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The paradox of marrow adipose tissue in anorexia nervosa

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Abstract

Anorexia nervosa (AN) is a psychiatric disorder characterized by inappropriate nutrient intake resulting in low body weight. Multiple hormonal adaptations facilitate decreased energy expenditure in this state of caloric deprivation including non-thyroidal illness syndrome, growth hormone resistance, and hypogonadotropic hypogonadism. Although these hormonal adaptations confer a survival advantage during periods of negative energy balance, they contribute to the long-term medical complications associated with AN, the most common of which is significant bone loss and an increased risk of fracture. In recent years, marrow adipose tissue (MAT) has emerged as an important potential determinant of the low bone mass state characteristic of AN. Unlike subcutaneous and visceral adipose tissue depots which are low in AN, MAT levels are paradoxically elevated and are inversely associated with BMD. In this review, we discuss what is known about MAT in AN and the proposed hormonal determinants of this adipose tissue depot.

Keywords

anorexia nervosa; marrow adipose tissue; bone mineral density

INTRODUCTION

Anorexia nervosa (AN) is a primary psychiatric disease characterized by the inability to maintain a normal body weight [1]. Individuals with anorexia nervosa maintain their low body weight by maintaining a state of negative energy balance either through restricting caloric intake and/or excessive energy expenditure through excessive exercise. Predominantly affecting women, the disease has a lifetime prevalence approaching 2.2% [2]. Importantly, the recovery rate is only approximately 50-60% and therefore this is a chronic disease for nearly half the women who are diagnosed [3, 4].

The negative energy balance characteristic of AN results in hormonal adaptations which minimize energy expenditure in the setting of restricted energy intake. These hormonal adaptations which include hypogonadotropic hypogonadism, hypercortisolemia and growth hormone resistance provide a survival advantage in the setting of decreased energy availability but when the decreased energy availability is prolonged, these adaptive mechanisms contribute to the medical complications associated with AN, the most common of which is significant bone loss [5]. Nearly 90 % of women with AN have bone mineral

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density (BMD) values more than 1 SD below comparably aged women and AN is associated with a significant increased risk of fracture [5, 6]. A prospective study of young women demonstrated a seven-fold increased risk of non-vertebral fractures in those with AN as compared to normal weight women [7]. Retrospective studies have also demonstrated a significantly increased risk of fractures with nearly 30% of girls and women with AN reporting a history of fracture [5, 8]. Therefore, understanding the determinants of this significant loss of bone mass and increased fracture risk is critical to reducing the morbidity associated with this chronic disease. In this review, we will discuss one potential determinant of bone mass in AN, marrow adipose tissue (MAT) and its association with BMD and other adipose tissue depots. The associations we will describe demonstrate a paradoxical association between MAT, peripheral adipose tissue depots and BMD in AN and this paradox suggests that the function of MAT may be fundamentally different than those of other adipose tissue depots.

Adipose tissue depots in AN

Body composition in AN—Body composition, and specifically body fat distribution, is significantly different in AN compared to normal-weight individuals. In adult women with AN, total body fat mass and percent total fat mass as measured by DXA are significantly lower compared to normal weight controls [9, 10]. and this difference is observed predominantly in the extremities. However, whereas percentage extremity fat (extremity fat/total fat mass) as measured by DXA is significantly lower in AN compared to normal-weight women, the percentage trunk fat (trunk fat/total fat mass) is similar in both groups [9, 10]. In addition, there are significant differences in body fat distribution when comparing adult women with AN to adolescents with AN. In contrast to adults, in adolescents with AN, although fat mass as measured by DXA is also significantly lower compared to normal-weight adolescent girls, extremity fat percentage is *similar* and percent trunk fat is significantly *lower* than controls [11]. This suggests that the mechanisms of fat distribution in adults versus adolescents with AN are different. Importantly, with the use of magnetic resonance imaging (MRI), subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) depots can be differentiated in cross-sectional images and in adult women with AN both SAT and VAT stores are lower when compared to normal weight controls [10, 12].

Body composition with weight-recovery—With weight recovery, adult women with AN gain significantly more trunk fat as compared to extremity fat. Short-term (< 9 months between low weight and recovery) weight recovery results in a significantly higher waist to hip ratio and significantly higher trunk/extremity fat ratio, as measured by DXA, as compared to control subjects [9, 10]. Those with the lowest percentage trunk fat at baseline have the greatest increase in percent trunk fat during recovery and cortisol has been shown to be associated with the change in trunk fat; both baseline urinary free cortisol levels and levels after weight gain are significantly correlated with the increase in trunk fat [9]. MRI measures of subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) depots similarly demonstrate that VAT is significantly higher in AN after weight-recovery as compared to normal-weight women [10]. With longer-term weight recovery (12 months), the VAT/SAT ratio decreases and is similar to the ratio in normal-weight controls, suggesting that long-term weight maintenance is required for the normalization of body fat depots [13].

