Published in final edited form as:

Am J Hum Biol. 2011 September ; 23(5): 577–585. doi:10.1002/ajhb.21202.

Why does starvation make bones fat?

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Abstract

Body fat, or adipose tissue, is a crucial energetic buffer against starvation in humans and other mammals, and reserves of white adipose tissue (WAT) rise and fall in parallel with food intake. Much less is known about the function of bone marrow adipose tissue (BMAT), which are fat cells found in bone marrow. BMAT mass actually increases during starvation, even as other fat depots are being mobilized for energy. Here I review the possible reasons for this poorly understood phenomenon. Is BMAT a passive filler that occupies spaces left by dying bone cells, a pathological consequence of suppressed bone formation, or potentially an adaptation for surviving starvation? To evaluate these possibilities, here I review what is known about the effects of starvation on the body, particularly the skeleton, and the mechanisms involved in storing and metabolizing BMAT during negative energy balance.

Keywords

bone marrow; marrow fat; starvation; adipogenesis

Introduction

The main function of adipose tissue—better known as fat—is to store energy as a buffer against fluctuations in food availability (Cahill, 1976). The most abundant human fat, white adipose tissue, serves both as a high-density, low-cost energy reserve and as an endocrine organ, secreting leptin and other hormones that signal energy status to the brain and regulate appetite and insulin sensitivity (Guerre-Millo, 2002; Hamrick, 2004; Trayhurn and Beattie, 2001). However, there are two other adipose tissue types that differ significantly from WAT. Brown adipose tissue (BAT), which gets its color from iron-rich mitochondria, actually burns rather than stores energy. Although brown fat has a critical role in nonshivering thermogenesis in human neonates, it was thought to regress thereafter. However, new data suggest that BAT persists into adulthood, primarily in the supraclavicular region, and may have a continuing role in temperature homeostasis (Cypess and Kahn, 2010; Cypess et al., 2009; van Marken Lichtenbelt et al., 2009; Virtanen et al., 2009).

Here I focus on a third fat depot that has similarities to both WAT and BAT: bone marrow adipose tissue (BMAT). Although adipocytes are normal components of bone marrow, these fat cells were traditionally thought to have no function (Gimble et al., 1996; Tavassoli, 1984). However, recent studies have shown that BMAT is a dynamic tissue whose mass increases markedly during starvation, a state of chronic negative energy balance (Ellison, 2001). In other words, even as subcutaneous and visceral WAT is lost throughout the rest of the body, bone marrow adipose reserves are expanding. The same phenomenon is seen in

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rodent models of calorie restriction (Devlin et al., 2010; Hamrick et al., 2008), and in starving wild animals including moose, deer, and hares (Hodges et al., 2006; Josefsen et al., 2007; Murray et al., 2006; Waid and Warren, 1984). Thus it appears that in humans and in other mammals, the bone marrow fat depot is sensitive to metabolic conditions, and grows during negative energy balance for unknown reasons. While the metabolic and endocrine functions of WAT, and to a lesser extent BAT, have been characterized, much less is known about the function of BMAT (Gimble et al., 2006; Kawai and Rosen, 2009; Rosen et al., 2009).

Why would starvation induce greater fat deposition in bone marrow, even as other adipose depots are being mobilized for energy? This is a tough question to answer, since relatively little is known about what marrow fat does in living humans, and even less about its possible evolutionary role. The seeming paradox of increasing BMAT stores while in a state of energetic deficit suggests that marrow fat might confer an advantage in surviving or recovering from starvation—in other words, that it could be an adaptation. However, as Ellison and Jasienska (2007) point out, this is a hypothesis that must be tested against the alternative hypotheses that BMAT is pathological or the result of constraint. Defining the predicted characteristics of BMAT in each case—constraint, pathology, or adaptation—may help to discriminate among these alternatives. First, if BMAT arises as the byproduct of constraint on bone marrow cell function, then we might expect it to be neutral, with no effect on the odds of surviving starvation or on the health of the surrounding bone. In this case, we might expect BMAT to regress after starvation as bone marrow osteoblast function returned. Second, if BMAT is pathological, resulting from a starvation-induced disruption of bone marrow mesenchymal stem cell function, then we might expect it to have negative effects on bone strength during and after starvation. Here, the argument is that since endosteal osteoblasts and adipocytes derive from the same population of mesenchymal stem cells (Hong et al., 2005), a shift away from the osteoblast lineage would send more cells down the adipocyte lineage (Muruganandan et al., 2009; Nuttall and Gimble, 2004), reducing bone mass and potentially increasing fracture risk. The third possibility, that increased BMAT is an adaptation for surviving starvation, is the most speculative. If this hypothesis is correct, then there should be sufficient energy stored in BMAT to increase the chances of survival during energetic deficit, as well as evidence for BMAT mobilization in starving individuals. To evaluate these hypotheses, here I review what is known about the effects of starvation on the body, particularly the skeleton, and about the origin of and possible functions of marrow adipocytes. Finally, I propose criteria for testing whether marrow fat may be a starvation adaptation in humans and other mammals.

