Factors influencing bone loss in anorexia nervosa: assessment and therapeutic options

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ABSTRACT

Decreased mineral density is one of the major complications of anorexia nervosa. The phenomenon is even more pronounced when the disease occurs during adolescence and when the duration of amenorrhea is long. The mechanisms underlying bone loss in anorexia are complex. Oestrogen deficiency has long been considered as the main factor, but cannot explain the phenomenon on its own. The essential role of nutrition-related factors—especially leptin and adiponectin—has been reported in recent studies. Therapeutic strategies to mitigate bone involvement in anorexia are still a matter for debate. Although resumption of menses and weight recovery appear to be essential, they are not always accompanied by a total reversal of bone loss. There are no studies in the literature demonstrating that oestrogen treatment is effective, and the best results seem to have been obtained with agents that induce bone formation—such as IGF-1—especially when associated with oestrogen. As such, bone management in anorexia remains difficult, hence, the importance of early detection and multidisciplinary follow-up.

Attitudes to food and eating disorders are of considerable importance in our modern societies on account of their physiological and health implications. The increase in the frequency of eating disorders as a whole is well established epidemiologically, and anorexia nervosa (AN) has become a major public health concern in recent years. Its prevalence is 0.2%–1% as opposed to 2% for bulimia.1 According to the DSM-V, AN is characterised by a refusal to maintain a minimum normal weight, significant weight loss, self-esteem that is excessively dependent on body shape and weight, and a distortion of body image. Amenorrhea is no longer required for the diagnosis of AN based on DSM-V criteria.2 Most of the studies on eating disorders focus on AN—which includes a restricting but also binge-purge subtype and is primarily characterised by weight loss—and bulimia nervosa, which is characterised by alternating bouts of uncontrolled binge eating and compensatory behaviours. In many cases, eating disorders are intertwined (eg, anorexia-bulimia) or incomplete, and their impact on weight balance is variable. Some studies on atypical forms of AN—in males, or prepubescent anorexia—can also be found in the literature.

This article focuses on eating disorders, and primarily restricting or binge-purge subtypes of AN in adolescents and young adults. Indeed, in the event of significant weight loss, the evolution of AN is marked by significant morbidity, particularly for bone tissue, and a higher risk of osteoporosis. In a recent meta-analysis, the authors found that spinal bone mineral density (BMD) in normal-weight women with bulimia nervosa was significantly lower than in healthy control women. These data suggest that the adverse effects of an eating disorder on BMD cannot be attributed to weight loss alone.3 The mechanisms underlying bone loss in these patients are numerous (hormonal, endocrine and nutritional). These negative consequences are further aggravated by the fact that eating disorders usually occur during adolescence, which is a critical period for the acquisition of peak bone mass.

Key messages

What is already known about this subject?

► Bone involvement is a frequent complication of anorexia nervosa leading to an increased risk of fracture.

What does this study add?

► Low body mass index (BMI), amenorrhea and low IGF-1 level are well recognised factors explaining bone involvement, low leptin level, and high adiponectin level have been more recently investigated and seem promising.

How might this impact on clinical practice?

► Management of low bone mass requires an increase of BMI and menstrual cycles recovery.
The purpose of this paper is to assess the extent of bone involvement in AN, in epidemiological, diagnostic and physiopathogenic terms, and to attempt to evaluate its therapeutic consequences. Moreover, this article is a narrative review and not a systematic review.

**ASSESSMENT OF BONE INVOLVEMENT IN AN**

**Bone mineral density**

BMD can be assessed non-invasively using dual-energy X-ray absorptiometry. In populations of young women or female adolescents with AN, in which some patients are under 20 years old, it is preferable to use the Z-score—that is, the number of SD between a subject’s value and the mean value of subjects of the same age and sex—rather than the T-score—that is, the number of SD between a subject’s value and the mean value of young subjects of the same sex. Osteoporosis is defined as a Z-score of less than −2 SDs, and osteopenia as a Z-score of between −2 and −1 SDs.

BMD in anorexic patients and healthy subjects has been compared by different authors. Anorexia patients always exhibit lower BMDs; osteoporosis is found in about 20%–30% of the patients, and osteopenia in 50%–90% of them.

