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Review

Bone disease in anorexia nervosa

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ABSTRACT

Anorexia nervosa is a serious psychiatric disorder accompanied by high morbidity and mortality. It is characterized by emaciation due to self-starvation and displays a unique hormonal profile. Alterations in gonadal axis, growth hormone resistance with low insulin-like growth factor I levels, hypercortisolemia and low triiodothyronine levels are almost universally present and constitute an adaptive response to malnutrition. Bone metabolism is likewise affected resulting in low bone mineral density, reduced bone accrual and increased fracture risk. Skeletal deficits often persist even after recovery from the disease with serious implications for future skeletal health. The pathogenetic mechanisms underlying bone disease are quite complicated and treatment is a particularly challenging task.

Key words: Anorexia nervosa, Bone disease, Fractures

INTRODUCTION

Anorexia nervosa constitutes a psychiatric disorder characterized by serious morbidity and mortality, displaying the highest mortality rates among mental disorders. Recently, with the publication of the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), there has been a revision of diagnostic criteria for the disease, which include caloric restriction relative to requirements leading to serious underweight, intense fear of gaining weight and distorted body image.[1] Amenorrhea has been excluded from the criteria in the revised version of DSM; nevertheless, all studies concerning female patients with anorexia nervosa have until now included amenorrheic subjects.

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The lifetime prevalence of anorexia nervosa in the general population is estimated at between 0.3% and 0.9% in women, while it is less than 0.3% in men. It primarily affects adolescent girls and young women, although anorexia nervosa has occasionally been described in pediatric patients as well as in elderly women.[2] The incidence of anorexia nervosa rose steadily especially during the '70s and '80s, while it has remained stable over the last two decades. It is currently rising again among adolescent girls (15 to 19 years old), possibly reflecting a trend towards earlier diagnosis.[3]

The etiology of this eating disorder remains obscure, but there is a clear genetic basis. In a large

Swedish twin study, it was demonstrated that heritability accounted for 56% of the liability for anorexia nervosa, with barely 5% of it being attributed to a shared environment.[4] Certain traits during childhood have been associated with higher risk of developing the disease, such as mental rigidity, obsessive behavior and perfectionism.[5]

ENERGY HOMEOSTASIS AND ENDOCRINE ALTERATIONS

In the course of the progression of anorexia nervosa, a series of alterations in energy homeostasis and certain endocrine changes occur (Table 1), most of them possibly reflecting an adaptive response to malnutrition in an attempt to retain energy reserves.

Patients with anorexia nervosa exhibit a unique body composition phenotype with an extremely low percentage of body fat, as compared with healthy women with similar body mass index (BMI).[6] Leptin is primarily produced by fat tissue, reflecting energy stores.[7] In patients with anorexia nervosa, leptin levels are very low and correlate to BMI[8-12] in a linear manner, an association that is lost at very low BMI values.[8] Adiponectin is an adipocytokine with an important role in energy homeostasis and insulin sensitivity. In patients with anorexia nervosa, adiponectin levels have been found higher than in matched controls,[13-15] albeit not invariably.[9,16] Insulin[9] and amylin (a peptide that is co-secreted with insulin by β-cells)[17] levels are also reduced, whereas ghrelin (an orexigenic peptide secreted primarily by the oxyntic cells of the stomach) levels are elevated, as compared with normal controls.[18-20] Food ingestion does not lead to the normally observed reduction in ghrelin levels.[21] In addition, patients with anorexia nervosa display high fasting peptide YY (PYY) levels (an anorexigenic, gut-derived peptide which is secreted in response to food ingestion),[22] which remain elevated even after an increase in body weight,[23] indicating a possible causative role of PYY in this eating disorder. Conversely, fasting gastric inhibitory polypeptide (GIP) levels (a peptide secreted from K-cells in the duodenum in response to food ingestion) are low and glucagon-like peptide-2 (GLP-2) levels (a peptide secreted by L-cells of the distal jejenum, ileum and colon) are similar to those of healthy controls.[17]

Table 1. Major energy homeostasis and hormonal alterations in patients with anorexia nervosa

Leptin	↓
Insulin	↓
Ghrelin	↑
PYY	↑
GIP	↓
Amylin	↓
GLP-2	↔
Estrogens	↓
Testosterone	↓
DHEAS	↔ or ↓
GH	↑
IGF-I	↓
Cortisol	↑
T3	↓
TSH	↔ or ↓

Amenorrhea was a diagnostic criterion for anorexia nervosa until the latest revision of DSM. Amenorrhea in patients with anorexia nervosa is of hypothalamic origin[24,25] and is due to a regression of the LH secretory pattern to prepubertal or pubertal standards.[26] The mediator between low energy stores and impaired hypothalamic function is probably leptin,[27,28] although there is evidence that ghrelin might have an independent impact on LH pulsatility.[29,30] Hypogonadotropic hypogonadism has also been described in male patients, together with low testosterone levels[31] and relatively low gonadotropin levels.[32] Female anorectics likewise exhibit low testosterone levels,[33] while dehydroepiandrosterone sulfate (DHEAS) levels have been found either normal[33,34] or low.[35]

High growth hormone (GH) levels correlating negatively with BMI are observed in patients with anorexia nervosa.[36-39] Nevertheless, insulin-like growth factor-I (IGF-I) levels are consistently low, in correlation with BMI,[37,40-42] indicating resistance to GH action. Moreover, administration of pharmacological doses of GH is unable to induce an increase in IGF-I levels, further establishing a state of GH resistance.[43]

Hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis with high plasma and urine cortisol levels, along with abnormal overnight dexamethasone

suppression test, have also been described,[34,44,45] while hypercortisolemia may be associated with the severity of depressive symptoms or reduced appetite drive.[46,47]

Triiodothyronine (T3) levels are low[48-50] with a simultaneous increase in reverse T3 levels,[49] while thyroid-stimulating hormone (TSH) usually remains within normal limits,[48,49] creating a hormonal profile resembling the sick euthyroid syndrome. Thyroxine (T4) may also be decreased,[48,50] albeit with normal free thyroxine index (FTI).[51] Delayed patterns of TSH response to thyrotropin-releasing hormone (TRH) stimulation have also been described,[49] suggesting an additional central adaptation to starvation.