The bone marrow fat depot

Bone marrow is a multicellular tissue found throughout the skeleton, including in the endosteal cavities of long bones and in axial elements including the vertebrae and pelvis. Marrow is composed of hematopoietic cells, osteoblasts, mesenchymal stem cells, and fibroblasts, as well as adipocytes (Compston, 2002). At birth, there is little BMAT: the entire skeleton is filled with hematopoietic (“red”) marrow, which is dedicated to red blood cell formation. Adipocytes start to appear in childhood, beginning in distal limb bones and moving proximally, with particularly rapid accumulation during puberty. By age 20, the appendicular skeleton is nearly all converted from red to fatty “yellow” marrow (Moerman et al., 2004; Moore et al., 1991; Moore and Dawson, 1990; Siegel and Luker, 1996; Waitches et al., 1994). In the axial skeleton, hematopoiesis continues into adulthood, but there is fatty infiltration of the vertebral bodies with aging (Justesen et al., 2001; Meunier et al., 1971; Rozman et al., 1989).

Although the phenomenon of marrow conversion from hematopoietic to fatty has been observed for decades, the reasons for this transformation and the mechanisms involved remain unknown. It is also not clear whether marrow adipocytes are WAT, BAT, a mix of both, or neither; the cells have metabolic similarities to both white and brown fat (Kawai and Rosen, 2009). The traditional perspective is that conversion from red to yellow bone marrow is normal, since it occurs in all individuals as part of skeletal maturation and aging. Indeed, the prevailing hypothesis over the last few decades has been that BMAT is a filler, passively occupying space vacated by other cells as hematopoiesis in the appendicular skeleton wanes (Gimble et al., 1996; Tavassoli, 1984). However, elevated BMAT and low bone mass are also seen in pathological conditions including anorexia, osteoporosis, skeletal unloading or disuse, and sometimes (but not always) obesity, suggesting marrow fat may be bad for bone (Bredella et al., 2009; Bredella et al., 2010; Dudley-Javoroski and Shields, 2008; Ecklund et al., 2009; Trudel et al., 2009; Yeung et al., 2005). It has even been reported that there is a reciprocal relationship of bone mass and marrow fat in young, healthy individuals (Di Iorgi et al., 2010; Di Iorgi et al., 2008; Wren et al., 2011), although high marrow fat can cause BMD to be underestimated (Bolotin et al., 2003; Hangartner and Johnston, 1990). Given that adipocytes and osteoblasts are derived from the same mesenchymal stem cell progenitors, it is reasonable to ask whether increased marrow adipogenesis is a cause or a consequence of decreased osteogenesis (Rosen and Spiegelman, 2001). On the other hand, increased marrow fat is not always deleterious to bone mass. For example, in humans, bone mass and marrow fat both accumulate rapidly during puberty (Bredella, 2010). Across strains of inbred mice, there is no correlation between femoral BMD and adipocyte number (Rosen et al., 2009). These examples suggest that bone mass and marrow fat formation are not always inversely correlated, and that their relationship is context specific. Thus understanding why starvation causes BMAT accumulation might provide insights into its roles in normal skeletal maturation and in pathological conditions.