**Bone remodelling markers**

Bone remodelling markers can be used to explore both bone formation and bone resorption. In the literature, the most frequently used markers of bone formation are osteocalcin and bone alkaline phosphatases (BAP). Commonly used bone resorption markers include deoxypyridinoline, C-terminal extension peptides (CrossLaps or CTX) or N-terminal extension peptides (NTX), and telopeptides (carboxyl-terminal telopeptide of type one collagen). These markers are mainly used in postmenopausal women, but their interpretation in young women and adolescent girls is more difficult since growth (modeling) impacts on their values. In the literature, results vary widely, group sizes are often small, and a distinction needs to be made between those studies involving adolescent girls and those involving adult anorexia patients. Like postmenopausal women, anorexia patients exhibit an increase in bone resorption, but studies have reported that they also exhibit a significant decrease in bone formation. This results in greater bone loss than in women of the same age with hypogonadism. This decrease in bone formation probably depends on the severity of the disease and the age at onset. The underlying mechanism is probably a decrease in IGF-1, a factor that stimulates osteoblast differentiation and therefore bone formation. However, the decrease in bone formation markers is not found in all of the studies. Indeed, in a study comparing young adult anorexia patients (n=113) to controls, we found no significant difference between the groups where bone remodelling markers were concerned. Furthermore, some authors have reported low levels of bone formation markers and similar levels of bone resorption markers in adolescents with AN compared with healthy controls, while in adult women with AN compared with healthy controls, they observed decreased levels of bone formation markers and elevated levels of bone resorption markers. The difference may be due to the fact that physiological oestrogen levels are low in prepubertal adolescents, whereas most adult women with AN are hypoestrogenaemic relative to healthy controls.

**Fractures and AN**

Only a few studies have investigated the risk of fracture in anorexia patients. However, despite this reservation, all of the studies concur that the risk of fracture is higher in patients with AN. Fractures occur more frequently at the usual sites of osteoporotic fractures, that is, most often the vertebrae, then the radius, and then the upper extremity of the femur.

Grinspoon et al found a history of fracture in 26% of patients, 97% of whom had low BMD. The mean duration of the disorder was 5.5 years. In patients who have anorexia for a mean duration of 5.8 years, the risk of fracture is seven times higher than in healthy women of the same age. The prevalence of fractures in AN and other eating disorders has also been investigated using data from a Danish register. A higher incidence of fractures was found in anorexia patients after diagnosis (especially in the first year), with the risk of fracture persisting for up to 10 years thereafter. In patients diagnosed with anorexia after 20 years of age, the risk of fracture was higher than in those diagnosed before the age of 20. In a retrospective study involving 208 anorexic subjects (193 female and 15 male) with 13-year follow-up, Lucas et al reported 58 fractures. Compared with the expected number of fractures, the risk was multiplied by three. Fractures occurred more often in patients followed up in a hospital setting than in an outpatient setting, and stress fractures due to bone deficiency were also frequent in this population. The results of this study suggest that the cumulative incidence of fractures within 40 years of being diagnosed with AN is 57%.

The risk of fracture is higher in patients with active AN, and this higher risk persists for as long as 10 years after the disease was diagnosed, especially in patients over 20 years of age. A possible explanation for this could be the absence of bone mass recovery in older anorexia patients, in whom the progression of the disorder is potentially more serious.

**MECHANISMS OF BONE LOSS**

The pathophysiological mechanisms involved in bone metabolism abnormalities in AN are complex. Various mechanisms have been proposed and are probably interrelated, including oestrogen deficiency, growth hormone and IGF1 metabolism disorders, hypercorticism, vitamin D deficiency, adipose tissue metabolism disorders (leptin, adiponectin), and factors involved in adipocyte/osteoblast differentiation, such as preadipocyte factor-1.
Figure 1 Main mechanisms of bone involvement in anorexia nervosa.

(Pref-1). Indeed, since osteoblast and adipocyte cells come from the same cell line, the decrease in osteoblast differentiation probably causes precursors to take the adipocyte pathway. However, while the main biological pathways are now better understood, the respective weights of the above-mentioned factors in explaining bone impairment remain to be established (Figure 1).