In adolescents, those who recover weight over a 12-month period have a significant increase in fat mass and the ratio of trunk/extremity fat but the ratio is similar to the trunk/extremity fat ratio in normal-weight controls [11]. Similar to adults, in adolescents with AN, those with the lowest percentage of trunk fat at baseline had the greatest increase in percent trunk fat with weight recovery, yet the hormonal correlates of trunk fat change differ in these two groups [11]. Unlike in adults, in adolescents with AN, urine free cortisol measurements did not correlate with changes in trunk fat but change in IGF-1 levels significantly correlated with change in trunk fat percentage as well as change in the trunk/extremity fat ratio [11]. This normalization of the trunk/extremity fat ratio after 12 months of weight recovery is similar to the normalization of body fat distribution observed in adults with AN after 12 months [11, 13]. Therefore, although the distribution of peripheral adipose tissue depots is significantly different in adolescents with active AN as compared to adults, with long-term weight recovery, there is a similar normalization of body fat distribution in both populations.

MAT in AN—The significant decrease in both SAT and VAT depots in AN compared to normal weight controls is expected [10, 12]. In contrast, the majority of studies have demonstrated increased MAT depots in AN compared to normal weight controls and inverse associations between MAT and subcutaneous adipose tissue stores [12, 14, 15]. In the one study reporting lower levels of MAT in women with AN as compared to controls, the patients were predominantly inpatients and therefore likely sicker and of a lower weight than the majority of patients with AN [16]. As the authors state, the findings likely represent atrophy or degeneration of bone marrow which has been previously described in very low weight individuals with AN [16-18]. A study of bone marrow specimens of 44 individuals with AN showed 50% had gelatinous degeneration and importantly the bone marrow findings correlated with the amount of weight loss [18].

MAT with recovery—With recovery, the bone marrow and MAT levels normalize. In a study comparing women with AN to women with a history of AN but who had recovered weight and menstrual cyclicity, we found that the women who had recovered from AN had similar MAT levels in the L4 vertebra as compared to the normal weight controls, whereas the women with AN had significantly higher levels of L4 MAT [19]. Similarly, in the study of individuals with AN who had bone marrow biopsies, a subset had a repeat biopsy after weight recovery which demonstrated normalization of the marrow [18]. Therefore, although the role of MAT remains unknown, the increase in MAT observed in AN appears to be a response to the low-weight state and reversible with weight recovery, suggesting that it may serve a function, currently unknown, during periods of nutrient deficiency.

MAT's association with BMD in AN

In many populations, including healthy women, MAT is inversely associated with BMD [20, 21]. This relationship between MAT and BMD is also observed in AN [12]. Importantly, MAT is associated with parameters of decreased bone integrity [22], suggesting that the increased levels of MAT in AN may be a determinant of decreased bone strength. In adolescents with AN, L4 MAT has been inversely associated with high-resolution peripheral quantitative CT derived finite element analysis estimates of bone strength [23]. Whether the

higher levels of MAT in this population directly contribute to the increased fracture risk is not known.

Potential determinants of MAT in AN (Table 1)

Cortisol—Cortisol, a counterregulatory hormone released during states of physiologic stress including starvation is increased in many women and adolescents with AN [24-27]. Therefore, cortisol has been postulated to be a hormonal determinant of MAT. However, frank hypercortisolism is not universally seen in this disorder. Furthermore, in a study using quantitative CT measuring intravertebral fat in women with AN and women with hypercortisolemia due to Cushing's syndrome [14] we showed that although women with AN demonstrated significantly higher levels of intravertebral MAT as compared to controls, the women with Cushing's syndrome did not [14]. Therefore, it is not likely that cortisol is an important hormonal determinant of MAT.

Preadipocyte factor (Pref)-1—Preadipocyte factor (Pref)-1 is a member of the epidermal growth factor family of proteins and a negative regulator of adipocyte and osteoblast differentiation [28]. Although Pref-1 inhibits adipocyte differentiation, we have demonstrated significant positive associations between Pref-1 and MAT in women with AN [19, 29]. Importantly, these positive associations were observed in cross-sectional studies and therefore it is not known whether the relationship between Pref-1 and MAT is causative. Longitudinal studies will be necessary to better elucidate the relationship between Pref-1 and MAT.

Estrogen—Estrogen may also be an important determinant of MAT. Estrogen suppresses adipocyte differentiation and therefore the estrogen deficiency due to hypogonadotropic hypogonadism characteristic of AN may contribute to MAT accumulation. *In vitro* studies demonstrate that 17-β estradiol decreases PPARγ-agonist induced adipocyte differentiation of human mesenchymal stem cells [30]. In murine models, estrogen deficiency, for example through ovariectomy, also enhances adipocyte infiltration of bone marrow and estrogen supplementation can prevent increases in marrow adiposity in these estrogen deficient animals [31]. Similarly, in women, marrow adipocyte volume/tissue volume (AV/TV) and adipocyte number increase after menopause and AV/TV decreases with estrogen replacement concomitant with an increase in BMD at the lumbar spine [32]. Whether estrogen is a determinant of MAT in AN is not known.