From a teleological point of view, almost every hormonal alteration mentioned above constitutes an adaptive response to emaciation. Reproduction, an energy consuming process, is halted as well as all anabolic processes, while there is a reduction in basal metabolic rate. Moreover, the increase in GH and cortisol promotes gluconeogenesis and lipid mobilization in order to attain adequate glucose levels.

However, many of these adaptive mechanisms can produce a negative effect on bone physiology (Figure 1), as will be discussed later.

CHARACTERISTICS OF BONE DISEASE

Bone disease is a common finding in patients with anorexia nervosa and includes a possible im-

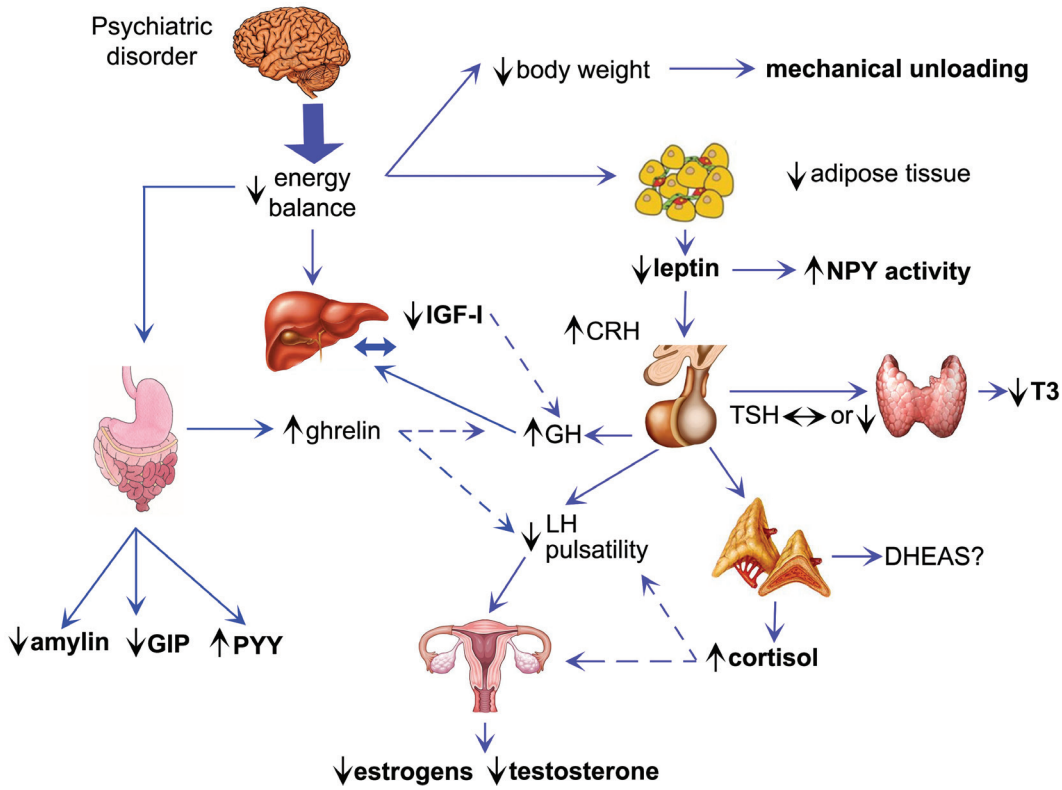

Figure 1. Mechanisms of adaptive alterations in energy homeostasis and hormonal profile in anorexia nervosa.

→ impact - - → possible impact ⟷ resistance in action

Reduced energy balance results in altered secretion of gastrointestinal peptides and in a reduction in body weight and body fat. Low leptin levels affect the secretory pattern of LH, leading to hypogonadotrophic hypodonadism. Increased CRH results in hypercortisolemia and GH resistance results in low IGF-I levels. T3 levels decrease.
[GIP: gastric inhibitory polypeptide, PYY: peptide YY, NPY: neuropeptide Y, CRH: corticotropin releasing hormone, GH: growth hormone, IGF-I: insulinlike growth factor I, TSH: thyroid-stimulating hormone, T3: triiodothyronine, DHEAS: dehydroepiandrosterone sulfate, LH: luteinizing hormone].

pact on linear growth, reduced bone mineral density (BMD), changes in bone turnover and structural and microarchitectural alterations leading to increased fracture risk.