Sex hormones
A few studies have investigated changes in BMD in AN patient populations.4–11 Women who develop anorexia before the age of 18 have significantly lower BMD than those who develop the disease later, which reflects the impact of the disease on peak bone mass acquisition. Although amenorrhea is no longer required for the diagnosis of AN based on DSM-V criteria, menstrual dysfunction remains common in this disease. Serum levels of oestrogen and testosterone are lower in adults and adolescents with AN compared with controls, and oestrogen deficiency has been reported to be a significant etiological factor for bone loss in this population. In anorexia nervosa, the mechanisms underlying oestrogen deficiency are better understood and probably multifactorial. Other potential factors include hypothalamic dysfunction and weight loss, and the dysregulation of neurohormones, such as GnRH, should also be considered (see below). In the literature, a correlation has been reported between BMD, duration, and age at onset of amenorrhoea.4 5 13 14 Menstrual resumption (associated with weight gain) is often considered a sign of improvement and/or recovery in females with AN. Oestrogen is an antiresorptive and reduces osteoclastic activity by depressing the secretion of RANKL and inflammatory cytokines, and stimulating the secretion of osteoprotegerin.15 Testosterone also impacts bone, both directly and through its aromatisation from oestradiol. Low testosterone levels have adverse effects on bone, and an increase in testosterone levels following weight gain is a strong predictor of a recovery in BMD in girls with AN.16–18

Oestrogen deficiency alone cannot explain bone involvement in anorexic patients, which suggests that other factors are involved. Indeed, in patients who have recovered from anorexia, the gain in bone density precedes the resumption of menses, and oestrogen treatment does not prevent bone loss in these patients as indicated below.4–6

Hormones and factors involved in regulating food intake
The role of the latter has been substantiated, and a correlation between BMD and IGF-1 in 113 patients with AN (r=0.4, p<0.0001).4 In another study, we also found that a recovery in weight with a BMI>17 kg/m² after 1-year follow-up predicted the recovery in hip BMD at 2 years.13 Other authors5 14 have also reported a positive correlation between bone formation markers (osteocalcin and BAP) and nutrition markers such as BMI, percentage of fat mass, and IGF-1, and a negative correlation between oestradiol and bone resorption markers.
Altersations in the GH-IGF-1 axis have also been reported in some studies. The levels of these hormones increase during puberty and stimulate the proliferation of osteoblast precursors and their differentiation. IGF-1 is a bone-trophic hormone that stimulates bone formation and growth by acting on osteoblasts and collagen synthesis. In patients with AN, high levels of plasma growth hormone (GH) are associated with low levels of IGF-1, suggesting a resistance to GH. Stoving et al. studied GH secretion over 24 hours in eight anorexic patients and observed an increase in the number of peaks, as well as in their duration and intensity. They also reported an increase in basal secretion (×20, compared with ×4 for pulsatile secretion). The increase in GH peak intensity is probably related to weight loss, and the increase in peak number to oestrogen deficiency. There was no difference in the half-life of GH between patients and healthy controls. Several authors have reported a decrease in IGF-1 levels, but also in IGF-1 carrier proteins—especially IGFBP-3 and IGFBP-2 (and sometimes IGFBP-1)—in anorexic patients.

The decrease in circulating levels of carrier proteins may partly explain the resistance to GH, thus preventing the transfer of IGF-1 to target organs. Moreover, IGFBP-3 may be a good predictor of bone loss in anorexic patients, independently of BMI and IGF-1.

The role of leptin in regulating bone mass and density is complex. While it seems to decrease bone density through central action, peripheral leptin seems to increase it. Serum leptin levels are logically lower in AN and have been found to correlate with lower fat mass and bone density measures.

In a recent study, we investigated factors influencing bone loss in 146 anorexic patients and, in multivariate analysis, we found that leptin level was the main factor (adjusted R²=0.12; p=0.0014) explaining the changes in hip BMD.

For adiponectin, some authors have reported an increase in serum levels, but results varied depending on the molecular weight fraction of plasma adiponectin that was measured. Some authors found that adiponectin levels increased in anorexic patients. The decrease in circulating levels of carrier proteins may partly explain the resistance to GH, thus preventing the transfer of IGF-1 to target organs. Moreover, IGFBP-3 may be a good predictor of bone loss in anorexic patients, independently of BMI and IGF-1.

