Journal of Pediatric Endocrinology

Open Access

Austin Publishing Group

Review Article

Anorexia Nervosa and Bone Disease

Díez-Suárez A[1]*, Ruiz-Laña B[2] and Azcona-Sanjulián MC[2]

[1]Department of Psychiatry and Medical Psychology, Clinica Universidad De Navarra, Spain

[2]Department of Pediatrics, University of Navarre Hospital, Spain

***Corresponding author:** Díez-Suárez A, Department of Psychiatry and Medical Psychology, University of Navarre Hospital, Spain

Received: October 07, 2016; **Accepted:** November 15, 2016; **Published:** November 17, 2016

Abstract

Anorexia Nervosa (AN) is a psychiatric disorder with serious medical complications. AN affects 0.3% of young women and 0.1% of men. More than half of women and about a third of men with AN develop osteopenia or osteoporosis and their lifetime fracture prevalence is 60% higher than healthy women. Multiple factors are involved in bone disease in AN: nutrition, hormonal alterations (hypogonadism, growth hormone system alterations, adrenal axis modifications, thyroid axis modifications, alterations in appetite regulatory peptides, amylin and related peptides) and excessive exercise. Furthermore there are genetic factors that contribute to modify the risk of bone disease. All patients with AN should be assessed by DEXA at diagnosis and every 1-2 years depending on the results of the evaluation. Their calcium and vitamin D intakes should also be determined. The most effective way to normalize bone mass in patients with anorexia nervosa is to improve the state of malnutrition and gonadal function. Treatments that have shown to be effective in the treatment of low bone mineral density in AN are: oral contraceptives combined with IGF-1 or with DHEA, physiologic transdermal estrogen replacement, bisphosphonates and teriparatide.

Anorexia Nervosa

Definition and diagnostic criteria

Anorexia Nervosa (AN) is a psychiatric disorder characterized by abnormally low body weight secondary to food restriction, intense fear for gaining normal weight and distorted perception of body image, known as dismorphophobia. These patients reduce the amount of caloric intake and some of them also develop purgative behaviors, such as self-induced vomiting or taking drugs associated with weight loss as diuretics or laxatives. Although these purgative symptoms and the intense fear of gaining weight are shared with bulimia nervosa, patients with AN always show an abnormally low body weight, while individuals with bulimia typically are normal to above normal weight. About half of patients with AN develop symptoms of bulimia sometime during their illness. Most patients with AN increase their physical activity in order to lose weight.

People with AN develop serious medical complications. cardiovascular, gastrointestinal, dermatologic, hematologic, metabolic and endocrine symptoms are a direct result of the reduction of intake and consequent malnutrition. They show several hormonal changes due to hypothalamic dysfunction and malnourishment, which in most cases improve with the weight recovery. Bone disease, osteoporosis or osteopenia, is present in more than half of the patients with AN, especially if they are amenorrheic.

Patients with AN are a heterogeneous group regarding their psychiatric condition. Some of them show disordered eating behaviors without any other psychopathology and some other show complex disorders with serious comorbidities and high suicide risk. Mood, anxiety, psychotic and obsessive-compulsive disorders are more prevalent in patients with anorexia nervosa compared with general population. Most frequent psychiatric symptoms are depressed mood, irritability, social withdrawal and anxiety symptoms. These symptoms, mainly anxiety, usually worsen in relation to meal times and to the associated pressure from family and friends.

According to the new **Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5)** [1], to be diagnosed as having AN, patients must display:

A. Persistent restriction of energy intake relative to requirements leading to significantly low body weight, in the context of age, sex, developmental trajectory and physical health. Significantly low weight is defined as a weight that is less than minimally normal or for children and adolescents, less than that minimally expected.

B. Either an intense fear of gaining weight or of becoming fat or persistent behavior that interferes with weight gain, even though significantly low weight.

C. Disturbance in the way one's body weight or shape is experienced, undue influence of body shape and weight on self-evaluation or persistent lack of recognition of the seriousness of the current low body weight.

The main difference with the previous Edition of the DSM, the DSM-IV is that Criterion D, amenorrhea, defined as the absence of at least three menstrual cycles in women, has been removed in the DSM-5. Main reasons for this change were: there were many patients who met all other criteria of AN but not amenorrhea; it could be not be applied to several groups of women (pre-menarchal, postmenopausal or females taking oral contraceptives) or to males. However, amenorrhea is considered a factor risk of bone disease because women who develop it have poorer bone health than do women who fail to meet this criterion.

Some other modifications for A and B criteria in the DSM-5 regarding DSM-IV are described below:

Criterion A: The word "refusal" was omitted as this was considered as difficult to assess, pejorative, as it implies intention.

Citation: Díez-Suárez A, Ruiz-Laña B, Azcona-Sanjulián MC. Anorexia Nervosa and Bone Disease. J Pediatri Endocrinol. 2016; 1(2): 1010.

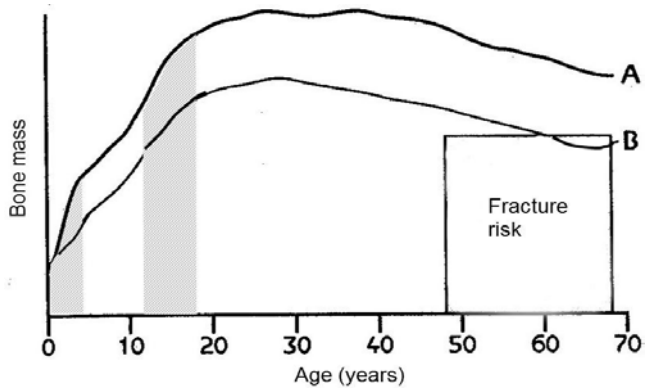

Figure 1: Bone mass acquisition.