There has been some concern that anorexia nervosa might influence the potential to reach target height. Accelerated growth occurs mostly during puberty in the year preceding menarche and girls diagnosed with anorexia nervosa during puberty are at increased risk for delayed menarche, which might have an impact on growth. On the other hand, IGF-I is of paramount importance to normal bone growth during puberty.[52] Many studies have demonstrated diminished height in girls and boys suffering from anorexia nervosa,[53-55] suggesting that up to 14% of patients are below the 5th percentile for height.[53] However, Prabhakaran et al found that young anorectic girls were taller than age matched controls and that duration of disease correlated negatively with height.[56]

Incomplete catch-up growth has also been described,[54,57] albeit with short duration of follow-up. Data regarding height after the age of 18, when adult height has presumably been reached, are also inconsistent. Modan-Moses et al[55] demonstrated that young girls with anorexia nervosa have decreased height at diagnosis after weight recovery but also at the age of 18, whilst Rozé et al[58] found that after the age of 19, girls who had been diagnosed before the age of 13 and before menarche achieved a median height above target height. However, a percentage of girls (36%) were unable to reach target height. Inconsistency of findings might be attributed to differences in disease duration, severity, age at onset and the degree of restoration of body weight.

Reduced BMD is a fairly common finding in patients with anorexia nervosa. BMD is reduced by at least 1.0 SD at one or more skeletal sites in 92% of adult patients and by at least 2.5 SD in 38% of them,[59] while half of adolescent girls have a lumbar spine (LS) z-score below -1 and 21% of them have a z-score below -2.[60] Male patients are also subject to bone disease and 75-78.3% of them exhibit LS z-scores below -1.[61]

Adult women with anorexia nervosa display reduced BMD at all skeletal sites as compared with healthy controls,[59,62,63] a reduction already observed by the first year of diagnosis.[64] Moreover, in the event that they fail to restore normal weight, they experience further decrease in BMD by an annual rate of 2.6% at the LS and 2.4% at the hip.[65] There is a positive correlation between body weight, BMI and BMD at all skeletal sites,[59,63,64] while duration of amenorrhea is correlated with LS BMD deficits.[66,67] Age at diagnosis constitutes another important prognostic factor. Women diagnosed before the age of 18 demonstrate lower BMD values than women diagnosed later, irrespective of the duration of amenorrhea.[67] This finding is consistent with diminished bone accrual during adolescence, the crucial time for optimal bone acquisition.

Adolescent girls with anorexia nervosa display low BMD values at both the LS and the hip.[68,69] Furthermore, due to a reduction in bone accrual, as compared to normal controls, their BMD z-scores drop steadily over time.[70] Late menarche and longer disease duration are negative prognostic factors for bone disease in these patients.[71]

DXA scans provide areal BMD measurements which rely largely upon bone size, and decreased bone size has been described in patients with anorexia nervosa.[72,73] However, volumetric BMD is not influenced by bone size variations and has been found invariably diminished in both adult and adolescent patients.[62,73-77]

Moreover, there is evidence that despite adequate treatment and weight gain, complete recovery from bone disease might not be achieved,[78-80] although this finding has not always been confirmed.[81]

Bone metabolism is highly dependent on a delicate balance between bone resorption and formation. During adolescence, there is an increase in markers of both resorption and formation, compatible with normal bone accrual. In adolescent girls suffering from anorexia nervosa, a decrease in both phases of bone turnover has been observed,[70] as well as a correlation between bone turnover suppression and BMI values.[82] Data concerning bone turnover in adult women with anorexia nervosa are contradictory. Uncoupling, with increase in bone resorption and decrease in bone formation,[83,84] increase in bone resorption with intact bone formation[85] and normal bone turnover[86] have all been described.

An increase in OPG and RANKL levels, accompanied by a reduction in OPG/RANKL ratio, has been observed in adolescent females.[82] On the other hand, sclerostin levels in adolescents appear similar to those of healthy controls,[87] indicating that suppression of bone formation in the underweight state is not mediated through a decrease in Wnt signaling, although other important proteins involved in the Wnt pathway have not yet been studied in patients with anorexia nervosa.

Apart from deficits in BMD, bone disease in patients with anorexia nervosa includes several structural defects that result in impaired mechanical properties of the skeleton.[75,88,89] Reduced cortical thickness at the radius, which is correlated with disease duration and age at onset,[76] has been described in both adolescent[75] and adult[76] anorexic females. Moreover, hip structural analysis has demonstrated lower bone cross-sectional area (CSA) and wider endocortical diameter, indicating reduced cortical thickness, both at the femoral shaft and neck.[89] Similar findings have been described at the hip region of adolescent boys suffering from the disease.[88]

Bone microarchitecture alterations can lead to increased fragility and propensity to fractures independent of BMD values.[90] Several studies, using high resolution pQCT (HRpQCT) and Flat Panel volume CT [technology similar to HRpQCT, albeit with lower resolution (150 μm vs. 82 μm)], report such alterations in patients with anorexia nervosa, including reduced trabecular number,[62,76,77] decreased trabecular thickness[62,74] and increased trabecular separation[62,74,76,77] as well as increased cortical porosity,[75] which might all contribute to an increase in fracture risk. Indeed, finite element analysis data have demonstrated reduced stiffness and failure load.[75,77] There is evidence that such alterations might also be related to disease duration.[6]

Divasta et al, in a case series, demonstrated that patients with anorexia nervosa do not have an increased risk for asymptomatic vertebral fractures;[91] however, the follow-up period was quite short (18 months). Another case series by Rigotti et al[92] indicated increased fracture risk in patients with anorexia nervosa, compared to that expected for the age-matched normal population; nevertheless, sample size was small.