Changes in body composition

AN is characterised by marked reductions in fat mass, and less marked but significant reductions in lean mass. Lower lean mass is an important determinant of lower bone density and impaired bone structure in adults and adolescents with AN. Soyka et al. have shown that increases in lean mass following weight gains are strongly predictive of coincident increases in bone density in adolescents with AN.

Furthermore, recent imaging studies (using MRI spectroscopy) have shown an increase in bone marrow fat in women with AN compared with normal-weight controls and women who have recovered from AN, even though patients with anorexia typically exhibit a reduction in subcutaneous and visceral fat. This is associated with an increase in Pref-1, a factor involved in adipocyte/osteoblast differentiation. These abnormalities can be explained by the common mesenchymal origin of these two cell lines.

Medullary adipocytes are a special population of adipocytes whose secretions in the spinal environment appear to contribute to the decrease in BMD. Furthermore, as patients recover from AN, marrow adipose tissue (MAT) tends to return to normal levels. In a study comparing women with AN to women with a history of AN but who had recovered weight and menstrual cyclicity, Fazeli et al. found that the women who had recovered from AN had similar MAT levels in the L4 vertebra compared with the normal-weight controls, whereas the women with AN had significantly higher levels of L4 MAT.

Stress hormones

The role of hypercortisolism in some patients also remains to be clarified. As is the case with patients taking exogenous corticosteroids, hypercortisolism can lead to low BMD via decreased bone formation-reducing osteoblast activity and increased bone resorption—promoting osteoclast activity.

High cortisol levels have been reported in this population, although with normal circadian rhythms. Similarly, an increase in free urinary cortisol is frequently found, with a dexamethasone test suppressing hypercortisolism. This hypercortisolism could be the result of an alteration in hypothalamic function, or promoted by the hypersecretion of CRH. In a previous study, we reported hypercortisolism in only 22% of anorexics with severe bone loss. Audi et al. found no significant difference in free urinary cortisol levels between anorexic patients and controls. Alternatively, this increase could be an adaptive mechanism to maintain a euglycemic state when nutritional intakes are low, but could contribute to the decrease in BMD.

Calcium/vitamin D

Although still unclear, the role of calcium/vitamin D deficiency in bone loss seems to be moderate. Most
studies have failed to demonstrate a relationship between calcium or vitamin D intake and bone parameters in AN. Most adults and adolescents with AN have a higher calcium and vitamin D intake than a control population due to greater use of supplements. In the study conducted by Audi et al., the authors reported vitamin D deficiency (25-OH D3 <30 ng/mL) in 24.6% of anorexic patients. We also observed vitamin D deficiency in 42% of anorexics, but also in 44% of controls. Nevertheless, optimising calcium and vitamin D status is recommended to optimise bone status, especially in young, growing adolescent patients (as well as in the general population of the same age).

**EVOLUTION OF BONE DENSITY AFTER WEIGHT RECOVERY OR WEIGHT GAIN**

A few studies have evaluated the evolution of BMD in groups of patients with a history of AN, but who had recovered weight. Despite the improvement in BMD when weight returned to normal, some studies reported persistently low bone mass. In a study with 12-month to 24-month follow-up, Bachrach et al. did not report significant changes in spine, hip and whole-body BMD. In another cohort of 51 patients followed up for 11.7 years after diagnosis of AN, bone mass remained low despite weight recovery. Hartman et al. also reported a decrease in BMD in former anorexia patients who had recovered and maintained a satisfactory BMI for an average of 21 years, compared with a control population matched for age and sex. The authors did not report any fracture events. In a study conducted by Zipfel et al., monitoring of spine BMD showed bone gain after weight recovery, with a decrease in the percentage of osteopenic and osteoporotic patients (35 with a 13% gain, and 54 with a 21% gain, respectively). Recently, Jáuregui-Lobera et al. showed that, despite the efficacy of treatment (in terms of weight recovery and return of regular menses), bone condition varied slightly after a follow-up of 11 months. Indeed, in 80% of their patients, bone mass as measured by quantitative CT remained at a low level. Recovery of BMD in AN seems to be a slow process. On the other hand, they noted a correlation between final BMI and final BMD in patients for whom the duration of follow-up was >11 months, but not when follow-up was <11 months.