Starvation and fat

Human starvation tolerance far exceeds that of smaller mammals and birds, which may be as little as one day, but as a species we are more dependent on regular food intake than some amphibians and reptiles, which can survive for years without eating (Wang et al., 2006). Although the longest recorded human therapeutic fast in an obese individual is 382 days (Stewart and Fleming, 1973), in lean individuals starvation tolerance is probably closer to several months (Wang et al., 2006). Starvation physiology has been reviewed in detail elsewhere (Finn and Dice, 2006; McCue, 2010; Prentice, 2005; Wang et al., 2006), but a few key points illustrate how starvation may relate to marrow fat accumulation in bone.

The term “starvation” can refer to a range of energetic stresses, from transient and mild to prolonged and severe, and can involve global caloric restriction or deficits in specific macronutrients (protein, fat, carbohydrate) or micronutrients. While most studies have focused on BMAT in global calorie restriction, high marrow adiposity has also been seen in protein malnutrition (kwashiorkor) in infants and children (Dickerson and John, 1969; Khalil et al., 1977; Rao and Sandozi, 1970); little is known about whether low-fat or low-carbohydrate diets, or specific micronutrient deficits, have similar effects. Thus here the focus is on global caloric restriction.

Adaptations to negative energy balance fall into two major categories: reducing energy expenditure, and shifting the body’s main fuel source from glucose to stored fat. Strategies to decrease energy expenditure include suppressing body temperature and metabolic rate, and delaying growth and/or reproduction (Dulloo and Jacquet, 1998; Dulloo and Jacquet, 2001; Ellison, 2003; Prentice, 2005), but it is not clear how these changes would increase

BMAT formation. There is clearer evidence for a link between marrow fat formation and physiological adaptations to starvation.

Such adaptations have been divided into three phases (McCue, 2010). Phase I of starvation begins as soon as the last meal eaten has been digested and the body enters the postabsorptive state. In practice, Phase I is less an adaptation to long term food shortage than to the brain's need for a steady supply of glucose between meals; most of us are postabsorptive, and therefore meet the definition of starvation, at least three times every day, in the late morning, late afternoon, and overnight (Newsholme and Leech, 2009). Phase I is necessarily brief, since the body stores little energy as glucose or glycogen. Circulating blood glucose is about 5 g (~100 mg/dL in 5 L of blood), with perhaps another 40 g contained in total body water. There are also ~80 g of glycogen in the liver and another ~350 g in muscle, which can be converted to glucose by phosphorylation. Thus the body's entire glucose and glycogen stores total only about 480 g, which will be exhausted within 24 hours (Anghel and Wahli, 2007). Indeed, after only 12 hours of starvation, about half of the body's energy is drawn from free fatty acids (FFAs) rather than glucose (Newsholme and Leech, 2009).

Once glycogen stores are fully depleted, Phase II of starvation commences, marked by greater mobilization of fat stores. Fat metabolism liberates glycerol and FFAs, with the former providing a substrate for gluconeogenesis in the liver and kidney (Reshef et al., 2003), and the latter a substrate for beta-oxidation, forming acetyl-CoA that can be metabolized in the citric acid cycle and acetoacetyl-CoA that can be converted into ketone bodies to help fuel the brain (McCue, 2010). Profound physiological changes accompany Phase II, and several of these may be related to marrow fat formation (Fig. 1). The rise in circulating FFAs increases peroxisome proliferator-activated receptor (PPAR)-alpha (PPAR α) and PPAR-gamma (PPAR γ), promoting fat metabolism and increasing insulin sensitivity (Guerre-Millo et al., 2001; Kroetz et al., 1998). PPAR α in turn upregulates fibroblast growth factor-21 (FGF21), which has two key functions. First, FGF21 stimulates peroxisome proliferator-activated receptor gamma coactivator protein-1alpha (PGC1 α), which boosts fatty acid oxidation and gluconeogenesis (Fazeli et al., 2010b; Inagaki et al., 2007; Reitman, 2007). Second, FGF-21 may mediate the starvation-induced onset of GH resistance via signal transducer and activator of transcription-5 (STAT5), which causes low serum IGF-1 (Fazeli et al., 2010a; Inagaki et al., 2008). Indeed, women with anorexia nervosa, who typically consume less than half of the calories needed to meet their daily energy needs (Affenito et al., 2002; Misra et al., 2006), exhibit GH resistance and low IGF-1, as well as low estrogen, insulin, and leptin levels, and moderate hypercortisolemia (Misra and Klibanski, 2010).