As mentioned above, patients with anorexia nervosa may suffer permanent skeletal damage, which can imply higher fracture risk, even many years after diagnosis. Indeed, in larger epidemiological studies it has been demonstrated that patients with a lifetime history of anorexia nervosa have an increased risk for both vertebral and nonvertebral fractures,[93] even after recovering weight.[93,94] The increase in fracture risk ranges between 1.98[94] and 2.9[93] and it is already prevalent by the first year of diagnosis,[94] increasing steadily with age, while classic osteoporotic fractures (of the distal forearm, spine and proximal femur) are more frequent many years after diagnosis.[93]

PATHOGENESIS OF BONE DISEASE

The underlying mechanisms responsible for skeletal disease in anorexia nervosa are quite complex and not as yet fully elucidated. A combination of alterations, adaptive to malnutrition, possibly interacts to produce negative effects on bone metabolism, primarily by affecting bone formation and to a lesser degree bone resorption (Figure 2).

Estrogens play a major role in skeletal homeostasis. They decrease bone resorption, while they seem to have a positive independent effect on bone formation.[95-97] Postmenopausal osteoporosis is attributed to the increased bone resorption caused by the reduction of estrogen levels and hypogonadism constitutes a major cause of secondary osteoporosis in the young.[98] Nevertheless, amenorrhea is not the only mechanism of bone loss in anorexia nervosa. Indeed, while women with hypothalamic amenorrhea, but with normal BMI, exhibit lower LS and hip BMD as compared with controls, women with anorexia nervosa have even lower BMD values, indicating that other factors contribute to bone disease.[99]

Androgens, apart from being aromatized to estrogens, have direct effects on osteoblast differentiation and proliferation.[100] In women with anorexia nervosa, there is a positive correlation between androgen (testosterone and DHEAS) levels and BMD,[33] while in adolescent boys, LS BMD is correlated with testosterone levels.[31]

Hypercortisolemia has deleterious effects on bone strength. Cortisol acts on osteoblasts and osteocytes

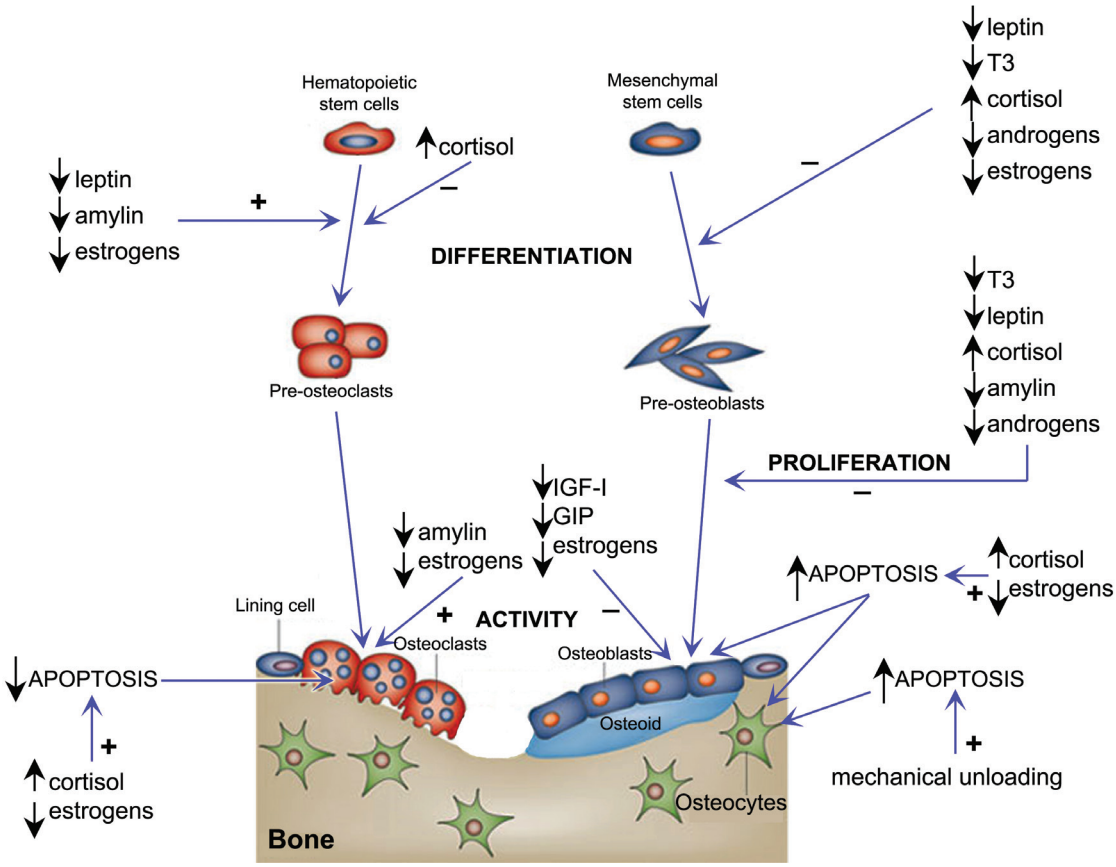

Figure 2. The effect of adaptive alterations on bone microenvironment. Bone formation is significantly affected in anorexia nervosa. Endocrine alterations decrease the differentiation, proliferation and activity of osteoblasts, while they enhance osteoblasts' and osteocytes' apoptosis. On the other hand, an increase in the differentiation and activity of osteoclasts, along with a reduction in their apoptosis, results in increased bone resorption.

