COMMENTARY

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Bone Marrow Composition, Diabetes, and Fracture Risk: More Bad News for Saturated Fat

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In this month's issue, Patsch and colleagues[1] offer ample food for thought for anyone interested in marrow adipocytes, the enigmatic endosteal fat cells whose developmental origins, function, and impact on bone mass are currently subjects of active investigation.[2] Marrow fat is often associated with low bone mass, as in anorexia nervosa, aging, and osteoporosis, but is also present in normal bone in complex age-, sex-, and site-specific patterns.[3–5] Although marrow adipocytes were historically assumed to be neutral, quiescent space fillers,[6] recent studies have demonstrated that marrow adipose tissue has a role in systemic energy metabolism[7,8] and that bone marrow fat mass and bone mass are inversely correlated even within normal subjects.[9,10] Marrow fat is now understood as a metabolically active depot that can be mobilized in starvation and that exerts potential beneficial as well as deleterious effects on skeletal and overall metabolism. However, many questions remain about exactly how marrow fat might increase fracture risk, and how this risk varies with age, sex, and comorbidities.

Patsch and colleagues[1] tackle two key outstanding questions about marrow fat: whether the composition of marrow fat, as opposed to the quantity, is related to fracture risk; and whether there is an interaction between marrow fat, diabetes, and skeletal fragility. To address these questions, the authors measured vertebral bone marrow adiposity via magnetic resonance imaging (MRI), areal bone mineral density (aBMD) by dual-energy X-ray absorptiometry (DXA), and volumetric BMD (vBMD) by quantitative computed tomography (QCT) in the lumbar spine (L_1–L_3) in postmenopausal women with and without prior fracture history and with or without type 2 diabetes. Marrow fat quantification included both the total lipid and the proportions of saturated, unsaturated, and residual lipid, differentiated by the presence or absence of double bonds.

Overall, the results corroborate patterns seen in previous studies: aBMD at the hip and spine was highest in women with type 2 diabetes but no fracture, and lowest in nondiabetic women with prior fracture, whereas vBMD of the spine was lower in women with fracture versus women without fracture, both within controls and within diabetics. Interestingly, there were no differences in total marrow fat content among groups, regardless of diabetes or fracture status, in contrast to at least one recent study that found higher vertebral marrow fat in subjects with prevalent vertebral fractures.[11] However, both diabetes and fracture history were correlated with differences in marrow fat composition. As shown in Table 2 in Patsch and colleagues,[1] the degree of unsaturation was lower in individuals with both diabetes and fractures (DMFx) compared to controls without fracture (Co) and diabetics without fracture (DM), and the degree of saturation was higher in DM and DMFx versus Co. In other words, people with diabetes had more saturated marrow fat, and people with diabetes and history of fracture had less unsaturated marrow fat, compared to controls without fracture. However, while type 2 diabetes and fracture were each related to bone marrow adiposity, these correlations were independent of one another. After adjustment for age, ethnicity, and aBMD, there was no interaction between type 2 diabetes, fracture, and total marrow fat, nor any of the subsets of marrow fat—saturated, unsaturated, or residual. Patsch and colleagues'[1] interpretation was that diabetes and fracture have additive, negative effects on bone marrow composition. Given the cross-sectional study design, further studies will be needed to validate the direction of causality.

These findings challenge our current understanding of the relationship between marrow fat and bone in several key ways, and generate a host of intriguing questions for future work. First and foremost is the provocative conclusion that it is the composition, rather than the amount, of marrow fat that is correlated with fracture history and diabetes. This finding corroborates previous studies that found lower unsaturation in osteoporosis and in diabetes, both of which involve elevated fracture risk,[5,12] but contrasts with studies that have shown an inverse relationship between the quantity of marrow fat and BMD or bone mass.[3,9,10,13] Additionally, this finding raises the issue of causality—does marrow fat become less unsaturated before a fracture, or afterward? Does altered metabolism in diabetes change marrow lipid composition and thereby increase

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skeletal fragility? As Patsch and colleagues[1] note, the finding that a high ratio of saturated to unsaturated lipid confers more fracture risk than the amount of lipid alone may help to explain why people with diabetes have more fractures than would be expected based on their BMD alone.[14] However, the question remains unanswered as to exactly *how* marrow fat, and in particular lower unsaturated marrow fat, is deleterious to bone. As has been widely noted, endosteal adipocytes and osteoblasts are derived from the same pool of progenitor cells, such that an increase in adipocyte differentiation might lead to a decrease in osteoblast differentiation,[15] and adipocyte accumulation also seems to impair osteoblast function.[16] The study by Patsch and colleagues[1] challenges us to understand whether less unsaturated lipid and/or more saturated lipid are somehow themselves deleterious to bone, or whether these composition changes are indicators of other underlying mechanisms that increase skeletal fragility. As the authors note, there is a relationship between dietary fat intake and fracture, with high dietary intake of polyunsaturated fats being associated with lower hip fracture risk.[17] It remains to be seen whether this dietary effect is mediated by marrow fat composition.