These studies suggest that bone mass recovery is not complete, despite weight recovery and recovery from the disease. However, these results have not always been confirmed, and some authors have not found significant long-term differences in BMD between patients and controls. In a recent systematic review of 19 studies, the authors confirmed that weight gain and/or weight restoration in adolescent females with AN is associated with BMD stabilisation during the first year of follow-up, and that significant improvements can be achieved in the long term (after 16-month follow-up). However, more research is needed to confirm the apparent association between long-term (30 months) normal-weight maintenance and menses resumption and 80%–100% normalisation of the BMD of the lumbar spine and whole body, respectively.

**TREATMENT**

**Non-drug treatment**

Weight recovery and resumption of menses

Weight recovery seems to be crucial for increasing bone mass, but is not always sufficient for total recovery of the latter, as previously mentioned. In a previous study, we found that resumption of menses was a strong predictor of bone mass gain in the spine, but not in the hip, where weight recovery appeared to be the main predictor. Patients who regained weight and resumed menses after 1 year of follow-up had the highest increase in spine and hip BMD at 2 years. On the other hand, in those whose weight remained low and who were still amenorrhoeic, bone loss persisted (spine: 4%±6.3% vs −1.9%±5.6%; p=0.008; hip: 3%±7.1 vs −3.7%±10; p=0.04).

In a 3-month refeeding programme involving 55 patients with AN, the authors reported an increase in hip and spine BMD of +2.6%±3.5% and +1.1±3.6%, respectively, with BMI >17.5 kg/m² in all patients. Twenty-five of the patients were followed up for 1 year. In those patients whose BMI fell below 17.5 kg/m², hip BMD decreased significantly, while in those who maintained a BMI >17.5 kg/m², spine and hip BMD increased over 15 months (+4.8%±6.2% and +7.1±12.1%, respectively).

Weight regain is accompanied by a significant increase in bone formation markers (osteocalcin, bone alkaline phosphatase, P1NP) and the normalisation of bone resorption marker (NTX, CTX) levels. Hotta et al. also reported that BMI >16.4 kg/m² correlated positively with an increase in BMD. Castro et al. also described a decrease in spine and femur BMD of 2.1% and 1.3%, respectively in anorexic patients with BMI <19 kg/m² and amenorrhoea. At the same time, in patients with BMI >19 kg/m² and resumption of menses, spine and femur BMD increased significantly.

Physical activity

The findings in the literature are contradictory. While physical activity is necessary to acquire and maintain peak bone mass in adults, its protective role against osteoporosis in anorexic patients is still a matter of debate. Assessing physical activity is also very difficult in this population, in which hyperactivity is not rare. For some authors, physical activity increases cortical BMD, while for others it has no effect, regardless of level of physical activity, and could even have a deleterious effect. In another study by Bolton et al., the authors reported that exercise intensity, rather than duration, had an effect on spine BMD, and that intense activity led to a decrease in spine BMD compared with moderate or no activity. Of course, in the most serious cases, high levels of physical activity are not recommended.
Drug treatment

Calcium and vitamin D

In most studies, no correlation was found between calcium or vitamin D intake and BMD in anorexic patients.\(^1\)\(^2\)\(^3\)\(^4\) While vitamin and calcium supplementation seems essential, especially in deficient patients, it is not sufficient to reverse bone loss.