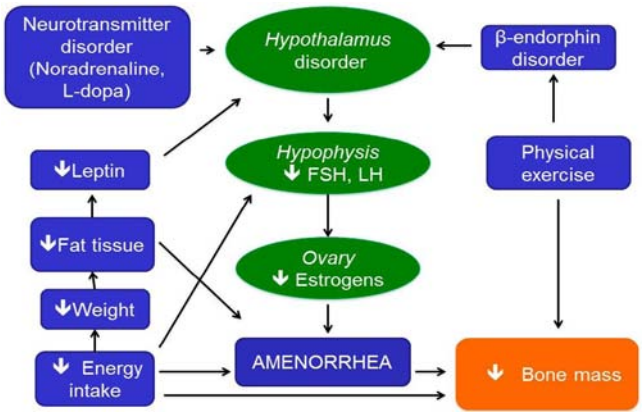

Figure 2: Factors that influence bone disease in patients with Anorexia Nervosa.
Abbreviations: FSH: Follicle Stimulating Hormone, LH: Lutein Stimulating Hormone.

The limit "85% of expected body weight" that appeared as a guidance in the DSM-IV disappears, to better capture low body weight for growing adolescents or patients who have lost significant weight but have not yet fallen that 85%, for example those who were previously overweight.

Criterion B: Considering that many patients with AN deny fear to gain weight, a clause to focus on behavior was added to clarify this point.

Subtypes of AN, restricting and binge-eating/purging type are maintained in DSM-5. The patient will be classified as having the binge-eating/purging type if he or she has engaged in recurrent episodes of binge eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics or enemas) during the past three months and diagnosed with the restricting type if he or she had not. Considering the significant cross-over between sub-types and resultant difficulty in specifying the subtype for the "current episode" of illness, DSM-5 recommends that the sub-typing be specified for the last 3 months.

Epidemiology

AN affects 0.3% of young women and 0.1% of men, while bulimia nervosa is more frequent, about 1% [2]. It is considered the third most common chronic illness in adolescents after asthma and obesity.

A two-fold increase in the incidence of AN has been described from 1930s to 1980s, mostly affecting females aged 15 to 24 years. [3,4]. The overall incidence rate of AN is around eight per 100,000 persons per year and remained stable during the 1990s, compared with the increase described in 1980s [3]. These data are obtained from primary care settings, due to the fact that only a minority of patients with eating disorders is treated in mental healthcare.

Etiology

During adolescence, the risk of developing AN and other eating disorders is higher because adolescents become more concerned about their body image and frequently start dieting. Considering that obesity is one of the main public health problems in developed countries, measures focused on weight reduction, such as dieting and physical exercise, are often recommended by doctors. Family or personal histories of obesity are described as risk factors for eating disorders [5]. Young women who diet moderately are six times more likely to develop an eating disorder than those who do not diet and those who diet at a severe level, show an 18-fold risk. This increased incidence is higher in girls with associated psychiatric conditions and lower in boys [6]. Pediatricians and primary care doctors should consider that physical exercise seems to be a less risky strategy for controlling weight in adolescents, mainly in female adolescents with psychiatric diseases.

Predisposing personality traits, such as introversion, immaturity, perfectionism, low self-esteem, insecurity, alexithymia and competitiveness, are considered risk factors [5]. Some other situations that may predispose to develop an eating disorder are: the habit of eating alone, the divorce of the parents and the influence of the teenage media [7].

Treatment of anorexia nervosa

Treatment of AN requires a multidisciplinary approach, including specialists in psychiatry, endocrinology, nutrition, pediatrics or physicians with enough experience in eating disorders. The main objective of treatment is to recover weight and menses. After performing a thorough physical exam and complete analysis, the first decision is whether the patient requires hospitalization or can be treated as outpatient. If electrolyte or hemodynamic complications are diagnosed, the first step is stabilization. Subsequently nutritional treatment begins by oral nutrition or by nasogastric tube if necessary. Family-based or cognitive-behavioral psychotherapy is required in order to reduce purging behavior, if any, dismorphophobia or erroneous cognitions about weight and food. The use of psychotropic drugs in AN does not improve the core symptoms of the disorder, but it may be useful in some cases to treat depressive symptoms or to reduce anxiety.

Osteoporosis

Osteoporosis is a systemic skeletal disorder characterized by a reduction of bone density and bone quality, which produces bone weakness and increases risk of fractures. Bone density is measured in grams of mineral per area of volume and it is determined in any given individual by peak bone mass and amount of bone loss. Bone quality refers to architecture turn-over, damage, accumulation and mineralization [8].

The World Health Organization has defined the diagnostic criteria for Osteoporosis in postmenopausal women on the basis of Bone Mineral Density (BMD) assessment measured by Dual Energy X-Ray Absorptiometry (DEXA). The difference between the bone mass of an individual and the ideal peak bone mass reached by a young adult is named T value and it is expressed in Standard Deviation (SD). Osteoporosis is defined as a BMD equal to -2.5 SD or below the peak value. If T value is between -2.5 and -1 SD, it corresponds to osteopenia and if it is above -1 SD it is considered to be normal [9,10].

Due to the continuous growth in bone size, in pediatric population it is necessary to adjust BMD according to the average values for age and sex. This value is named Z and it is expressed in SDS [8].

Morbidity

Based on the diagnostic criteria defined by the WHO, 22 million women and 5.5 million men were estimated to have osteoporosis in the European Union in 2010 [11]. It is more prevalent among women due to a loss of ovary function after menopause, although it also affects a large number of men and premenopausal women.

Osteoporosis causes more than 8.9 million fractures each year worldwide and over 33% of all those fractures occur in Europe. The most common are hip, spine, forearm and humerus fractures. At the age of 50 years, the probability of suffering one of these fractures is 22% and 46% in men and women, respectively [12].