The effect of increased NPY activity, adiponectin and SSRIs use is not presented for editing reasons.

directly, enhancing their apoptosis,[101] while it reduces both osteoblast and osteoclast formation.[102] However, it increases the lifespan of osteoclasts[103] leading to a temporary increase in bone resorption. Both endogenous hypercortisolism, as in Cushing's syndrome, and use of oral glucocorticoids have been associated with a significant increase in fracture risk.[104,105] In patients with anorexia nervosa there is a negative correlation between hypercortisolemia and bone formation markers, whereas there is no association between cortisol levels and bone formation in healthy controls.[45] Moreover, 12-hours overnight mean serum cortisol levels correlate negatively with LS and hip BMD.[46]

IGF-I enhances bone formation through its action on mature osteoblasts,[106] and circulating levels of IGF-I are of paramount importance for the preservation of cortical bone mass.[107] IGF-I levels in patients with anorexia nervosa are positively correlated with BMD[99] and negatively correlated with microarchitecture deficits, irrespective of BMI levels.[62] Moreover, low IGF-I levels are associated with reductions of bone formation markers,[41] while even small IGF-I elevations are associated with increases of bone turnover markers.[70]

T3 acts on osteoblasts regulating their differentiation, proliferation and apoptosis by direct and indirect mechanisms.[108-110] Hypothyroidism is associated with prolonged bone turnover[111] and with increased fracture risk.[112,113] The contribution of thyroid axis alterations to anorexia nervosa bone disease is currently unclear.

There is a clear association between BMI and

BMD as well as the risk for fractures. Postmenopausal women with low BMI have lower BMD values than women with higher BMI and are also characterized by more rapid bone loss.[114] Up to 40% of young women with constitutional thinness (healthy women with BMI values <16.5 Kg/m^2) display significantly lower BMD values compared to young, healthy, normal-weight women. Moreover, these women also exhibit reduced tibial and radial cortical thickness and impaired trabecular bone parameters in the distal tibia.[6] Finally, BMI has been associated with fracture risk, with a significant increase in fracture risk at BMI values below 20 Kg/m^2 and remaining fairly stable at BMIs between 25 Kg/m^2 - 35 Kg/m^2. This increase is particularly significant for hip fractures, even after adjusting for BMD.[115]

Increased mechanical loading leads to positive changes in bone mass and geometry,[116-118] while unloading such as during regional or systemic immobilization leads to bone loss.[119-121] Moreover, weight loss following gastric bypass surgery can lead to a reduction of BMD, especially at the hip region,[122,123] a predominantly weight-bearing site. Mechanical unloading is accompanied by increased RANKL expression.[124] Osteocyte apoptosis is a prerequisite for the initiation of bone resorption and for bone loss in the event of disuse or mechanical unloading.[124,125] Osteocyte apoptosis results in enhanced osteoclastogenesis, possibly through increased RANKL expression and increased RANKL/OPG ratio.[124]

Wnt signaling is important for skeletal responses to loading.[126] Sclerostin seems to mediate unloading-associated bone loss,[127] which can be prevented with administration of a sclerostin antibody.[128] It is postulated that upregulation of SOST following unloading leads to decreased bone formation by repressing the Wnt pathway.[127] In humans, unloading has been associated with increased serum sclerostin levels[129,130] correlating negatively with bone formation markers.[129] Diet induced weight loss results in an increase in sclerostin levels that is attenuated by exercise training.[131] In patients with anorexia nervosa sclerostin levels have been found similar to normal controls;[87] however, evaluation was performed in the underweight state and there are currently no prospective data concerning sclerostin levels during the weight loss period. On the other hand, patients with anorexia nervosa are often engaged in excessive exercise which might be protective against sclerostin increments.

Reductions in body lean mass have been described in patients with anorexia nervosa,[62,75,132,133] although not invariably.[74,77,134] Moreover, decreased calculated skeletal muscle mass has been demonstrated,[133] as well as alterations in muscle structure and function,[135-137] even in subjects who are physically active.

Published data regarding leptin's action on bone physiology are somewhat contradictory. Leptin stimulates the differentiation of stromal cells to osteoblasts,[138] increases proliferation of osteoblasts and inhibits osteoclastogenesis, without affecting mature osteoclasts.[139] Moreover, systemic administration of leptin to adult mice results in reduced bone fragility.[139] Conversely, leptin-deficient and leptin receptor-deficient mice, despite displaying an obese and hypogonadal phenotype, are characterized by high bone mass caused by increased bone formation.[140] This phenotype is reversed by intracerebroventricular infusion of leptin, which, in wild type mice, causes bone loss.[140] Based on the above experimental data, a central inhibitory and a peripheral stimulatory effect of leptin on bone metabolism have been suggested. Studies in humans evaluating leptin levels in relation to skeletal health have also come to conflicting conclusions, indicating either a beneficial role of leptin[141,142] or a detrimental one.[143,144] In women with anorexia nervosa, low leptin levels have been correlated with lower LS and hip BMD,[74] as well as with microarchitecture alterations, even after adjusting for BMI levels.[62]

In vitro studies have demonstrated the expression of both adiponectin and its receptors in bone forming cells, as well as in osteoclasts, suggesting a direct role of adiponectin in skeletal physiology.[145,146] Adiponectin has been found to affect osteoblastogenesis either positively[147] or negatively,[146] while suppressing osteoclastogenesis.[147] It is possible that locally produced adiponectin exerts more differential effects on bone than circulating adiponectin.[146] Although data regarding the effects of adiponectin on BMD in humans are largely inconsistent, there is enough evidence to hypothesize a negative correlation between circulating adiponectin levels and BMD.[148] A negative association between adiponectin levels

and BMD has also been described in patients with anorexia nervosa.[149]