Here it should be noted that Phase II of starvation resembles the moderate caloric restriction (Paiva-Silva et al., 2006) used in animal experiments and practiced by health enthusiasts. The potential benefits of CR have received intense recent interest, given data suggesting that a moderate reduction in caloric intake increases lifespan and improves health across organisms from *Drosophila* to non-human primates (Fontana et al., 2010). However, experimental or voluntary CR is less severe than starvation in several key respects. As Martin and colleagues (2010) recently noted, "control" laboratory mice and rats are actually sedentary, overweight, and have higher body fat than normal wild rodents. Experimental CR of 25-40% relative to *ad libitum* caloric intake (not relative to actual energy requirements) may actually return them to their normal metabolic state (Austad, 2001). Indeed, mice on long-term CR of 30% below *ad libitum* consumption continue to grow and to gain body mass, albeit more slowly than controls (Devlin et al., 2010; Tatsumi et al., 2008). Similarly, humans practicing voluntary CR, such as the participants in the Biosphere II experiment, tend to exhibit initial weight loss followed by stabilization at a body mass index (BMI) of

18-19 kg/m² (Walford et al., 2002); humans starve to death at BMIs of roughly 12-13 kg/m² (Henry, 2001). Moderate dietary restriction may be an example of hormesis, in which the physiological response to a mild stress (Paiva-Silva et al., 2006) response improves health, while a more severe version of the same stress (starvation) does not (Gems and Partridge, 2008).

If food deprivation is prolonged, fat reserves are eventually exhausted, the brain can no longer rely on ketone bodies, and Phase III of starvation begins. The body begins breaking down muscle tissue so that amino acids can be converted to glucose in the liver to maintain brain function. This process, known as protein wasting, rapidly leads to death, as protein loss of over 50% is fatal (McCue, 2010; Wang et al., 2006). Thus there should be strong selection pressure favoring any adaptation that delays the onset of Phase III. Could marrow fat be one such adaptation?

Marrow fat in starvation

If increasing marrow fat in starvation is adaptive, there should be mechanisms that allow marrow fat to accumulate and to be mobilized during starvation; BMAT should contain enough stored energy to increase survival; and, most importantly, there should be a benefit to storing fat early in starvation rather than metabolizing it immediately. Let us consider each point in turn.

Mechanism for accumulation

It is clear that starvation triggers marrow fat accumulation, but what is the mechanism? First, low leptin appears to be key. Despite massive obesity, both the ob/ob mouse (which lacks leptin) and the db/db mouse (which lacks the leptin receptor) have high marrow fat. Leptin treatment reduces BMAT in ob/ob mice and in wildtype rats (Hamrick et al., 2005; Hamrick et al., 2007; Hamrick et al., 2004), and in a mouse model of Type 1 diabetes (Motyl and McCabe, 2009), supporting a relationship between hypoleptinemia and high marrow fat. Hypoleptinemia and BMAT accumulation may also exacerbate the starvation-induced suppression of hematopoiesis. Leptin is known to stimulate blood cell formation, and hematopoiesis is impaired in human starvation, including anorexia nervosa, and in the ob/ob and db/db mouse models (Bennett et al., 1996; Brichard et al., 2003; Fantuzzi and Faggioni, 2000). Although it is unclear whether starvation influences differentiation of hematopoietic stem cells, as has been demonstrated for mesenchymal stem cells, it does appear that marrow adipocytes suppress overall hematopoiesis (Naveiras et al., 2009), whereas marrow osteoblasts support it (Calvi et al., 2003). Thus once the balance between osteoblasts and adipocytes is altered in favor of the latter, hematopoiesis would be decreased.