Physiopathology

Osteoporosis has three main physio-pathological causes: 1) a failure to reach an optimal peak bone mass during development; 2) excessive bone resorption, causing architectural deterioration of the skeleton; 3) an inadequate formation response to increased resorption during bone remodeling [13] (Figure 1).

Reaching the best possible skeleton development during growth is probably one of the most important issues in order to maintain an adequate bone health. Women with a high peak bone mass are more protected against deterioration that occurs after menopause, when the loss of ovary function decreases bone strength due to excessive bone resorption and inadequate formation [14].

Patients with AN have several conditions that prevent them from achieving their optimal bone mass peak. The food restriction they suffer causes malnutrition and a low intake of nutrients, like calcium [15], vitamin D [16], phosphorus and magnesium, which are necessary for bone formation. In addition, the decreased energy input causes multiple hormonal changes which are focused on saving energy. These changes, such as high GH and low IGF-I levels, secondarily interfere with growth and maintenance of bone mass. Finally, the estrogen deficiency that women with AN develop, similar to postmenopausal women, cause bone mass decrease [17]. The age of onset ofthe anorexia nervosa is crucial: those who initiate food restriction before adulthood will have lower bone mass than those who start suffering AN later, despite having similar period of amenorrhea [18,19].

Diagnosis

Bone mass can be estimated using different radiological techniques, such as Dual Energy X-Ray Absorptiometry (DEXA) Digital Osteosonography, Magnetic Resonance (MRI), X-Ray, High-Resolution Peripheral Quantitative CT (HR-pQCT) and Computerized Tomography (CT). CT is not recommended in children due to its high radiation dose [20,21].

Hormonal and biochemical markers tested in blood and urine can help us in the assessment of bone metabolism. Bone biopsy would be the ideal diagnostic test; it would give us an accurate view of the mineralization and architecture of the skeleton. Nevertheless it is not used due to its invasiveness.

Dual Energy X-Ray Absorptiometry (DEXA)

The current state of the art for the evaluation of bone mineral density is Dual Energy X-Ray Absorptiometry (DEXA). It is based on the attenuation that suffers an X-Ray beam aimed to the bone of the patient. It determinates the density of a specific area (g/cm^2) usually from the lumbar vertebrae L2, L3 and L4 and the femoral neck. It is a very accurate technique, with a coefficient of variation less than 1%, emits low ionizing radiation and it takes 5-10 minutes.

Digital Osteosonography: Bone mineral density determination by ultrasound (Digital Osteosonography) has some advantages compared to other techniques: it is fast, cheaper, portable, emits no radiation and does not need expertise in image devices. Digital Osteosonography measures two parameters: ample dependent Speed of Sound (SOS) and Broadband Ultrasound Attenuation (BUA) [22]. SOS measures the speed of the sound through the bone (m/s). If bone density is high, the sound would be able to pass through it quickly and SOS will be high. On the contrary, if the bone tested is osteoporotic sound will pass through it slower and SOS will be low. BUA (dB/MHz) measures the absorption that sound suffers passing through the bone [23]. This parameter gives us information about the mineral density and the architecture of the bone. Low levels of BUA will indicate high bone mass.

However, its sensitivity and specificity is low compared to DEXA. In a group of adolescent survivors of bone tumors that we assessed for osteopenia, quantitative digital osteosonography showed low sensitivity (36.4%) for predicting osteopenia [24]. We also performed a study in 113 girls with eating disorders that showed decreased bone mass by DEXA and by digital osteosonography. In patients with anorexia nervosa, which have the lowest weight and Body Mass Index (BMI), bone mass values by osteosonography are higher compared to those obtained by DEXA. However, in the bulimia nervosa group, which was not malnourished, the opposite happened. These data suggest that digital osteosonography does not seem to be a method that can replace DEXA in patients with low BMI [25].

Magnetic resonance imaging: Magnetic Resonance Spectroscopy has been used recently to assess marrow fat content. Women with AN have increased marrow fat and the degree of fatty acids inversely correlates with bone mineral density, suggesting that saturated lipids may have negative effects on bone mineral density [26].

High-Resolution Peripheral Quantitative Computerized tomography (HR-pQCT): In the last 10 years, a new technique has emerged: High-Resolution Peripheral Quantitative CT (HR-pQCT). It is a fast non-invasive method for assessing bone architecture and volumetric Bone Mineral Density (BMD). The effective radiation dose is relatively low (effective dose 3 mSv) and does not involve radio sensitive organs.

Nevertheless, this is still a research device and there are not enough clinical studies to recommend it for daily clinical use [27,28].

Bone disease in anorexia nervosa

All patients with AN should be assessed by DEXA at diagnosis and every 1-2 years depending on the results of the evaluation. Their calcium and vitamin D intakes should also be determined. About 85% of patients with AN have osteopenia or osteoporosis [29,30] and their lifetime fracture prevalence is 60% higher than healthy women [30]. In our study, considering only the patients with AN, 62.5% had osteopenia and 10% osteoporosis [31].

About one third of males with a diagnosis of AN develop osteopenia or osteoporosis and this bone disease is related to higher duration of illness, lower BMI and low testosterone levels [17].

Factors Involved in Bone Disease in Anorexia Nervosa

Multiple factors are involved in bone disease in AN. These factors include: nutrition, hormonal alterations (hypogonadism, growth hormone system alterations, adrenal axis modifications, thyroid axis modifications, alterations in appetite regulatory peptides, amylin and related peptides) and excessive exercise. Furthermore, there are genetic factors that contribute to influence the risk of bone disease.

Nutrition

The effects of undernutrition on bone are independent of hypogonadism, because it has been observed that in conditions of hypogonadism which are not associated to under-nutrition, BMD is less affected than in AN. Weight recovery protects against further bone loss. However, AN may cause permanent deficits in BMD despite weight recovery [32].