The system of neuropeptide Y (NPY), PYY and Y receptors is a major regulator of energy homeostasis. There is growing evidence that it is also important in bone metabolism, especially through binding to the Y2 receptor. Y2 knockout mice (Y2-/-) are characterized by increased cancellous bone volume, with increased trabecular number and thickness.[150] Selective deletion of Y2 hypothalamic receptors induces the same skeletal phenotype, indicating that the regulation of bone mass is based on a central mechanism.[150]

NPY knockout mice (NPY-/-) display higher cancellous bone volume and higher cortical volume and thickness. In contrast, NPY over-expression in the arcuate nucleus leads to weight gain and tibial BMC reductions through a decrease in osteoblastic activity.[151] Moreover, NPY intracerebroventricular infusion induces bone loss.[140] Leptin constitutes an important regulator of NPY activity and low levels of leptin lead to enhanced hypothalamic NPY expression.[140] It is postulated that low levels of leptin may hinder cortical bone formation through NPY signaling.[152]

There is evidence that PYY regulates skeletal physiology through binding mainly to Y2 receptors. Studies on PYY mutant mice have so far arrived at contradictory conclusions. PYY knockout mice have been found to demonstrate reduced BMD, low trabecular bone volume and impaired mechanical strength.[153] Moreover, female PYY(-/-) mice showed a greater sensitivity to ovariectomy-induced bone loss.[153] However, enhanced osteoblastic activity with greater cancellous bone mass has also been described,[154] while PYY over-expression has been associated with reduced osteoblastic and enhanced osteoclastic activity.[154] In anorexia nervosa, high circulating levels of PYY have been associated with lower BMD, mainly in the LS,[22] and with reduced bone turnover markers in adolescent patients.[155]

Amylin enhances proliferation of osteoblasts[156] and inhibits osteoclastic activity and osteoclastogenesis,[157] while systemic administration in adult mice increases skeletal mass.[158] Amylin levels in patients with anorexia nervosa are positively correlated with hip BMD, even after adjusting for percentage of body fat mass.[17]

GIP enhances osteoblasts' function.[159] GIP receptor knockout mice (GIPR-/-) exhibit decreased bone size, mainly due to a reduction in bone formation,[160] while GIP administration prevents the bone loss associated with ovariectomy.[161] However, in patients with anorexia nervosa no association between GIP levels and BMD values could to date be demonstrated.[17]

Experimental data suggest that ghrelin, apart from stimulating GH release, may also exert direct effects on bone metabolism. Ghrelin directly stimulates osteoblasts, increasing their proliferation and differentiation.[162,163] Moreover, ghrelin infusion leads to increased BMD;[163] however, ghrelin knockout models present with unaltered bone metabolism.[164] In healthy adolescent girls, a correlation between ghrelin secretion and BMD has been observed, independent of body composition, the GH-IGF-I axis, cortisol and estradiol, a correlation that is not observed in adolescent girls with anorexia nervosa,[165] indicating that ghrelin probably does not play a major role in the skeletal status of these patients.

Although the use of psychotropic medication has not proved wholly successful in anorexia nervosa, up to 53% of patients receive some kind of psychiatric regimen, with selective serotonin reuptake inhibitors (SSRIs) being the most widely used.[166] SSRIs have been associated with accelerated hip bone loss in postmenopausal women,[167] lower hip BMD in aged men[168] and double risk for fragility fractures in men and women over 50 years old.[169] Moreover, there is evidence that SSRIs use during childhood might have deleterious effects on bone mineral accrual.[170] SSRI treatment in growing mice led to abnormal bone accrual due to pathological osteoblastic activity that was dose-dependent and more pronounced at weight-bearing sites.[171] The role of SSRI treatment in anorexia nervosa bone disease remains unknown.

Adequate calcium and vitamin D intake is considered necessary for normal bone accrual. Daily consumption of 1300 mg calcium and 600 IU vitamin D are recommended for adolescents and 1000 mg calcium and 600 IU vitamin D for young adults, respectively.[172] Although malnourished, a high proportion of anorectic patients are consuming calcium and multivitamin supplements.[173] As a result, adolescent patients display from similar[174] to higher vitamin D levels[60] compared to age and race matched controls.

TREATMENT OF BONE DISEASE

Treatment of bone disease in patients with anorexia nervosa is often a rather difficult task. Restoration of normal weight is of great importance, though mostly difficult to sustain due to a high propensity for relapse into disordered eating behavior. Various therapeutic options have been evaluated but have proved only modestly effective (Table 2).