A second possibility is that dysregulation of the GH-IGF-1 and/or estrogen axes alters marrow adipogenesis. The *little* mouse, which has a spontaneous mutation of the growth hormone-releasing hormone receptor, is lean and has low GH levels, but high BMAT (Menagh et al., 2010). In contrast, two genetically altered mouse models, the liver IGF-1 deficient (LID) and labile acid subunit-deficient (Calabrese et al., 2009) mice, have high circulating GH, low serum IGF-1, and little BMAT (Yakar et al., 2009). As noted above, human anorexia nervosa patients tend to exhibit high marrow fat against a background of low leptin, high circulating GH and GH resistance (Bredella et al., 2009; Lawson and Klibanski, 2008). Thus low GH levels and/or GH resistance, independent of IGF-1, appear to be associated with increased marrow adiposity. High marrow fat is also seen in postmenopausal women, suggesting low estrogen levels may contribute to marrow adiposity (Syed et al., 2008).

Finally, marrow fat deposition may be induced by increased fat metabolism. As discussed above, starvation causes hyperlipidemia as fat reserves are mobilized. High levels of free fatty acids (FFAs) increase levels of PPAR γ 2, an essential transcription factor for adipocyte formation (Anghel and Wahli, 2007). Stimulation of PPAR γ 2 by thiazolidinediones, drugs used to treat Type 2 diabetes, has been shown to increase marrow fat formation in animal models (Ackert-Bicknell et al., 2009; Kawai et al., 2009). Conversely, inhibiting PPAR γ 2 in a mouse model of Type 1 diabetes inhibits marrow fat formation (Botolin and McCabe, 2006). Although it is not well understood whether marrow fat accumulates due to hypoleptinemia, GH resistance, low IGF-1, low estrogen, high PPAR γ 2, or a combination of factors, the key is that all of these physiological changes are associated with starvation (Fig. 1).

Is marrow fat mobilized during starvation?

Although increased marrow fat is frequently noted in starving animals and humans, data on whether it is eventually metabolized are conflicting. For example, in women with anorexia, some studies report high marrow fat (Bredella et al., 2009; Ecklund et al., 2009), but others find gelatinous transformation of bone marrow, in which there is little marrow fat and most tissue has been replaced by a fluid rich in hyaluronic acid (Hutter et al., 2009; Tavassoli et al., 1976). The resolution to this discrepancy may be that marrow fat is not mobilized until Phase III of starvation, the final stage when protein wasting leads rapidly to fatality. Although there are almost no experimental data on bone marrow dynamics in late starvation, one study of fasting in barn owls reports that marrow fat is metabolized in Stage III starvation (Thouzeau et al., 1999). Furthermore, while high sympathetic tone can increase fat metabolism, there is evidence that BMAT is less responsive to epinephrine, compared to other fat depots such as WAT (Tran et al., 1981; Tran et al., 1984).

Another possible mechanism for BMAT persistence is autophagy, a mechanism that allows starving cells to digest unneeded intracellular components in order to prolong survival (Yorimitsu and Klionsky, 2005). By removing aged or damaged intracellular components, autophagy may rejuvenate cells, and thus is one potential mechanism of lifespan extension in caloric restriction (Bergamini et al., 2007). The starvation-induced decrease in leptin promotes autophagy by inhibiting mTOR, a protein that normally promotes lipogenesis and suppresses autophagy (Chakrabarti et al., 2010; Maya-Monteiro and Bozza, 2008). These data suggest that BMAT might be resistant to lipolysis until other fat depots have been exhausted. However, further studies of WAT vs. BMAT dynamics in animal models of calorie restriction as well as treatment with adrenergic agonists and antagonists are clearly needed to validate this hypothesis.

How much marrow fat is in the skeleton?

To get an idea of how much marrow fat is contained in the skeleton, and whether it is enough to confer a meaningful survival advantage, consider the energy represented by WAT vs. BMAT. Humans have substantial WAT reserves, and women carry a greater percentage of body mass as fat, such that absolute quantities are similar in men and women (Ellison, 2001). For example, a 73 kg (161 lb) male with 20% body fat and a 60 kg (132 lb) woman with 25% body fat each have about 15 kg of WAT (ICRP, 2002). At 9 kilocalories (kCal) per gram, this fat represents about 135,000 stored kCal, or enough energy to survive for about two months at 2,000 kCal/day (Anghel and Wahli, 2007).

