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Bone Mass in Anorexia Nervosa and Thin Postmenopausal Women-Related Secondary Amenorrhea

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1. Introduction

Adolescence is a critical period because there are changes in both mental and physical conditions leading to adulthood. The consequence of acute or chronic deficiency of bone mineral accumulation during adolescence may lead to severe morbidity or precocious mortality (Loro et al., 2000; Bachrach, 2001; Steelman & Zeitler, 2001)

1.1 Bone mass acquisition in normal teenagers

The first three years of life seem to be very important in the skeleton bone mass apposition. The bone mineral density (BMD) increases during childhood, but the maximum increment occurs in the critical phase of growth, reaching a plateau at the end or after the puberty in girls as well as in boys (Theintz et al., 1992; Bachrach, 2001; Schoenau et al., 2001). Bone mass increases as the bone size increase. In females, BMD is increased rapidly after 11 years of age and reaches maximum at around the age of 13-14 years or quickly after menarche. Until the age of 18 years, about 90% of the peak bone mass has been acquired. At puberty, there is an acceleration of bone mineralization, especially of the trabecular bone and by the end of sex maturation it is more than twice as compared with that at the pubertal onset (Theintz et al., 1992; Bailey, 1999).

In general, the girls have a greater BMD than boys in the first half of the second decade of life. During the intermediate stage of puberty (Martin et al., 1997), the bone mineral content (BMC) and the bone thickness are lower in girls, thus predisposing women to a higher complication risk of reduced BMD (Baroncelli & Saggese, 2000). Nutrition, body weight and total body lean mass are determinants of the bone mass in adolescent girls. Calcium intake is essential for optimization of the bone mass acquisition in healthy pubertal adolescents (Garcia e Costa et al., 1995). The accumulation of calcium in the skeleton varies with the daily intake and 1200

mg of calcium is often recommended during adolescence (Theintz et al., 1992; Ilich et al., 1997; Moreira-Andrés et al., 1995). The body weight may determine the BMD in adolescents (Cheng et al., 1998). Physical activity is known to increase the axial bone mass at the puberty (Theintz et al., 1992; Ilich et al., 1997; Bailey, 1999; Moreira-Andrés et al., 1995)
The blood levels of the thyroid hormone, growth hormone (GH), sex steroids and IGFs, which are essentially important for the skeletal growth and development, are increased during puberty. Estrogens as aromatized in osteoblasts, stimulate the GH-IGF-1 axis and may decrease bone resorption by influencing the production and activation of TGF-β and reducing the IL-6 synthesis in the bone marrow stromal cells. (Kusec et al., 1998).

2. Body composition in anorexia nervosa

Manipulations of the diet may affect the bone development during puberty. A balanced nutrition and adequate calcium intake are essential for optimal bone growth and development (Martin et al., 1997). The prevalence of anorexia nervosa is increasing in several countries of the world including in Portugal (do Carmo et al., 1996a; do Carmo et al., 2001).
The endocrine dysfunction associated with anorexia nervosa and other eating disorders may involve multiple systems and mechanisms designed to preserve energy and protect essential organs. The most affected systems are the reproductive and skeletal.
The changes in neuroendocrine signals sensitive to satiety and food intake are essentially important to keep the balance between energy store and energy expenditure. These adaptive changes include the thyroid hormone, GH, and cortisol axes, as well as the gastrointestinal tract (do Carmo et al., 1996b; Warren, 2011).
The effects of exercise on BMD are complex and incompletely understood. In premenopausal women, the changes in BMD at the proximal femur and lumbar spine differ depending on the physical activity program. Physical exercise –related beneficial effects on the BMD may be lost in intensive exercise and subsequently results in a significant loss of bone mass. Weight loss, amenorrhea, anovulation and inadequate luteal phase are evident. The effects of amenorrhea on the BMD can be mediated through the loss of body fat mass (Robinson et al., 1995).
The loss of bone mass occurs with anorexia nervosa, hypothalamic amenorrhea and in ovarian deficiencies. Replacement of estrogen and progesterone does not seem to reverse the loss of the bone mass (Karlsson et al., 2000).