Fibroblast growth factor (FGF)21—Fibroblast growth factor (FGF)21 is a hormone secreted during states of starvation in both animal models and humans. In murine models, FGF21 is secreted early during starvation and is a regulator of ketogenesis, whereas in humans, FGF21 levels increase during late starvation (after 7-10 days of fasting) and circulating levels increase only after a peak in serum ketone levels [33-35]. Therefore, FGF21 appears to have divergent functions in mice as compared to humans. In one study evaluating the effects of FGF21 on bone, mice that transgenically overexpress FGF21 were found to have uncoupled bone turnover with increased bone resorption and decreased bone formation, coincident with increased levels of MAT [36], although a second murine study did not find a bone or MAT phenotype in diet-induced obese mice who were treated with

recombinant human FGF21 [37]. In humans, we have shown that FGF21 levels are associated with worsened parameters of bone microarchitecture in AN [38] and hypothesized that MAT would be positively associated with FGF21 in AN. In a study of women with AN and normal-weight women, we found a significant inverse association between MAT of the L4 vertebra and FGF21 [39]. Whether this is a compensatory decrease in FGF21 in response to elevated MAT or an example of the divergent role of this hormone in mice as compared to humans is unknown.

Ghrelin—Ghrelin is an orexigenic hormone secreted by the fundal cells of the stomach. Ghrelin levels are significantly higher in girls and women with anorexia nervosa as compared to normal weight individuals as would be expected in a nutritionally deficient state [40-42]. In a rodent model, ghrelin has been shown to promote marrow adipogenesis but likely through a receptor other than the GHS1a receptor to which it is known to bind [43]. We measured MAT in women randomized to either four weeks of a GHS1a receptor agonist (relamorelin) (n=7) or placebo (n=11) and found that although L4 MAT was similar in both groups before treatment (p=0.28), there was a trend towards decreased L4 MAT in the women randomized to the GHS1a receptor agonist as compared to placebo (Figure 1). The women randomized to relamorelin, the GHS1a receptor agonist, had significantly lower levels of acyl ghrelin after four weeks of treatment as compared to the placebo group [44]. Whether this decrease in MAT was due to decreased levels of endogenous acyl ghrelin (which may mediate MAT promoting effects through a receptor other than the GHS1a receptor) or due to other changes mediated by the GHS1a receptor agonist is unknown but warrants further study.

Leptin—Levels of leptin, an adipokine secreted predominantly by SAT are low in AN [45, 46]. In AN, leptin is positively associated with both BMD [29, 47] and parameters of microarchitecture [48] and we have demonstrated an inverse association between L4 vertebral MAT and leptin in women with AN [29]. Importantly, as leptin is strongly associated with SAT in this population [29], it is unknown whether this association is observed simply because of the inverse association between MAT and SAT or whether the low levels of leptin are an independent hormonal determinant of the elevated levels of MAT.

IGF-1 and IGFBP2—IGF-1 is a nutritionally dependent hormone secreted by the liver in response to growth hormone. In states of starvation, including AN, IGF-1 levels are low [49]. Because IGF-1 is a known bone trophic hormone, [50-52] the low levels are likely an important contributor of low bone mass in AN, as evidenced by the fact that IGF-1 is positively associated with BMD in this population [53]. In contrast, levels of IGFBP2, a binding protein of IGF-1 are elevated in AN [49, 54, 55] and are inversely associated with a marker of bone resorption, osteocalcin [54]. We have found that MAT is positively associated with IGFBP2 and inversely associated with IGF-1 in women with AN [29]. In contrast, we demonstrated a positive association between IGF-1 and MAT in normal weight, healthy controls [29], although in a population inclusive of normal weight, overweight and obese women, MAT and IGF-1 were inversely associated [56]. This suggests that IGF-1 may have differential effects in various states of nutrient sufficiency. A better understanding of

the association between MAT and growth hormone-IGF1 axis may allow for a better understanding of the role and function of MAT.

Adiponectin—Similar to MAT, levels of adiponectin, a hormone secreted by adipocytes, are paradoxically higher in normal weight individuals as compared to obese individuals [57] and total adiponectin levels are increased in AN in most studies [58, 59]. In animal models, adiponectin has been shown to be secreted by MAT [59]. Although adiponectin does not appear to be a hormonal determinant of MAT in animal models but instead a secretory product of MAT, it may explain the paradox of elevated levels of adiponectin in individuals with low levels of SAT and VAT, such as those with AN [60].