How does this compare to the BMAT depot? Total bone marrow comprises approximately 5% of adult body weight, and about 70% of that is yellow (Hindorf et al., 2010). Thus a 60 kg woman has about 3.0 kg of bone marrow, of which 2.1 kg (70%) is BMAT, while a 73 kg man has about 3.7 kg of bone marrow, 2.6 kg (70%) of it BMAT. Using the Henry (2005)

equations for basal metabolic rate (BMR), with an activity multiplier of 1.82 (females) or 2.10 (males) for heavy activity, this woman and man would expend roughly 2,200 and 3,000 kCal/day, respectively. Thus, at 9 kCal/g, the woman's 2.1 kg of marrow fat would contain 19,000 kCal, and the man's 2.6 kg would contain 23,000 kCal, or enough energy for each to survive for 6-8 days at high activity levels (Table 1). However, this estimate is based on normally nourished individuals. As noted above, BMAT increases in negative energy balance; Bredella and others (2009) found that women with anorexia nervosa have approximately 75% higher lipid:water ratio in their vertebral bodies, femoral metaphysis and diaphysis compared to controls. Thus the BMAT depot in starving individuals is probably larger than this estimate. The question is why storing BMAT during early starvation would be more beneficial than simply metabolizing it.

Why store marrow fat in starvation?

One possible benefit of BMAT storage in early caloric deficit is that it would take advantage of the starvation-induced decrease in BMR (Dulloo and Jacquet, 1998; Mifflin et al., 1990). In the Minnesota Starvation Experiment, BMR decreased by about 25% relative to baseline after 24 weeks of semistarvation (Keys, 1950; Dulloo and Jacquet, 1998); BMR decrements of 20-30% are seen in women with anorexia nervosa (Casper et al., 1991; Platte et al., 1994; Polito et al., 2000). Thus the relative energetic value of fat tissue increases over time; if BMAT could be shielded from lipolysis until BMR falls, its energetic value would be higher than if it were metabolized immediately.

How much more would BMAT be worth at a lower BMR? To return to the example above, the BMAT in an average man or woman represents enough energy for 6-8 days at normal BMR and heavy activity level (Table 1). Now consider the effect of three starvation-induced changes in energy expenditure and storage (Table 1): 1) a 25% decrease in BMR, 2) a decrease in activity level from heavy to light, and 3) a 25% increase in BMAT mass. First, if BMR were 25% lower, as seen in starving humans (Dulloo and Jacquet, 1998), the energy contained in marrow fat would last for 8-9 days. Second, decreasing activity levels from heavy to light lowers the activity multiplier from 1.82 to 1.55 (females) or 2.10 to 1.56 (males), which would save 300-800 kCal/day, respectively (Henry, 2005). At both lower BMR and lower activity level, the BMAT depot would last for about 10 days. Finally, consider the effect of increasing BMAT by 25% early in starvation—a conservative estimate, as much greater enrichment of BMAT in women with anorexia vs. controls has been reported (Bredella et al., 2009; Ecklund et al., 2009). If BMAT mass increased to 2.6 kg in the woman and 3.2 kg in the man, the time represented by BMAT would increase even more, to 13 days. Thus a combination of reducing energy expenditure and increasing BMAT might extend the survival time represented by BMAT from 6-8 days to 13 days.

To summarize, this thought experiment suggests that storing energy in BMAT in early starvation would roughly double its energetic value in late starvation, but only by one week. Given such a modest benefit, starvation-induced BMAT storage may not provide a sufficient advantage to be favored by natural selection. However, these are only estimates, and if the BMAT depot can increase in mass by more than 25%, and/or BMR and energy expenditure can be decreased by more than estimated here, then the potential value of BMAT could be higher.