2.1 Hypoestrogenism and bone mass in anorexia nervosa

Hyperprolactinemia, excessive physical activity, intense psychological stress, malnutrition and anorexia nervosa cause functional deficiency of LHRH and subsequently leads to loss of bone mass (Hergenroeder et al., 1991). Decreased pulse amplitude and frequency in the early follicular phase cause a failure of folliculogenesis and the resulting deficiency of ovarian steroids subsequently leads to loss of the bone mass (Warren, 2011). Estrogen deficiency was proposed as the main factor contributing to low BMD in anorexia nervosa.
Moreover, the degree of the BMD has been shown to be related to the duration of amenorrhea (Bachrach et al., 1991; do Carmo et al., 1994). The BMD at the lumbar spine determined by various methods is reduced in adolescent girls with amenorrhea, as compared with those who have regular cycles. However, the significant difference in BMD is found to be reversed after body weight correction (Hergenroeder et al., 1991; Karlsson et al., 2000). In fact, the increase in BMD may precede the resumption of menses in anorexic patients (Bachrach et al., 1991).

Estrogen deficiency in anorexia nervosa is an important risk factor associated with the loss of bone mass and development of osteoporosis, while malnutrition, thinness and lack of IGF-1 increase the risk of osteoporosis by estrogen-dependent and independent mechanisms (Grinspoon et al., 1999; Karlsson et al., 2000).

2.2 Other hormonal factors

In eating disorders with weight loss and poor calcium intake/absorption, the loss of bone mass is closely correlated not only with the hypoestrogenism but also with the hypercortisolism and reduced levels of IGF-1. Hypercortisolism may exacerbate hypogonadism by inhibiting GH-IGF-1 axis, reduced bone formation and increased bone resorption thus contributing to the development of osteoporosis in young patients with anorexia nervosa (Hergenroeder et al., 1991; Steelman & Zeitler, 2001).

3. Effects of anorexia nervosa on the bone mass

Understanding of the modulating factors of the BMD during adolescence is essentially important.

3.1 Adolescence

Low bone mass, which frequently causes complication in anorexic adolescent girls, occurs in the critical stage of bone development. (Kooh et al., 1996; Bachrach et al., 1991). Anorexia nervosa in adolescents may influence the linear growth and the height of the individual. The results of a study have shown that patients with anorexia nervosa had an average height of 3 cm less than the expected mean height. Reduced plasma concentration of IGF-1 may be one of the potential factors leading to reduced stature of the patients (Soyka et al., 1999). Malnutrition-associated IGF-1 deficiency may also contribute to severity of low bone mass in this population as compared to other situations of estrogen deficiency (Bachrach et al., 1991; Grinspoon et al., 1999).

Malnutrition
Intensive exercise
Calcium and Vitamin D deficiencies
Hypogonadism - hypoestrogenism
Hypercortisolism
Low IGF-1
Reduced bone formation
Increased bone resorption

Table 1. Risk factors casing reduced bone mass in the patients with anorexia nervosa.

The impact of an increased level cortisol on BMD, decreased intake of calcium and vitamin D or excessive exercise is less understood (Carmichael et al., 1995).
Intensive physical activity, especially the load-bearing exercise, has positive effects on BMD of children and adolescents. Strenuous physical activity, however delayed sexual maturation and reduced BMD (Grinspoon et al., 1999). Anorexic girls with intense physical activity also experience weight loss and amenorrhea. A study failed to demonstrate the relationship between the amount of both physical activity and BMD in

normal teenage anorexic girls (Soyka et al., 1999). Some patients may have a relatively normal BMD, despite low weight, due to prior exposure to environmental (eg, pre-pubertal exercise) or hereditary factors, such as vitamin D receptor polymorphisms or COLIA 1 genes, which may have a protective function (Sainz J et al., 1997; Grinspoon et al., 1999; Sainz J et al., 1999). A study in adolescents with anorexia nervosa has shown an association between BMI and BMD (Bachrach et al., 1990). Another study has detected a marked reduction in total body fat and lean mass in girls with anorexia nervosa. However, the total lean body mass was the only variable in body composition that influenced significantly the total and regional bone. BMC at the lumbar spine and BMD at the lateral lumbar spine were detected (Soyka et al., 1999).