Oestrogens

Despite the association between anorexia and oestrogen deficiency, and the strong correlation between bone loss and duration of amenorrhoea, the efficacy of oestrogen-progestin (OP) therapy on bone mass has generally not been demonstrated in the literature. It is worth pointing out that, in most studies, oestrogen intake was achieved by OP contraceptive treatment. Seeman et al\(^4\) reported an improvement in lumbar spine BMD after 30 months of OP therapy in pill form compared with a control group, but the values were still significantly lower than in the control group. Moreover, no effect on femoral neck BMD was reported. In a randomised study, Klibanski et al\(^5\) investigated the efficacy of oral OP therapy associated with calcium supplementation in 48 anorexic patients. In the treatment group (n=22), 16 patients received hormone replacement therapy (Premarin and Provera), and six patients received an contraceptive pill/oral hormone replacement therapy (Premarin and Provera), which activate osteoclasts, and (2) increasing TGFβ and osteoprotegerin, which inhibit osteoclast differentiation and activation. However, the role of oestrogens in bone formation is minor, and in anorexia the main mechanism of bone loss is the uncoupling of bone remodelling, with an increase in bone resorption and, to some extent, a decrease in bone formation. Others have reported the suppression of IGF-1 secretion by high doses of oestrogens contained in oral oestroprogestins.\(^6\)

Finally, it is important to highlight the compliance and tolerance issues associated with such treatments in these patients, which lead to the administration of highly random doses, which could also explain the failure of these therapies.

Testosterone

Lower levels of testosterone have been described in AN and have been associated with low BMD. However, in a randomised, double-blind study in women with AN, transdermal testosterone was found to have no effect on BMD at a dose targeted to keep testosterone levels within the normal range.\(^7\)

IGF-1

In anorexic patients, several authors have reported a deficiency in IGF-1, a hormone involved in bone growth through its stimulating effect on osteoblasts. As such, some authors felt that it would be of interest to investigate the impact of IGF-1 treatment on BMD. In a randomised study involving 60 patients, Grinspoon et al\(^8\) compared the efficacy of treatment with IGF-1 alone (30 µg/kg subcutaneously two times per day), IGF-1 combined with oestrogens (ethinyl oestradiol), oestrogen treatment alone, and no treatment. The evaluation lasted 9 months. A significant increase in total bone mass was found in the IGF-1 treatment groups compared with placebo (1.1%±0.5% vs −0.6%±0.8%; p=0.05). Only the combined IGF-1 and oestrogen treatment group showed a significant increase in spine BMD compared with the control group (1.8%±0.8% vs −1%±1.3%; p=0.05). However, at other sites, there was no significant increase in BMD in response to IGF-1 treatment, whether alone or combined, compared with placebo. This study therefore suggests that IGF-1 treatment may play a role in preventing bone loss in these patients, but further work is needed to confirm these data and to specify the doses to be administered.

Bisphosphonates

Bisphosphonate (BP) treatment is not recommended in young women due to its teratogenic side effects in animal models at high doses. They can cross the blood-barrier and lead to foetal hypocalcaemia. In women with the potential to regain fertility, contraception is recommended during and after treatment. However, two BPs (alendronate and risedronate) have been approved by the FDA (Food and Drug Administration) for treatment

The failure of oestrogen treatment can be explained by its mode of action, which is essentially based on (1) inhibiting bone resorption by suppressing the secretion of certain cytokines, such as interleukin 1 (IL-1), IL-6, TNFα and PGE2, which activate osteoclasts, and (2) increasing TGFβ and osteoprotegerin, which inhibit osteoclast differentiation and activation. However, the role of oestrogens in bone formation is minor, and in AN the main mechanism of bone loss is the uncoupling of bone remodelling, with an increase in bone resorption and, to some extent, a decrease in bone formation. Others have reported the suppression of IGF-1 secretion by high doses of oestrogens contained in oral oestroprogestins.
of premenopausal osteoporosis in patients with steroid-induced osteoporosis. There are some studies on the use of BPs in AN patients in the literature. In 15 female anorexic patients with osteoporosis (mean age: 16.8±1.6 years) (vs 17 controls), alendronate (10 mg/day) combined with vitamin and calcium supplementation resulted in a significant increase in BMD (spine: 3.5±4.6% vs 2.2±6.1%; femoral: 4.4±6.4% vs 2.3±6.9%). However, the authors found no additional benefits of this treatment for the patients, who had regained weight and resumed menses. Thus, while alendronate treatment did not lead to the findings of Shibli-Rahhal et al and found a 6–10% increase in spine BMD after 6 months of teriparatide, as well as an increase in serum P1NP levels in the first draft. BC amended and modified the draft. IL wrote the first version of the draft that was checked by BC.