Starvation and the skeleton

Of course, the major alternative hypothesis is that marrow adipocytes are not a survival adaptation, but rather a pathology or constraint caused by starvation-induced bone loss. The intimate anatomical proximity of marrow and bone, and the fact that osteoblasts and adipocytes both derive from mesenchymal stem cells (Beresford et al., 1992; Dorheim et al.,

1993), suggest that the starvation-induced increase in marrow fat and decrease in bone mass may share common mechanisms (Fig. 1). Indeed, the physiological changes seen in starvation—particularly the decreases in IGF-1 and estrogen and the increase in PPAR γ —have been shown to drive precursor cells to the fat lineage and away from the bone lineage (Gimble et al., 1996; Lecka-Czernik et al., 1999). Furthermore, starvation causes profound bone loss, resulting in an enlarged medullary cavity that could hold more fat. Clinical observations of anorexia nervosa (AN) patients indicate low bone mass, low bone formation and high bone resorption, along with low leptin and IGF-1 levels (Abella et al., 2002; Lawson et al., 2010; Miller et al., 2006; Misra and Klibanski, 2006). These skeletal changes mirror those seen in calorie restricted mice, which have lower bone formation indices and higher bone resorption indices compared to normal mice (Devlin et al., 2010).

Understanding why starvation causes bone loss might reveal whether marrow fat is friend or foe. Starvation-induced catabolism of fat and muscle makes sense, as the former is an energy source, and the latter is energetically expensive to maintain. However, bone resorption does not provide energy for maintaining brain or body, and actually costs energy to carry out. If conditions improve, the lost bone must be replaced, imposing further metabolic costs. Why resorb bone in starvation?

One possibility would be to liberate minerals, primarily calcium, from the skeleton. Calcium is critical for cell physiology, and insufficient calcium intake quickly stimulates bone resorption to liberate calcium bound to bone hydroxyapatite (Potts, 2005). A reduction in food intake might lead to hypocalcemia and trigger such bone resorption. However, at least in young individuals, one would expect this to affect primarily trabecular bone, which has a much higher surface volume for osteoclasts to operate on compared to cortical bone. (In older individuals, trabecularization of cortical bone greatly increases the surface area accessible to osteoclasts (Zebaze et al., 2010).) In animal models of caloric restriction and in humans with anorexia (reviewed above), both cortical and trabecular bone are lost.

A second possibility is mechanical. If the individual weighs less, the loads on the skeleton decrease, triggering bone resorption (e.g. Frost, 1987; Frost, 2003). Based on biomechanical principles, one would expect preferential bone loss on the endosteal surface, as this bone is under the least mechanical strain. A final possibility is that medullary cavity size might increase to make more space for storing marrow fat, either for overall survival (as discussed above) or to aid in recovery of intramedullary processes such as bone growth and hematopoiesis. Several authors have suggested that the function of BMAT could be to provide energy and/or to secrete autocrine or paracrine hormones that help to restore osteoblast function after starvation (Bathija et al., 1979; Gimble et al., 2006; Nuttall and Gimble, 2004). This is an intriguing possibility, but one that is hard to test since bone may also be lost endosteally for mechanical reasons.

Conclusion

In summary, although there is some evidence suggest that storing BMAT early in starvation could contribute to survival, the effect is probably modest. The physiological changes that occur with prolonged starvation, including low leptin, estrogen, and IGF-1 levels, GH resistance, and increased expression PPAR γ 2, are known to increase BMAT deposition. The combination of starvation-induced changes in BMR and energy expenditure, along with even a modest increase in BMAT mass, could double the survival time represented by the BMAT depot, but this is speculative without more experimental data. The alternative hypotheses that BMAT results from a constraint or pathology affecting bone formation in negative energy balance cannot be refuted with current data.

Many interesting questions remain about the interactions of starvation, BMAT, and bone. Little is known about how BMAT mass changes during starvation recovery, although bedrest-induced BMAT persists for at least a year after reambulation (Trudel et al., 2009). It would be interesting to know whether mild caloric deficits are sufficient to cause increased BMAT accumulation, and whether humans who experience frequent fluctuations in food availability have more BMAT than those with steadier food sources. Furthermore, while experimental caloric restriction generally causes higher BMAT, its effects on bone vary with age: Why does CR in young, rapidly growing animals impair skeletal acquisition (Devlin et al., 2010), whereas CR initiated in adulthood may actually retard skeletal aging (Hamrick et al., 2008; Tatsumi et al., 2008)? It is also unclear why high marrow fat is associated with low bone mass in pathological conditions such as osteoporosis and starvation, but also with peak bone mass accrual in adolescence.