Second, the finding that fracture and diabetes are each independently associated with changes in marrow fat composition raises the possibility that marrow adiposity in general, and the ratio of unsaturation to saturation in particular, may arise via more than one mechanism. The question of what mechanism(s) trigger abnormal marrow fat formation is obviously of great clinical interest, but an even more interesting question is what the "normal" quantity and composition (saturated versus unsaturated) of marrow fat is across a person's lifetime. Progressively higher bone marrow adiposity has long been noted as normal component of skeletal maturation (eg, Neumann, 1882; discussed in Tavassoli[18]). Through childhood, the predominantly hematopoietic marrow of the infant is replaced by fatty marrow in a distal-to-proximal gradient, such that the limbs of the adult skeleton contain predominantly yellow marrow.[4] Thus, marrow adiposity is not necessarily deleterious to bone, and criteria for determining when it is deleterious remain to be delineated. In fact, the most rapid increase in marrow adiposity in humans occurs at puberty, a time of rapid skeletal acquisition, an important reminder that concurrent increases in marrow fat and bone mass are not always mutually exclusive.[3] A similar phenomenon is seen in inbred mice, in which marrow adiposity and bone mass are inversely correlated in the C57Bl/6J strain,[19] but positively correlated in the C3H strain.[20]

Animal models also provide some key insights into the mechanism(s) of abnormally high marrow adiposity. In the *ob/ob* (obese) leptin-deficient mouse, high marrow fat occurs in association with hypoleptinemia and is reduced by leptin treatment.[21] Hypoleptinemia is also seen along with high marrow fat in humans with anorexia nervosa,[3] but is less characteristic of other skeletal pathologies of high marrow adiposity, such as osteoporosis, diabetes, or unloading.[22–25] Other hormonal states linked to marrow fat in humans and/or in animal models include high preadipocyte factor 1 (Pref-1), particularly in anorexia;[26] peroxisome proliferator-activated receptor γ (PPARγ) agonism;[27] low estrogen, seen in anorexia and osteoporosis;[28] low osteocalcin;[29] and disruption of the growth hormone–insulin-like growth factor–1 (GH-IGF-1) axis.[30] Furthermore, the recent complementary findings that marrow adipocytes are negative regulators of hematopoiesis and marrow osteoblasts are positive regulators of hematopoiesis[31,32] suggest the possibility that high marrow fat could be a byproduct of downregulated hematopoiesis, and thus stimulating blood cell formation might consequently reduce marrow adiposity, but whether such a reversal would also increase bone mass is an open question.

Perhaps the ultimate challenge raised by Patsch and colleagues[1] will be to determine whether the total quantity of marrow fat and/or the ratio of saturated to unsaturated fat can be manipulated environmentally (eg, through diet) or pharmacologically (eg, by leptin treatment), and whether such manipulations improve bone mass or decrease fracture risk. For example, high marrow adiposity is ameliorated by weight recovery in anorexia,[20,33] and high saturation of bone marrow fat might be too. The work of Krings and colleagues[7] and Lecka-Czernik[8] suggests that gene expression of bone marrow adipocytes changes over a person's lifetime, becoming less like brown fat and more like white fat with aging and diabetes, and it will be extremely interesting to see whether those changes in gene expression are linked to marrow fat composition changes, and whether marrow fat gene expression might also be moderated by environmental or pharmacological influences.

To summarize, current evidence indicates that bone marrow fat is a dynamic tissue that is distinct from white fat and brown fat, and that perhaps has markedly different effects on bone across the life course and in normal versus disease states. The work of Patsch and colleagues[1] emphasizes that the characteristics of marrow fat—specifically the proportion of saturated versus unsaturated lipid—may be clinically relevant regardless of the absolute quantity of fat, and that such composition changes are independently associated with prior fracture and with diabetes. Future studies will undoubtedly extend these observations to other ages, to males, and to a broader array of disease states characterized by high marrow fat. However, it must be acknowledged that magnetic resonance imaging (MRI) remains an expensive imaging modality for everyday use, and the results of this study require replication and validation before marrow fat composition can be used to inform clinical decisions. Ultimately, marrow fat composition has the potential to be a particularly useful adjunct to DXA in populations in which BMD is less predictive of fracture risk, such as patients with diabetes. Further work should focus not only on understanding the function of marrow fat, but also on developing more cost-effective ways to quantify it.

Disclosures

The author states that she has no conflicts of interest.

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