The most important nutrients involved in bone formation are both vitamin D and calcium. In AN, some studies have demonstrated that calcium absorption is decreased and its excretion is increased [33]. However, other studies have not observed the same or even have found that more girls with AN than healthy girls met the Recommended Dietary Allowance (RDA) for calcium and vitamin D [16,29]. Therefore, the role of these nutrients in bone loss in anorexia nervosa is unclear.

Hormonal alterations

Hormonal abnormalities are very common in AN and involve multiple hypothalamic-pituitary pathways. Most hormonal changes are produced in response to starvation (Figure 2).

Hypothalamic-pituitary gonadal axis: hypogonadotropic hypogonadism is a characteristic finding in women with AN. The gonadal hormones, estrogen and testosterone have a very important role in bone architecture in combination with Growth Hormone (GH) and insulin like growth factor-1 (IGF-1), especially during pubertal period. Estrogen inhibits osteoclastic bone resorption and may have bone anabolic effects. They are responsible for the pronounced increase in bone mass accrual along adolescent years. Estrogen mediates this effect through suppression of several proinflammatory cytokines that stimulate osteoclast differentiation, such as Interleukin (IL)-1-beta, IL-6 and Tumoral Necrosis Factor -alpha (TNF-alpha). They also increase secretion of TNF-beta and osteoprotegerin, which suppress osteoclast activity and inhibit osteoblast apoptosis. In both females and males, aromatizations of androgen to estrogen are responsible for decreased bone resorption and testosterone has a direct antiresortive and bone anabolic effects [34].

There are also abnormalities in Gonadotropin Releasing Hormone (GnRH) which provoke changes in gonadotropin pulsatility and decrease estrogen levels [35]. With weight recovery the GnRHpulsatility normalizes. Decrease in testosterone [36] and dehidroepiandrosterone levels have been reported [37]. Low levels of testosterone have shown to predict low BMD [38]. Testosterone is aromatized to estrogen and thus inhibits bone resorption and may have independent anabolic effects.

Menarche is delayed in 35% of adolescents with AN. Duration of amenorrhea predicts the extent of low BMD [39].

Growth hormone-IGF-I axis

Nutritional-mediated resistance to GH is developed in AN. GH and IGF-I are bone anabolic and stimulate osteoblast differentiation and proliferation. Therefore low levels of IGF-I contribute significantly to the low bone mass in AN [40]. GH levels predict bone turnover markers in healthy adolescents, however this does not happen in AN, due to the resistance to GH effects both at the level of liver and bone [41].

Girls with AN have increased levels of GH and low levels of IGF-I. The elevated levels of GH are the consequence of both positive feedback on the GHRH/GH axis from the low IGF-I and ghrelin-stimulated GH secretion. Low IGF-I levels help minimize energy expenditure on growth. IGF-I levels are very sensitive to nutritional therapy. IGF-I is a positive predictor of bone density and bone turnover markers in girls with AN. Changes in IGF-I levels over one-year period are positively associated with changes in levels of bone turnover markers over the same period [29].

Hypothalamic-pituitary-adrenal axis

High cortisol levels stimulate osteoclastic bone resorption and inhibit osteoblast differentiation and action. They also have an inhibitory effect on the GH-IGF-I axis, calcium gut absorption and calcium renal excretion. In AN, cortisol secretory pulses frequency is increased. These high cortisol levels are also related to the decreased metabolic clearance of cortisol and to the activation of a stress response pathway by chronic undernutrition to maintain euglycemia. Despite the sustained hypercortisolemia, patients with AN do not appear clinically Cushingoid. There is a strong inverse correlation between high cortisol levels and low bone formation markers (osteocalcin and C-terminal propetide type 1 procollagen) in AN and also with BMD. Elevated cortisol levels decrease calcium absorption in the intestine, decrease osteoblast proliferation and inhibit GH secretion. Cortisol also may increase bone resorption indirectly, both by decreasing gonadotropin secretion and by increasing Parathyroid Hormone (PTH) receptor expression in osteoblasts [42].

Dehydroepiandrosterone (DHEA) is the adrenal precursor of most sex steroids, its levels are low in AN and are a predictor of decreased BMD and increased bone resorption [43].

Thyroid axis

Malnutrition secondary to starvation is accompanied by

characteristic changes in peripheral thyroid hormone values, which together described the sick euthyroid syndrome. In AN, T4 and T3 are low or low normal, TSH levels are normal and T3 reverse levels are elevated. This levels are low in order to decrease energy utilization [44]. It is possible that low levels of T3 and T4 contribute to decrease bone mass. These low levels are an adaptative and protective response in a state of chronic undernutrition and therefore should not be treated. With weight recovery T3 levels rise and reverse T3 decrease [45].

Appetite regulating hormones: leptin, ghrelin, PYY, adiponectin, other

Several studies have shown abnormalities in both anorexigenic and orexigenic hormones which are also implicated in the regulation of bone metabolism.

Leptin: is a fat derived hormone important in signaling energy availability and inhibiting appetite. Leptin is low in AN due to low levels of adipose tissue and is associated with low BMD [29] independent of the duration of amenorrhea [46]. Low leptin, levels are also related to worsened michroarchitectural parameters. The role of leptin in AN-induced bone loss is unclear. Low leptin levels are an adaptative mechanism to reduce anorexigenic inputs in AN and are thought to play a part in hypothalamic-pituitary ovarian, dysfunction. Weight recovery is associated with increases in leptin levels.

Ghrelin: It is an orexigenic peptide produced in the fundus of the stomach that stimulates secretion of GH and ACTH. It increases in conditions of energy deficit and correlates inversely with BMI and fat mass. Ghrelin also suppresses LH pulsatility [47]. Its levels are elevated in AN [48] and it is an important predictor of BMD at the spine and hip [49].