Experimental approaches will help to resolve some of these questions. First, testing the effects of caloric restriction with simultaneous leptin replacement would clarify whether leptin is the predominant hormonal driver of BMAT formation, and whether bone loss is coupled to BMAT formation or independent of it. Second, treating calorie restricted animals with epinephrine will reveal whether sympathetic agonists increase marrow fat lipolysis, as earlier studies suggested. Finally, a study of calorie restriction followed by refeeding will allow careful monitoring of bone and fat changes when starvation ends, which should shed light on whether increased BMAT during starvation represents adaptation, pathology, or constraint.

In conclusion, there is solid evidence that BMAT increases with starvation, but the reasons for this remain poorly understood. Furthermore, the mechanisms that lead to increased BMAT in negative energy balance may be distinct from those that lead to high BMAT in other conditions, such as osteoporosis, skeletal unloading/disuse, and obesity (Bredella et al., 2010; Dudley-Javoroski and Shields, 2008; Trudel et al., 2009; Yeung et al., 2005). BMAT as a survival adaptation to starvation is plausible, but more work needs to be done to unravel the nature of this phenomenon and the mechanisms involved.

Acknowledgments

Thanks to Mary Bouxsein, Cliff Rosen, and two anonymous reviewers for helpful comments and discussion. This study was supported by NIH F32HD060419, T32DK007028, and RC1AR058389.

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Figure 1.

Starvation-induced physiological changes associated with increased adipogenesis, decreased osteogenesis, and suppression of hematopoiesis in bone marrow. Fuel sources shown in gray. Boxes indicate association with increased BMAT; italics indicate association with decreased osteogenesis. WAT, white adipose tissue. FFAs, free fatty acids. PPAR, peroxisome proliferator-activated receptor. FGF, fibroblast growth factor. PGC, peroxisome proliferator-activated receptor gamma coactivator protein. STAT5, signal transducer and activator of transcription. GH, growth hormone. IGF, insulin-like growth factor.

Table 1
Theoretical estimate of days of energy represented by BMAT with changes in metabolic rate and activity level

Subject	Height	Energetic state	BMR	Body mass	BMAT	Activity	kCal/day (BMR) ¹	kCal/day (Activity) ²	kCal/day (Total)	Bone marrow (kg) ³	BMAT (kg) ⁴	kCal in BMAT (9 kCal/g)	Days of energy in BMAT
Female, age 30	163 cm (5'4")	Normal	Normal	60 kg	Normal	Heavy	1,344	1,102	2,447	3.0	2.1	18,900	8
		Starvation	-25%	45 kg (-25%)	Normal	Heavy	1,188	975	2,163	3.0	2.1	18,900	9
					Normal	Light	1,188	654	1,842	3.0	2.1	18,900	10
Male, age 30	176 cm (5'9")	Normal	Normal	73 kg	+25%	Light	1,188	654	1,842	3.0	2.6	23,625	13
					Normal	Heavy	1,715	1,887	3,602	3.7	2.6	22,995	6
		Starvation	-25%	55 kg (-25%)	Normal	Heavy	1,456	1,601	3,057	3.7	2.6	22,995	8
					Normal	Light	1,456	815	2,271	3.7	2.6	22,995	10
					+25%	Light	1,456	815	2,271	3.7	3.2	28,744	13

¹ BMR equations from Henry 2005 (weight in kg, height in m): Females: $BMR = 10.4W + 615H - 282$, Males: $BMR = 14.4W + 313H + 113$, BMR in starvation calculated as 25% decrease from baseline (Dulloo and Jacquet 1998)

² Physical activity multipliers for light and heavy activity: 1.55 and 2.10 in males, 1.56 and 1.82 in females (Henry, 2005)

³ Hindorf and others 2010

⁴ Predicted 25% increase in BMAT during starvation may be an underestimate (Bredella and others 2009, Ecklund and others 2009)