWORDS**

• Marrow adipose tissue • Marrow fat • Adiposity • Bone marrow

**KEY POINTS**

- In general, an inverse relationship exists between marrow fat and bone density.
- Multiple diseases associated with increased fracture risk also present with increased marrow adipose tissue.
- The composition of marrow adipose tissue differs between anatomic sites.
- The exact stem cell lineage and precise function of marrow adipocytes remains controversial.

## INTRODUCTION

Osteoporosis and low bone mass (ie, osteopenia) are major public health concerns affecting a staggering 54 million in the United States.[1] Moreover, as the nation's demographic continues to shift toward an older population, these statistics are projected to continue to increase.[2] Approximately 2 million osteoporotic-related fracture occur each year, costing the nation $17 billion per year.[2] In addition to the financial burden, osteoporosis-related fractures often lead to multiple comorbidities (ie, hypertension, deficiency anemias, and fluid and electrolyte imbalance),[3] and patients frequently experience diminished quality of life owing to immobility, pain, and isolation.[4] Although therapeutic treatment options have aided significantly in the management of osteoporosis, some patients still experience undesirable, adverse side effects,[5–7] and therefore, continued development of refined options is necessary. As this quest continues, it is imperative to gain further insight in to the cellular and molecular responses occurring within the bone niche.

Bone is an incredibly dynamic tissue that undergoes continuous remodeling, involving bone-resorbing osteoclasts, bone-forming osteoblasts, and mechanical sensing osteocytes. Although much of bone biology has focused on these primary cell types, the bone marrow compartment also provides a unique environment in which communication between various cells can directly and indirectly impact the bone. One such cell population that has attracted much attention and scientific inquiry

Disclosure Statement: The authors have nothing to disclose.
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Endocrinol Metab Clin N Am ■ (2016) ■–■
http://dx.doi.org/10.1016/j.ecl.2016.09.004 **endo.theclinics.com**

in the past decade are marrow adipocytes, often referred to as marrow adipose tissue (MAT) and/or yellow adipose tissue. These adipocytes can be found interspersed throughout the marrow compartment. Recently, 2 "types" of MAT, constitutive MAT and regulated MAT, have been described based on their (1) cellular morphology, (2) region specificity, and (3) fatty acid composition.[8] Both in human and mouse tissues, constitutive MAT is described as containing large adipocytes localized at the distal tibia, and is primarily composed of unsaturated lipids.[8] Conversely, regulated MAT is found mainly in the proximal tibia, interspersed with active hematopoiesis, and composed of saturated lipids.[8] Although our understanding of MAT has advanced significantly in the past decade, many questions remain. It is therefore the aim of this review is to provide the most current opinions relative to MAT and bone, while providing a brief overview of clinical scenarios in which MAT is altered.

## CURRENT CONTROVERSIES AND FUNDAMENTAL QUESTIONS

### *Lineage of Bone Marrow Adipocytes*

Unlike peripheral adipocytes or white adipose tissue, which are primarily derived from mesenchymal stem cells through vascular infiltration,[9,10] the definitive lineage of marrow adipocytes remains largely unknown and controversial. For example, although these cells have classic adipocyte functions and pathology by their hallmark ability to store lipids, bone marrow adipocytes express the osteoprogenitor marker osterix, encoded by the *Sp7* gene.[11] Given the expression of *Sp7*, one theory is that the development of marrow adipocytes results from a shift in allocation of mesenchymal stem cells from the osteoblast lineage toward the adipocyte lineage, subsequently decreasing bone formation.[12–14] Another possibility is that the marrow adipocyte could arise from bone lining cells, poorly characterized flat fibroblastic cells that express some markers of the osteogenic lineage (eg, *Sp7*).

In addition to demonstrating features characteristic of white adipose tissue and *Sp7*, marrow adipocytes also exhibit some brown adipose tissue transcriptional markers and target genes (ie, *Prdm16, FoxC2, Pgc1α, Dio2, β3AR*, and *Ucp1*).[15] Some literature also describes fibroblast adventitial reticular cells of the venous sinusoids accumulating lipids to "convert" to adipocytes. Under these circumstances, marrow adipocytes are presumed to primarily function as space fillers in the marrow cavity for inactive or reduced numbers of hematopoietic cells,[16,17] Another, more recent discovery completely shifts the idea that bone marrow adipocytes exclusively develop from mesenchymal stem cell pools and suggests they may arise from hematopoietic stem cells. These data demonstrate that hematopoietic stem cells have the ability to hone to nontissue resident fat depots, differentiate to adipocytes, and undergo de novo generation.[9,18] Moreover, the identification of differential bone marrow adipose depots (ie, constitutive MAT and regulated MAT) has given rise to the possibility that adipocytes within the marrow space are a heterogeneous population, derived from multiple sources. Nonetheless, the controversy surrounding the origin of bone marrow adipocytes underscores the complexity of these unique cells and further investigation is warranted.

### *Bone Marrow Adipocyte Function*

Aside from the lineage tracing of marrow adipocytes, the next fundamental question that arises is that of MAT function. Our understanding of marrow adipocytes now extends well beyond their historical role as passive, "space-filling" support for the hematopoietic microenvironment. Although marrow adipocytes have a defined function as regulators of hematopoietic activity,[19] evidence also suggests MAT