In vitro, ghrelin increases osteoblast proliferation [50]. Ghrelin receptors are present on osteoblasts and ghrelin administration increases the activity of these cells [50]. AN appears to be a state of ghrelin resistance, as the appetite-stimulating effect and the potential bone formation effects observed in normal-weight individuals are not observed in individuals with AN. Ghrelin is a positive predictor of bone density in normal-weight girls even after controlling for body composition, GH and cortisol levels, consistent with a bone anabolic role [49].

Peptide YY (PYY): PYY also known as peptide tyrosine or pancreatic peptide YY is an anorexigenic peptide secreted by L-cells of the colonic mucosa in response to food intake, which acts through the Y2 receptor to inhibit Neuropeptide Y (NPY) secretion and food intake. Its levels are elevated in AN [51] and low in obesity and inversely correlate with BMI and fat mass. PYY is and independent predictor of markers of bone turnover [52]. High PYY levels in AN are associated with low levels of bone turnover markers in adolescent girls. Therefore, it is possible that elevated levels of PYY in AN contribute to reduced bone mass.

Adiponectin: levels in AN have been reported to be higher, lower and similar to normal-weight individuals [53-54]. BMD has been shown to be inversely associated with adiponectin levels in adolescent girls with AN [52].

Amylin and related peptides

Peptide hormones including amylin, Glucose-Dependent Insulinotropic Polypeptide (GIP) and glucagon like peptide-2 (GLP-2), released immediately after nutrient intake, may be involved in the regulation of bone turn-over by stimulating bone formation and decreasing bone resorption [55]. In women with AN, serum amylin levels are significantly lower than in healthy controls and are a predictor of BMD [56].

Other hormones such as **oxytocine** have been associated with decreased BMD. In women with AN, overnight oxytocine levels are associated with decreased BMD as compared to normal-weight controls [57].

Physical activity

The role of physical activity in BMD in AN is not clear. A study reported that less than three hours per week of physical activity was a risk factor for low BMD. However, other studies have not demonstrated a relationship between physical activity and bone metabolism in AN. Low BMD in AN predisposes to fractures and therefore excess of exercise may increase risk of fractures [58].

Genetics

Bone mineral density is a complex quantitative trait with normal distribution in general population. It is genetically determined in 50-90% of the cases [59]. Variations in BMD are associated with polymorphisms in several genes [60]. Therefore, an anorectic patient will have a higher risk of osteoporosis if he or she is genetically predisposed to osteoporosis.

The Vitamin D Receptor (VDR) gene was the first to be proposed as a major locus for its genetic control of BMD. Several SNPs within the VDR gene are associated with variations in BMD and fractures [61]. Another important gene is the estrogen receptor gene, specifically alpha-estrogen receptor gene. Several polymorphic sites have been described in relation to BMD [62].

We performed a study determining VDR haplotypes in girls with eating disorders and found higher values of bone mass, at lumbar spine, in girls with aaTT haplotype for Apa I and Taq I markers tan girls with AAtt [25].

Treatment of Bone Disease in Anorexia Nervosa

The most effective way to normalize bone mass in patients with anorexia nervosa is to improve the state of malnutrition, since the increase in the percentage of body fat leads to recovery of gonadal function. Women who develop anorexia during adolescence have partial recoveries in their BMD after achieving normal weight, BMI and gonadal function, because they probably had not reached maximum bone mass peak. Approximately half of patients who develop AN do not restore their nutritional status and menses. This situation requires the development of effective treatments to improve osteoporosis in patients with AN.

As explained above, gonadal steroids and IGF-1 are decreased in patients with AN. Treatments that have proven to be effective in the treatment of low bone mineral density in AN are: oral contraceptives combined with IGF-1 or with DHEA, physiologic transdermal estrogen replacement, bisphosphonates and teriparatide.

The effects of supplementation of **calcium and vitamin D** in patients with AN remain unclear. They have shown beneficial effects on bone mass in healthy children and adolescents [63]. In a recent meta-analysis, patients with AN reported similar dietary vitamin D intake compared to healthy controls. However, 25-OH-D and 1,25OH-D levels were significantly lower in patients without supplementation and these levels normalized after supplementation with cholecalciferol [16]. Considering these results, it is convenient to administer calcium and vitamin D supplements to ensure proper apposition of minerals in bone tissue.

High **estrogen** doses given as an oral combination of estrogen and progesterone pills have not showed to improve BMD in several studies. However, physiologic estrogen replacement administered transdermally in adolescents with anorexia nervosa for 18 months, increased spine bone mineral density in spine and hip, even after controlling for age andweight changes over time [64]. In contrast to oral high dose estrogen, physiologic estrogen is not IGF-1 suppressive.

In patients with AN, short-term administration of **recombinant human (rh) IGF-I** in dose of 30-40 mcg/kg/dose twice a day is successful in significantly increasing levels of bone formation markers over this period [65]. The administration of human recombinant IGF-I (rh-IGF-I) produces an increase in bone mass in patients with AN and this effect is higher combining rh-IGF-I and oral contraceptives [66].

The administration of a combination of **DHEA** and estrogen/progestin has demonstrated to be superior to placebo in preserving skeletal health in a group of adolescents and adults with AN [67].

Bisphosphonates, like alendronate and risedronate, are analogs of pyrophosphate that inhibit bone resorption by osteoclasts. Administration in adolescents is not approved, because the anti-resorptive action remains for several years and may affect linear growth by damaging the epiphyseal plate. It also has teratogen effects, so its use in women of child bearing age is contraindicated [68]. In a group of adolescents with AN, alendronate did not improve BMD in spine [69]. However, risedronate increased bone mineral density in adult women with AN in a 12 month clinical trial [70,71]. This discrepancy between studies is explained by the differences in bone turnover according to age: bone resorption is increased in adults with AN, but reduced in adolescents. Currently, bisphosphonates are indicated only to treat patients with low BMD and associated fractures.