**CONCLUSION**

Bone loss in AN occurs at an early stage, is severe, and carries a non-negligible risk of fracture. Its underlying mechanisms are little known and probably multifactorial. Duration of AN and amenorrhoea seem to play an important role. Therapeutic management is difficult and calls for multidisciplinary approaches. Treatment with OP contraceptive pills or hormone replacement therapy seems to be ineffective. Weight recovery and resumption of menses are essential for the proper development of BMD during AN. Although weight restoration may be the most effective treatment for restoring BMD in AN, most of the patients in the studies reported in the literature exhibited non-significant changes in BMI throughout the study duration. This finding confirms the need for alternative pharmacological interventions in this population, and the importance of early detection and management of these patients.

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**REFERENCES**

1 Smink FRI, van Hoeken D, Hoek HW. Epidemiology, course, and outcome of eating disorders. *Curr Opin Psychiatry* 2013;26;543–8.

2 American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*, 5th edn. DSM-V. Arlington: American Psychiatric Publishing, 2013.

3 Robinson L, Aldridge V, Clark EM, et al. A systematic review and meta-analysis of the association between eating disorders and bone density. *Osteoporos Int* 2016;27;1953–66.

4 Legroux-Gerot I, Vignau J, D’Herbomez M, et al. Evaluation of bone loss and its mechanisms in anorexia nervosa. *Calcif Tissue Int* 2007;81;174–82.

5 Soyka LA, Grinspoon S, Levitsky LL, et al. The effects of anorexia nervosa on bone metabolism in female adolescents. *J Clin Endocrinol Metab* 1999;84;4489–96.

6 Misra M, Klibanski A. Anorexia nervosa and bone. *J Endocrinol* 2014;221;R163–76.

7 Fazeli PK, Klibanski A. Effects of anorexia nervosa on bone metabolism. *Endocr Rev* 2018;39;895–910.

8 Viapiana O, Gatti D, Dalle Grave R, et al. Marked increases in bone mineral density and biochemical markers of bone turnover in patients with anorexia nervosa gaining weight. *Bone* 2007;40;1073–7.

9 Grinspoon S, Thomas E, Pitts S, et al. Prevalence and predictive factors for regional osteopenia in women with anorexia nervosa. *Ann Intern Med* 2000;133;790–4.

10 Zipfel S, Seibel MJ, Löwe B, et al. Osteoporosis in eating disorders: a follow-up study of patients with anorexia and Bulimia nervosa. *J Clin Endocrinol Metab* 2001;86;5227–33.

11 Vestergaard P, Emborg C, Steving RK, et al. Fractures in patients with anorexia nervosa, bulimia nervosa, and other eating disorders—a nationwide register study. *Int J Eat Disord* 2002;32;301–8.
Lucas AR, Melton LJ, Crowson CS, et al. Long-term fracture risk among women with anorexia nervosa: a population-based cohort study. Mayo Clin Proc 1999;74:972–7.

Legroux-Gérot I, Vignau J, Collier F, et al. Factors influencing changes in bone mineral density in patients with anorexia nervosa-related osteoporosis: the effect of hormone replacement therapy. Calcif Tissue Int 2008;83:315–23.

Hotta M, Shibasaki T, Sato K, et al. The importance of body weight history in the occurrence and recovery of osteoporosis in patients with anorexia nervosa. Eur J Endocrinol 1998;139:276–83.

Misra M, Klibanski A. Anorexia nervosa and its associated endocrinopathy in young people. Horm Res Paediatr 2016;85:147–57.

Soga LA, Moti M, Frenchman A, et al. Abnormal bone mineral accrual in adolescent girls with anorexia nervosa. J Clin Endocrinol Metab 2002;87:4177–85.

Baskaran C, Misra M, Klibanski A. Effects of anorexia nervosa on the endocrine system. Pediatr Endocrinol Rev 2017;14:302–11.

Drábkin A, Rothman MS, Wartanee E, et al. Assessment and clinical management of bone disease in adults with eating disorders: a review. J Eat Disord 2017;5:42.

Legroux-Gérot I, Vignau J, Biver E, et al. Anorexia nervosa, osteoporosis and circulating leptin: the missing link. Osteoporos Int 2010;21:1715–22.