CONCLUSIONS

Despite having low levels of VAT and SAT, individuals with AN have increased MAT which is inversely associated with BMD. Importantly, these increased levels of MAT are reversible with weight recovery and therefore the increase is likely associated with weight loss and characteristic of the low-weight state. Although the role and function of MAT remains unknown, we hypothesize that it serves an important purpose given the fact that this adipose tissue depot ***increases*** during a state of decreased nutrient availability, a state which is typically characterized by ***utilization*** of fat stores. Importantly, although there is an inverse association between MAT and BMD in healthy populations [20, 21, 61, 62] and women with AN[12], there are disease states, including HIV, in which both MAT and BMD are decreased [63]. A better understanding of these disparate associations between BMD and MAT may provide further insight into the role of this adipose tissue depot. Further studies are needed to elucidate the determinants of MAT which will allow us to better understand the function of this adipose tissue depot.

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Highlights

- Anorexia nervosa (AN) is psychiatric disorder characterized by low body weight
- AN is associated with significant bone loss and an increased risk of fracture
- Marrow adipose tissue (MAT) is a potential determinant of bone mass
- Although sc and visceral fat stores are low in AN, MAT levels are elevated
- Elevated MAT may be a determinant of low bone mass in AN

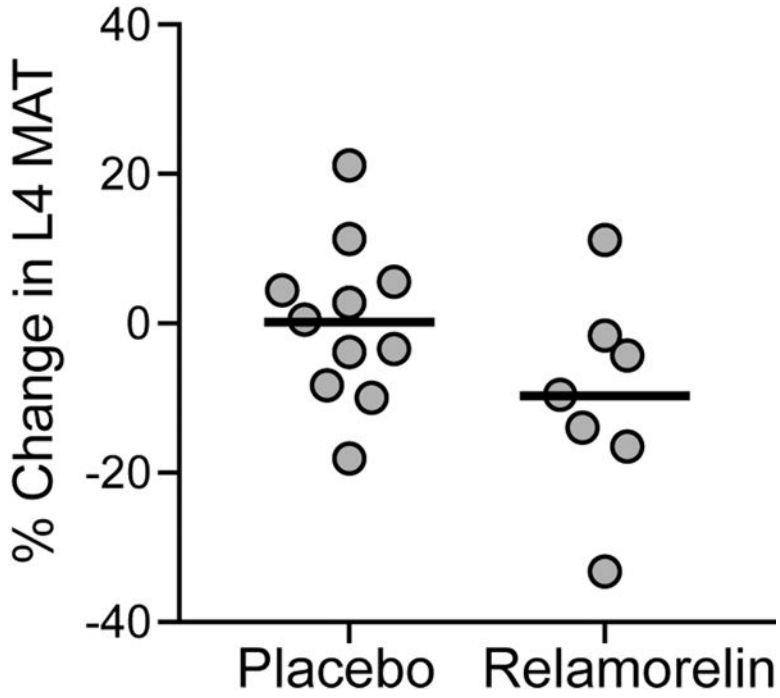

Figure 1.

Marrow adipose tissue (MAT) in the L4 vertebra decreased more in women treated with four weeks of a GHS1a receptor agonist (relamorelin) as compared to those randomized to placebo. There was a trend towards significance (p=0.1).

Table 1

Potential hormonal determinants of marrow adipose tissue (MAT) in anorexia nervosa

	Hormone levels in anorexia nervosa (compared to normal weight individuals)	**Association with bone**	**Association with MAT**
Cortisol	Elevated [24-27]	Inversely associated with BMD [27, 64]	No known association in AN
Preadipocyte factor-1	Elevated [29]	Inversely associated with BMD [29]	Positive association with MAT in AN [29]
Estrogen	Low [64]	Duration of amenorrhea inversely associated with BMD [64]	Estrogen suppresses MAT in postmenopausal women (unknown in AN) [32]
Fibroblast growth factor 21	Similar/low [38, 65, 66]	Inversely associated with parameters of bone microarchitecture [38]	Inverse association with MAT [39]
Ghrelin	Elevated [40-42]	Positive association with BMD in normal weight individuals but inverse association with BMD in AN [67, 68]	Stimulates marrow adipogenesis in rodent models [43]
Leptin	Low [45, 46]	Positively associated with BMD and parameters of bone microarchitecture [29, 47, 48]	Inverse association with MAT [29]
IGF-1	Low [49]	Positively associated with BMD [53]	Inverse association with MAT in AN [29]
IGFBP2	Elevated [49, 54, 55]	Inversely associated with BMD and osteocalcin (marker of bone formation) [29, 54]	Positive association with MAT [29]
Adiponectin	Majority of studies demonstrate elevated total adiponectin levels [58, 59]	Inversely associated with BMD in AN [69]	Adiponectin secreted by MAT in animal models [59]