The severity in the degree of BMD reduction was demonstrated even in young adolescents with a short duration of this clinical condition. A marked osteopenia (or low BMD) was detected in trabecular as well as in cortical bone. The lumbar spine T-score was often 2 SD below the mean in 50% of women with anorexia nervosa (Bachrach et al., 1991).

The degree of low BMD may be enough to cause clinical fractures in several skeletal sites of women in the third decade of life and increased the risk of fragility fractures (Brotman & Stern, 1985).

The patients with amenorrhea may have marked increase in BMD during the third decade of life, which is associated with a gain in body weight and a rise in caloric intake (Karlsson et al., 2000). Girls and women with anorexia nervosa need to be rehabilitated very early in order to maximize the increase of the BMD. Early intervention is absolutely necessary. The vertebral BMD may be reduced one year after diagnosing anorexia nervosa. It was demonstrated that the women who developed anorexia nervosa before the age of 18 years, their mean BMD at the lumbar spine was found to be lower than in girls who developed anorexia nervosa later on, regardless the duration of the amenorrhea (Bachrach et al., 1991).

The sexual and skeletal maturation stages were evaluated in association with the determinations of BMD: the BMD was found to be more related to stages of puberty and bone age than with the chronological age (Rubin et al., 1993).

A reduced bone mass was also found in young anorexics. (Resch H et al., 2000). Another study demonstrated bone fragility due to small size of bones originated by malnutrition and decreased volumetric BMD caused by hypoestrogenism (Karlsson et al., 2000).

The results of a research profile of the lateral lumbar spine BMD have demonstrated a marked osteopenia with a mean T-score < -1.0 SD in 63% of the cases and more than -2.0 SD in 26% of girls with anorexia nervosa (Soyka et al., 1999). A mean trabecular bone loss of 3% per year was detected in 10 adolescent girls with anorexia nervosa and amenorrhea. The onset of anorexia nervosa before acquiring the peak bone mass, and also a long-term amenorrhea may aggravate osteopenia (Bachrach et al., 1991).

Since the exact beginning of the nutritional restriction by the patient is difficult to establish, the period of disease is roughly associated with the duration of secondary amenorrhea.

Our group has evaluated the prevalence of low BMD, osteoporosis and the body soft tissues composition in Portuguese adolescent females with anorexia nervosa (Mascarenhas M et al., 2008). A subgroup of 39 adolescent girls with anorexia nervosa aged 18.6 years and mean BMI: 15.1 kg/m^2] was compared to a control subgroup of young girls and normal adult women with regular menstrual cycles [mean age: 18.9 years and mean BMI: 20.6 kg/m^2]. The BMD at the lumbar spine, at the femoral neck, at other parts of the body and the total lean and fat body masses were accessed by DXA (dual X-ray absorptiometry) using the QDR Discovery W (Hologic Inc.).

The BMI and the total fat and lean body masses were reduced in the anorexia nervosa group (P<0.0000) as well as the Also reduction in BMD at the lumbar spine, at the femoral neck, at the distal forearm and at other parts of the body was evident (Table 2). Although most of the skeleton was affected, the mean BMD was approximately 14% less in trabecular bone (measured by DXA at the lumbar spine) as compared to the control group. Our findings are consistent with the results of other study (Mascarenhas M et al., 2008).