Teriparatide is a synthetic form of parathyroid hormone with anabolic properties approved for the treatment of osteoporosis in adult women. It is not allowed in children and young adults with open epiphyses, because it may increase the risk of bone tumors. In a recent placebo-controlled trial of adult women with AN, teriparatide increased lumbar and spine BMD in a higher percentage compared to the previously described treatments (10% in six months) [14].

Conclusions and Future Directions

Osteopenia is one of the most common complications of AN, about 85% of patients develop this bone disease and their risk of fractures is increased. Most of the patients develop eating disorders during adolescence and this period is critical for bone peak mass acquisition. Pediatricians, psychiatrists and primary care physicians should be aware of this situation, to improve prevention and early diagnosis. Although amenorrhea has been withdrawn as a diagnostic criterion of the latest DSM, the DSM-5, it is still considered a crucial risk factor for bone disease. Vitamin D and calcium intakes, vitamin D levels and determination of BMD should be performed in every patient with AN at diagnosis and subsequently. New radiologic techniques, such as ultrasound methods or High-Resolution Peripheral Quantitative Computerized tomography may facilitate this evaluation because they are shorter, cheaper and emit less radiation, compared to the traditional DEXA. Further studies should be performed about potential combinations of treatments that have shown effectiveness in osteoporosis in AN, as hormone replacement therapy, growth factors, bisphosphonates or teriparatide.

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. Washington, D.C. 2013.
2. Hoek HW, Hoeken VD. Review of the prevalence and incidence of eating disorders. Int J Eat Disord. 2003; 34: 383-396.
3. Hoek HW. Incidence, prevalence and mortality of anorexia nervosa and other eating disorders. Curr Opin Psychiatry. 2006; 19: 389-394.
4. Lucas AR, Beard CM, O'Fallon WM, Kurland LT. 50-year trends in the incidence of anorexia nervosa in Rochester, Minn.: a population-based study. Am J Psychiatry. 1991; 148: 917-922.
5. Gual P, Perez-Gaspar M, Martinez-Gonzalez MA, Lahortiga F, De Irala-Estevez J, Cervera-Enguix S. Self-esteem, personality, and eating disorders: baseline assessment of a prospective population-based cohort. Int J Eat Disord. 2002; 31: 261-273.
6. Patton GC, Selzer R, Coffey C, Carlin JB, Wolfe R. Onset of adolescent eating disorders: population based cohort study over 3 years. BMJ. 1999; 318: 765-768.
7. Martinez-Gonzalez MA, Gual P, Lahortiga F, Alonso Y, De Irala-Estevez J, Cervera S. Parental factors, mass media influences and the onset of eating disorders in a prospective population based cohort. Pediatrics. 2003; 111: 315-320.
8. Osteoporosis prevention, diagnosis and therapy. JAMA: the journal of the American Medical Association. 2001; 285: 785-795.
9. Lorentzon M, Cummings SR. Osteoporosis: the evolution of a diagnosis. J Intern Med. 2015; 277: 650-661.
10. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. WHO Technical Report Series.1994; 843: 1-129.
11. Svedbom A, Hernlund E, Ivergard M, Compston J, Cooper C, Stenmark J, et al. Osteoporosis in the European Union: a compendium of country-specific reports. Arch Osteoporos. 2013; 8: 137.
12. Strom O, Borgstrom F, Kanis JA, Compston J, Cooper C, Mc-Closkey EV, et al. Osteoporosis: burden, health care provision and opportunities in the EU: a report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch Osteoporos 2011: 6: 59-155.
13. Raisz LG. Pathogenesis of osteoporosis: concepts, conflicts, and prospects. J Clin Invest. 2005; 115: 3318-3325.
14. Fazeli PK, Wang IS, Miller KK, Herzog DB, Misra M, Lee H, et al. Teriparatide increases bone formation and bone mineral density in adult women with anorexia nervosa. J Clin Endocrinol Metab. 2014; 99: 1322-1329.
15. Welten D, Kemper HCG, Post GB, Van Staveren W. A meta-analysis of the effect of calcium and bone mass in Young and middle aged females and males. J Nutrition 1995; 125:2802-2813.

16. Veronese N, Solmi M, Rizza W, Manzato E, Sergi G, Santonastaso P, et al. Vitamin D status in anorexia nervosa: A meta-analysis. Int J Eat Disord. 2015; 48: 803-813.

17. Fazeli PK, Klibanski A. Bone metabolism in anorexia nervosa. Curr Osteoporos Rep. 2014; 12: 82-89.

18. Mehler PS, Brown C. Anorexia nervosa- medical complications. J Eat Disord. 2015; 3: 11.

19. Misra M, Klibanski A. Anorexia nervosa and bone. J Endocrinol. 2014; 221: 163-76.

20. Johnston CC, Slemenda CW, Melton LJ. Clinical use of bone densitometry. N England J Med. 1991; 324: 1005-1009.

21. Osteoporosis Prevention, Diagnosis and Therapy. NIH Consensus Statement Online. 2000; 17: 1-45.

22. Graafmans WC, Lingen AV, Ooms ME, Bezemer PD, Lips P. Ultrasound measurements in the calcaneus: Precision and its relation with bone mineral density of the heel, hip and lumbar spine. Bone. 1996: 19: 97-100.

23. Langton CM, Njeh CF, Hodgskinson R, Currey JD. Prediction of mechanical properties of the human calcaneus by broadband ultrasound attenuation. Bone. 1996; 18: 495-503.