Stöving RK, Vignon J, d’Herbomez M, et al. Predictive factors of change in BMD at 1 and 2 years in women with anorexia nervosa: a study of 146 cases. Osteoporos Int 2012;23:2855–61.

Misra M, Miller KK, Cord J, et al. Relationships between serum adipokines, insulin levels, and bone density in girls with anorexia nervosa. J Clin Endocrinol Metab 2007;92:2464–92.

Legroux-Gérot I, Vignau J, Viltart O, et al. Adipokines and bone status in a cohort of anorexic patients. Joint Bone Spine 2019;86:95–101.

Dhanty PJ, van der Eerden BCJ, van der Velde M, et al. Ghrelin and unacylated ghrelin stimulate human osteoblast growth via mitogen-activated protein kinase (MAPK)/phosphoinositide 3-kinase (PI3K) pathways in the absence of GHS-R1a. J Endocrinol 2006;188:37–47.

Fukushima N, Hanada R, Teranishi E, et al. Ghrelin directly regulates bone formation. J Bone Miner Res 2005;20:790–8.

Fazeli PK, Bредеди ля MA, Misra M, et al. Preadipocyte factor-1 is associated with marrow adiposity and bone mineral density in women with anorexia nervosa. J Clin Endocrinol Metab 2010;95:407–13.

Fazeli PK, Bредеди ля MA, Freemantle L, et al. Marrow fat and preadipocyte factor-1 levels decrease with recovery in women with anorexia nervosa. J Bone Miner Res 2012;27:1864–71.

Ecklund K, Vignon J, Miller KK, et al. Effects of estrogen administration on trabecular bone loss in young women with anorexia nervosa. J Clin Endocrinol Metab 1999;84:2056–63.

Misra M, Miller KK, Grieco KA, Mulder J, et al. Osteoporosis treatment increases bone density in adolescent girls with anorexia nervosa. J Clin Endocrinol Metab 1995;80:898–904.

Golden NH, Lanzkovska J, Schebendach J, et al. The effect of estrogen-progestin treatment on bone mineral density in anorexia nervosa. J Pediatr Adolesc Gynecol 2002;15:135–43.

Misra M, Katz KD, Miller KK, et al. Physiologic estrogen replacement increases bone density in adolescent girls with anorexia nervosa. J Bone Miner Res 2011;26:2430–8.

Howgate DJ, Graham SM, Leonidou A, et al. Bone metabolism in anorexia nervosa: molecular pathways and current treatment modalities. Osteoporos Int 2013;24:407–21.

Miller KK, Meenanagh E, Lawson EA, et al. Effects of risedronate and low-dose transdermal testosterone on bone mineral density in women with anorexia nervosa: a randomized, placebo-controlled study. J Clin Endocrinol Metab 2010;95:207–13.

Robinson L, Aldridge V, Clark EM, et al. Pharmaceutical treatment options for low bone mineral density and secondary osteoporosis in anorexia nervosa: a systematic review of the literature. J Psychosom Obstet Gynaecol 2017;38:87–97.

Golden NH, Iglesias EA, Jacobson MS, et al. Alendronate for the treatment of osteopenia in anorexia nervosa: a randomized, placebo-controlled trial. J Clin Endocrinol Metab 2005;90:3179–85.

Miller KK, Griece KA, Mulder J, et al. Effects of risedronate on bone density in anorexia nervosa. J Clin Endocrinol Metab 2004;89:3903–6.

Fazeli PK, Wang IS, Miller KK, et al. Teriparatide increases bone formation and bone mineral density in adult women with anorexia nervosa. J Clin Endocrinol Metab 2014;99:1322–9.

Shibli-Rahhal A, McCormick L. Teriparatide treatment of osteoporosis in a patient with anorexia nervosa. Eat Weight Disord 2013;18:229–31.

Sienkiewicz E, Magkos F, Aronis KN, et al. Long-term metreparatide treatment increases bone mineral density and content at the lumbar spine of lean hypoleptinemic women. Metabolism 2011;60:1211–21.

Hebebrand J, Milos G, Wabitsch M, et al. Clinical trials required to assess potential benefits and side effects of treatment of patients with anorexia nervosa with recombinant human leptin. Front Psychol 2019;10:769.