Adequate weight gain induces the reversal of all adaptive hormonal alterations. Leptin levels invariably rise in response to weight gain[8,11,175] soon after initiation of refeeding,[11] in a manner parallel to increases of total body fat.[175] A minimum amount of leptin is required for normal menstruation but resumption of menses does not depend solely on leptin.[10] Weight gain does not always lead to restoration of menses,[10,176,177] perhaps due to a delay of the gonadal axis in responding to increasing leptin levels or because restoration of all endocrine axes is required for normal gonadal function. IGF-I levels rise quickly after refeeding[41] and weight gain leads to normalization of IGF-I and GH levels.[178] Urinary free cortisol (UFC), midnight cortisol levels and dexamethasone suppression test all return to normal,[44,45] while T3 levels gradually rise to normal levels and reverse T3 levels drop.[49]

Weight gain results in the restoration of the abnormal bone turnover in adult women with anorexia nervosa, namely through an increase of bone formation and a decrease of bone resorption,[176,179,180] the latter being observed especially in women who also experience resumption of menses,[177] reflecting the role of estrogens in the suppression of bone resorption. In adolescent girls, weight gain results in an increase of bone formation, which occurs shortly after initiation of refeeding,[181,182] and is coupled with a parallel increase of bone resorption.[70]

Weight gain also has beneficial effects on BMD, although these may be different between adult and adolescent patients given the expected bone accrual during adolescence.

In adult women, weight gain leads to a rapid increase in LS[176,177,179] and hip[65,177,179] BMD, already observed by the first months of weight restoration.[177] Both women with and without resumption of menses experience BMD improvement,[177] although it seems that weight gain constitutes a major factor for hip BMD, while, for LS BMD, resumption of menses is also required.[65] However, despite weight gain, deterioration of BMD has also, although rarely, been described.[183]

Table 2. Summary of the most important RCTs for the treatment of bone disease in patients with anorexia nervosa

Author / year	Intervention	Duration	N	Age	Outcome
Klibanski et al, 1995[71]	oral HRT / observation	18 months	48	16-42	↔ LS BMD
Strokosch et al, 2006[195]	triphasic OCP / placebo	~12 months	112	11-17	NS change in BMD vs placebo
Misra et al, 2011[196]	transdermal estradiol or ehtinylestradiol / placebo	18 months	110	12-18	↑ LS + hip BMD z-scores vs placebo
Bloch et al, 2012[197]	DHEA / placebo	6 months	26	17-47	NS change in BMD vs placebo
Gordon et al, 2002[198]	DHEA / OCP	12 months	61	14-28	↔ LS BMD, ↑ hip BMD NS vs placebo
DiVasta et al, 2012[199]	DHEA + OCP / placebo	18 months	80	13-27	↑ BMD LS + hip + wholebody vs placebo
Golden et al, 2005[202]	alendronate / placebo	12 months	32	12-21	↑ BMD LS + hip NS vs placebo
Miller et al, 2011[204]	risedronate + testosterone / risedronate / testosterone/ placebo	12 months	77	18-45	Risedronate: ↑ LS + ↑ hip BMD vs placebo. Testosterone NS effect
Grinspoon et al, 2002[206]	rhIGF-I + OCP / rhIGF-I / OCP / placebo	9 months	60	18-38	rhIGF-I: ↑ LS BMD vs placebo. OCP NS effect rhIGF-I + OCP ↑> rhIGF-I ↑

RCTs: randomized controlled trials, N: number of patients, HRT: hormone replacement therapy, OCP: oral contraceptive pill, DHEA: dehydroepiandrosterone, rhIGF-I: recombinant insulin-like growth factor I, NS: non significant.

In adolescent girls, results have been somewhat contradictory. Complete catch-up, with LS BMD values similar to normal controls, has been described in young girls with small duration of amenorrhea who manage to restore normal weight for two years.[184] Misra et al have demonstrated that restoration of both weight and menses can lead to rates of BMD very similar to those of healthy adolescents, although weight gain alone was not sufficient to produce such an effect.[185] On the other hand, Compston et al demonstrated that despite weight gain, girls with very low baseline BMI do not display any improvement in BMD values in any skeletal site, irrespective of restoration of menses.[182] A possible explanation for this finding could be that even though these girls experienced significant weight gain, they failed to achieve normal BMI levels.

Physical activity is known to produce positive effects on bone density and geometry.[116-118] However, although many patients with anorexia nervosa exercise regularly, there is some concern about the safety of exercise in these patients due to the hazard of further weight loss. Physical activity has been associated with improved bone status in most cross-sectional studies of anorexia nervosa patients, especially at the hip region.[186-188] Nevertheless, there is a correlation between the intensity of the exercise and its effect on BMD, indicating that moderate weight-bearing might be protective, whereas strenuous exercise might be deleterious for bone health.[189-191] Moreover, while physical activity seems to be safe and probably protective against bone loss in most patients, it can have detrimental effects in severely ill subjects.[191] Prospective studies evaluating the effect of optimal exercise intervention on bone health in patients with anorexia nervosa are warranted.

Most cross-sectional and observational studies suggest that the use of oral contraceptives in patients with anorexia nervosa is not associated with beneficial effects on BMD[59,184,192] and that their use may attenuate the positive effects of weight gain.[65] However, a possible protective role against continuing bone loss has also been implied,[64] mainly for the LS.[73,186]