24. Azcona C, Burghard E, Ruza E, Gimeno J, Sierrasesumaga L. Reduced bone mineralization in adolescent survivors of bone tumors: Comparison of Quantitative Ultrasound (QUS) and Dual Energy X-Ray Absorptiometry (DEXA). Journal of Pediatric Hematology/Oncology. 2003; 25: 297-302.

25. Diez-Suarez A, Azcona C, Patino A, Soutullo C, Graell M. Bone mass in children and adolescents with eating disorders. 43rd Annual Meeting of the European Society for Pediatric Endocrinology. Basel, sept 10-13 2004. Hormone Research. 2004; 63: 41.

26. Bredella MA, Fazeli PK, Daley SM, Miller KK, Rosen CJ, Klibanski A, et al. Marrow fat composition in anorexia nervosa. Bone. 2014; 66: 199-204.

27. Cheung AM, Adachi JD, Hanley DA, Kendler DL, Davison KS, Josse R, et al. High-Resolution Peripheral Quantitative Computed Tomography for the Assessment of Bone Strength and Structure: A Review by the Canadian Bone Strength Working Group. Curr Osteoporos Rep. 2013; 11: 136-146.

28. Link TM. Osteoporosis imaging: state of the art and advanced imaging. Radiology. 2012; 263: 3-17.

29. Soyka L, Misra M, Frenchman A, Miller K, Grinspoon S, Schoenfeld D, et al. Abnormal bone mineral accrual in adolescents girls with anorexia nervosa. J Clin Endocrinol Metab. 2002; 87:4177-4185.

30. Faje AT, Fazeli PK, Miller KK, Katzman DK, Ebrahimi S, Lee H, et al. Fracture risk and areal bone mineral density in adolescent females with anorexia nervosa. Int J Eat Disord. 2014; 47: 458-466.

31. Diez-Suarez, A. Valoracion de la masa osea y de sus marcadores geneticos en ninas y adolescentes afectas de trastorno de conducta alimentaria (Doctoral tesis). University of Navarra. Spain. 2004.

32. Misra M, Klibanski A. Anorexia nervosa and osteoporosis. Rev Endocr Metab Disord. 2006; 7: 91-99.

33. Abrams S, Silber T, Esteban N, Viera N, Stuff J, Meyers R, et al. Mineral balance and bone turnover in adolescents with anorexia nervosa. J Pediatr. 1993; 123: 326-331.

34. Michael HP, Vaananen HK, Hentunen TA. Estrogen and testosterone use different cellular path ways to inhibit osteoclasts and bone resorption. J Bone Miner Res. 2005; 20: 2224-2232.

35. Boyar R, Katz J, Finkelstein J, Kapen S, Weiner H, Weitzman E, et al. Anorexia nervosa. Immaturity of the 24-hour luteinizing hormone secretory pattern. New Engl J Med. 1974; 291: 361-365.

36. Miller KK, Grieco KA, Kianski A. Testosterone administration in women with anorexia nervosa. J Clin Endocrinol Metab. 2005; 90: 1428-1433.

37. Gordon C, Grace E, Emans S, Goodman E, Crawford M, Leboff M. Changes in bone turnover markers and menstrual function after short-term oral DHEA in young women with anorexia nervosa. J Bone Miner Res. 1999; 14: 136-145.

38. Miller KK, Lawson EA, Mathur V, Wexier TL, Meenaghan E, Misra M, et al. Androgens in women with anorexia nervosa and normal-weight women with hypotalamic amenorrhea. J Clin Endocrinol Metab. 2007; 92: 1334-1339.

39. Misra M, Aggarval A, Miller KK, Almazan C, Worley M, Soyka LA, et al. Effects of anorexia nervosa on Clinical, hematologic, biochemical and bone density parameters in community-dwelling adolescents girls. Pediatrics 2004; 114: 1574-1583.

40. Ohlsson C, Bengtsson B, Isaksson O, Andreassen T, Slootweg M. Growth hormone and bone. Endocr Rev. 1998; 19: 55-79.

41. Misra M, Miller K, Bjornson J, Hackman A, Aggarwal A, Chung J, et al. Alterations in growth hormone secretory dynamics in adolescent girls with anorexia nervosa and effects on bone metabolism. J Clin Endocrinol Metab. 2003; 88: 5615-5623.

42. Misra M, Miller K, Almazan C, Ramaswamy K, Lapcharoensap W, Worley M, et al. Alterations in cortisol secretory dynamics in adolescents with anorexia nervosa and effects on bone metabolism. J Clin Endocrinol Metab. 2004; 89: 4972-4980.

43. Zumoff B, Walsh BT, Katz JL, Levin J, Rosenfeld RS, Kream J, et al. Subnormal plasma dehydroisoandrosterone to cortisol ratio in anorexia nervosa: a second hormonal parameter of ontogenic regression. J Clin Endocrinol Metab. 1983; 56: 668-672.

44. Croxson MS, Ibbertson HK. Low serum Triodothyronine (T3) and hypothyroidism in anorexia nervosa. J Clin Endocrinol Metab. 1977; 44: 167-174.

45. Kiyohara K. Decreased thyroidal triodothyronine secretion in patients with anorexia nervosa: the influence of weight gain. BMJ. 1978; BMJ. 2: 526-528.

46. Legroux-Gerot I, Vignau J, Biver E, Pigny P, Collier F, Merchandise X, et al. Anorexia nervosa, osteoporosis and circulating leptin: the missing link. Osteoporos Int. 2010; 21: 1715-1722.

47. Vulliemoz NR, Xiao E, Xia-Zhang L, Germond M, Rivier J, Ferin M. Decrease in luteinizing hormone pulse frequency during a five-hour peripheral ghrelin infusion in the ovariectomized Rhesus monkey. J Clin Endocrinol Metab. 2004; 89: 5718-5723.