Results from prospective interventional studies have also been rather disappointing. In a single-arm trial, Muñoz et al[193] demonstrated that oral estrogen treatment for one year in adult women had no positive effects on LS BMD, despite small weight increases. Similar findings were described by Golden et al[194] in an open, non-randomized, controlled trial. The addition of oral contraceptive pills to standard treatment had no impact on LS or hip BMD changes, as compared to standard treatment alone, after one year of follow-up. In an open, randomized, controlled trial, Klibanski et al[71] evaluated the effects of oral contraceptive pills on LS BMD based on simple observation for 18 months. None of the groups demonstrated any significant BMD changes, nor was there any difference between the two groups. However, in post-hoc analysis, there was a difference in BMD change in a subset of patients with lower BMI values (BMI <70% of normal). The use of oral contraceptives in this subgroup led to the preservation of BMD, as compared with the no intervention group, who experienced further bone loss. Disappointing outcomes were further confirmed in a double blind, randomized, placebo-controlled trial by Strokosch et al.[195] Administration of an oral contraceptive pill had no effect on hip BMD as compared with placebo, while a transient superiority of the OCP on LS BMD after the 6th cycle of administration was observed, which was no longer significant at the end of the study. Misra et al[196] described encouraging findings in a double blind, placebo-controlled trial using "physiological" doses of estrogen replacement in adolescent girls. Skeletally immature girls were given escalating doses of ethinyl-estradiol to mimic the gradual increase of estradiol levels observed during normal puberty, while skeletally mature girls were given transdermal 17β-estradiol to avoid further IGF-I suppression caused by oral estrogens. Patients on estrogen replacement displayed higher increases in both LS and hip z-scores as compared with placebo. Furthermore, they exhibited similar rates of increase as compared with healthy adolescents of similar skeletal maturation.

In a 3-month single arm study,[35] it was demonstrated that oral DHEA administration can lead to increases in bone formation and decreases in bone resorption, although, due to its short duration, the study was unable to establish any beneficial effects on BMD. In a 6-month double blind, placebo controlled trial, Bloch et al[197] studied the effects of 100 mg daily oral DHEA administration on BMD and bone

turnover markers. There was no evidence of positive effect on BMD; nevertheless, there was a decrease in bone resorption markers, while bone formation did not change. Gordon et al[198] in a double blind, randomized trial compared the administration of 50 mg DHEA daily to the administration of an oral contraceptive pill for 12 months. There was no change in either treatment group in LS BMD. However, a significant increase in hip BMD, albeit similar in both treatment groups, was observed, which correlated with weight gain and increases in IGF-I levels. More encouraging findings were described by DiVasta et al[199] in an 18-month double blind, randomized, placebo-controlled trial evaluating the efficacy of the co-administration of 50 mg DHEA daily with an oral contraceptive pill. The dual treatment resulted in the preservation of BMD at all skeletal sites (LS, hip, whole-body), while patients in the control group experienced further bone loss and the difference between the two groups was statistically significant. Moreover, a positive effect of the dual therapy on hip structural and mechanical properties was also demonstrated using Hip Structural Analysis.[200]

Although there is some concern about the safety of bisphosphonate use in women of reproductive age, this class of medication has been widely used in premenopausal osteoporosis. Etidronate, alendronate and risedronate have all been used in patients with anorexia nervosa.

Nakahara et al[201] compared the administration of etidronate to calcium and alfacalcidol and to placebo in a 3-month study. Etidronate use was associated with increases of tibial speed of sound (SOS), similar to that observed with calcium and alfacalcidol, but significantly higher than placebo. In a double blind, randomized, placebo-controlled trial, Golden et al[202] evaluated the administration of daily doses of 10 mg alendronate for one year in adolescent patients with low BMD values. Alendronate use resulted in significant BMD increases in both LS and hip. However, there was no significant difference between groups. In a small, non-controlled trial, administration of risedronate was associated with a significant increase in LS BMD, unrelated to body weight changes.[203] Miller et al in a partially blind, randomized, placebo-controlled study evaluated the administration of risedronate and testosterone in adult women with low BMD.[204] Risedronate resulted in a significant increase in LS and hip BMD as compared with placebo, while testosterone did not have any effect on BMD but was associated with an increase in lean mass.

In a 6-day trial in adult patients with anorexia nervosa, administration of 30 μg/kg/bid of recombinant IGF-I was associated with increases in bone formation, without affecting bone resorption, while higher doses resulted in a simultaneous increase of bone resorption.[83] Similar findings were described in young adolescents,[205] suggesting that lower IGF-I doses could have a purely anabolic impact on bone. Grinspoon et al evaluated the administration of recombinant IGF-I alone or in combination with an oral contraceptive pill in a randomized, placebo-controlled trial.[206] The use of OCP alone did not affect LS BMD, in contrast to the use of IGF-I which resulted in a significant increase in LS BMD. However, patients who received the combination displayed higher increases, implying that the combination of an anabolic and an antiresorptive agent could be a promising option for patients with anorexia nervosa.

Iketani et al[207] in a non-randomized trial evaluated the efficacy of the daily administration of 45 mg of menatetrenone (vitamin K2) for a mean of 0.9 years in young women with anorexia nervosa, versus no treatment. Both groups displayed a reduction in LS BMD, which, however, was significantly smaller in the treatment arm.

The inadequate response to treatment in anorexia nervosa bone disease is possibly due to the significantly altered bone formation. Anabolic treatment with teriparatide or IGF-I (alone or in combination with risedronate or transdermal estrogens) is currently under investigation.[208]

CONCLUSION

Anorexia nervosa can have deleterious effects on bone metabolism, especially during adolescence when bone accrual is a major determinant of peak bone mass. Complete recovery from bone disease is not universal and the increase in fracture risk is prevalent even years after treatment of the disease. Early recognition of skeletal deficits and proper prevention and treatment is of paramount importance.

Adequate weight gain remains the first line goal, although it is often difficult to achieve and preserve. Current treatment strategies for bone disease are not fully effective, but the combination of anabolic and antiresorptive agents seems a reasonable and promising choice. A multidisciplinary approach is a prerequisite for successful treatment.

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