48. Tolle V, Kadem M, Bluet-Pajot MT, Frere D, Foulon C, Bossu C, et al. Balance in ghrelin and leptin plasma levels in anorexia nervosa patients and constitutionally thin women. J Clin Endocrinol Metab. 2003; 88: 109-116.

49. Misra M, Miller KK, Stewart V, Hunter E, Kuo K, Herzog DB, Klibanski A. Ghrelin and bone metabolism in adolescent girls with anorexia nervosa and healthy adolescents. J Clin Endocrinol Metab. 2005; 90: 5082-5087.

50. Maccarinelli G, Sibilia V, Torsello A, Raimondo F, Pitto M, Giustina A, et al. Ghrelin regulates proliferation and differentiation of osteoblastic cells. J Endocrinol. 2005; 184: 249-256.

51. Misra M, Miller K, Tsai P, Gallagher K, Lin A, Lee N, et al. Elevated peptide YY levels in adolescents with anorexia nervosa. J Clin Endocrinol Metab. 2006; 91: 1027-1033.

52. Misra M, Miller KK, Cord J, Prabhakaran R, Herzog DB, Goldstein M, et al. Relationships between serum adipokines, insulin levels and bone density in girls with anorexia nervosa. J Clin Endocrinol Metab. 2007; 92: 2046-2052.

53. Housova J, Anderlova K, Krizova J, Haluzikova D, Kremen J, Kumstyrova T, et al. Serum adiponectin and resistin concentrations in patients with restrictive and binge/purge form of anorexia nervosa and bulimia nervosa. J Clin Endocrinol Metab. 2005; 90: 1366-1370.

54. Tagami T, Satoh N, Usui T, Yamada K, Shimatsu A, Kuzuya H. Adiponectin in anorexia nervosa and bulimia nervosa. J Clin endocrinol Metab. 2004; 89: 1833-1837.

55. Clowes JA, Khosha S, Eastell R. Potential role of pancreatic and enteric hormones in regulating bone turnover. J Bone Miner Res. 2005; 20: 1497-1506.

56. Wojcik MH, Meenaghan E, Lawson EA, Misra M, Klibanski A, Miller KK.

Reduce amylin levels are associated with low bone mineral density in women with anorexia nervosa. Bone. 2010; 46: 796-800.

57. Lawson EA, Donoho DA, Blum JI, Meenaghan EM, Misra M, Herzog DB, et al. Decreased nocturnal oxytocine levels in anorexia nervosa are associated with low bone mineral density and fat mass. J Clin Psychiatry 2011; 72: 1546-1551.

58. Castro J, Lazaro L, Pons F, Halperin I, Toro J. Predictors of bone mineral density in adolescents with anorexia nervosa. J Am Acad Child Adolesc Psychiatry. 2000; 39: 1365-1370.

59. Flicker L, Hooper JL, Rodgers L, Kaymakei B, Green RM, Wark JD. Bone density determinants in elderly women: a twin study. J Bone Miner Res. 1995; 10: 1607-1613.

60. Nelson DA, Kleerekoper M. The search for the osteoporosis gene. J Clin Endocrinol Metab. 1997; 82: 989-990.

61. Gennari L, Meriotti D, De Paola V, Martini G, Nuti R. Update on the pharmacogenetics of the vitamin D receptor and osteoporosis. Pharmacogenomics. 2009; 10: 417-433.

62. Gennari L, Merlotti D, De Paola V, Calabro A, Becherini L, Martini G, et al. Estrogen receptor gene polymorphism and genetic of osteoporosis: a Huge review. Am J Epidemiol. 2005; 161: 307-320.

63. Cadogan J, Eastell R, Jones N, Barker ME. Milk intake and bone mineral acquisition in adolescent girls: randomised, controlled intervention. BMJ. 1997; 315: 1255-1260.

64. Misra M, KatzmanD, Miller KK, Mendes N, Snelgrove D, Russell M, et al. Physiologic estrogen replacement increases bone density in adolescent girls with anorexia nervosa. J Bone Miner Res. 2011; 26: 2430-2438.

65. Misra M, McGrane J, Miller KK, Goldstein MA, Ebrahimi S, Weigel T, et al. Effect of rhIGF-I administration on surrogate markers of bone turnover in adolescents with anorexia nervosa. Bone. 2009; 45: 493-498.

66. Grinspoon S, Thomas L. Miller K, Herzog D, Klibanski A. Effects of recombinant human IGF-I and oral contraceptive administration on bone density in anorexia nervosa. J Clin Endocrinol Metab. 2002; 87: 2883-2891.

67. Divasta AD, Feldman HA, Giancaterino C, Rosen CJ, Leboff MS, Gordon CM. The effect of gonadal and adrenal steroid therapy on skeletal health in adolescents and young women with anorexia nervosa. Metabolism. 2012; 61: 1010-1020.

68. Srivastava T, Alon US. The role of biphosphonates in diseases of childhood. Eur J Ped. 2003; 162: 735-751.

69. Golden NH, Iglesias EA, Jacobson MS, Carey D, Meyer W, Schebendach J, et al. Alendronate for the treatment of osteopenia in anorexia nervosa: a randomized, double-blind, placebo-controlled trial. Journal of Clinical Endocrinology and Metabolism. 2005; 90: 3179-3185.

70. Miller KK, Meenaghan E, Lawson EA, Misra M, Gleysteen S, Schoenfeld D, 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. 2011; 96: 2081-2088.

71. Soyka L, Grinspoon S, Levitsky L, Herzog D, Klibansky A. The effects of anorexia nervosa on bone metabolism in female adolescents. J Clin Endocrinol Metab. 1999; 84: 4489-4496.

Citation: Díez-Suárez A, Ruiz-Laña B, Azcona-Sanjulián MC. Anorexia Nervosa and Bone Disease. J Pediatri Endocrinol. 2016; 1(2): 1010.