BMD g/cm^2	**ANOREXIA NERVOSA** *Age < 18 years* **Mean (±SD)**	**CONTROL SUBGROUP** *Age < 18 years* **Mean (±SD)**	***P***
L_1 – L_4	**0.856** (±0.1)	**0.992** (±0.1)	0.0167
Hip	**0.724** (±0.1)	**0.859** (±0.1)	0.0082
Distal foream	**0.518** (±0.0)	**0.555** (±0.1)	0.0432
Whole body	**1.056** (±0.1)	**1.095** (±0.1)	0.0156

BMD = bone mineral density; NSD = non-significant difference; SD = standard deviation

Table 2. The mean BMD at the lumbar spine, at the hip, at the distal forearm and at other parts of the body in the anorexia nervosa and control subgroups (adolescent girls less than 18 years old).

The portuguese adolescents with anorexia nervosa less than 18 years old had low mean total body fat and lean masses and low mean fat body percentage, as compared with the control group as seen in Table 3 (Mascarenhas M et al., 2008). Similar differences were observed by Soyka et al in 1999. In contrast to a study of Bachrach LK et al, 1991, we did not detect a reduced BMD in adolescent girls with a short duration of anorexia nervosa, Table 4 (Mascarenhas M et al., 2008). Soyka et al. (1999) found lower trabecular BMD in the lateral view of the lumbar spine. In this study the BMD at other regions of the skeleton, particularly in the proximal femur and distal forearm, were not evaluated.

	ANOREXIA NERVOSA *Age < 18 years* **Mean (±SD)**	**CONTROL SUBGROUP** *Age < 18 years* **Mean (±SD)**	***P***
Age *years*	**15.5** (±0.9)	**15.8** (±1.0)	*NSD*
Weight *kg*	**37.9** (±3.2)	**53.2** (±7.5)	*0.0000*
Height *cm*	**159.3** (±0.0)	**160.9** (±0.1)	*NSD*
BMI *kg/cm^2*	**15.0** (±1.3)	**20.5** (±2.0)	*0.0000*
Total fat mass *kg*	**6.6** (±2.3)	**15.9** (±4.1)	*0.0000*
Total lean mass *kg*	**30.7** (±2.3)	**36.4** (±5.1)	*0.0000*

BMI = body mass index; NSD = non-significant difference between the means; SD = standard deviation

Table 3. The mean age, weight, height, BMI, total body fat and lean masses in between anorexia nervosa and control subgroups (girls less than 18 years old).

After adjusting the age, height and weight we did not find any contributions of the total body fat and lean masses on the BMD at the different skeletal sites in the adolescent girls with or without anorexia nervosa (Table 4). Our data differ with other studies regarding to the total lean body mass of the normal teenager group (Soyka et al., 1999; Ellis et al., 1997).
The impact of severe anorexia nervosa in the final apposition of the BMD is independent of the duration of amenorrhea and appears in females that develop the disease before 18 years old (Biller et al., 1991).

BMD g/cm^2	**ANOREXIA NERVOSA** *Age < 18 years* **Mean (±SD)**	**CONTROL SUBGROUP** *Age < 18 years* **Mean (±SD)**	***P***
L_1 – L_4	**0.846** (±0.1)	**0.925** (±0.1)	*DNS*
Hip	**0.735** (±0.1)	**0.807** (±0.1)	*DNS*
Distal foream	**0. 504** (±0.0)	**0. 515** (±0.1)	*DNS*
Whole body	**1. 049** (±0.1)	**1. 054** (±0.1)	*DNS*

BMD = bone mineral density; NSD = non-significant difference between the means; SD = standard deviation

Table 4. The mean BMD at the lumbar spine, at the hip, at the distal forearm and at other parts of the body in anorexia nervosa and control subgroups (adolescent girls less than 18 years old).

Soyka and colleagues detected that total lean body mass predicted significantly the bone mass in normal adolescent girls, but not in the anorexia nervosa group (Soyka et al., 1999).
The anorexia nervosa group aged more than 18 years had also a low BMI and reduced total body fat and lean mass (Table 5). In this subgroup, the BMD at the lumbar spine, at the hip, at the distal forearm and at the other body bones were reduced, as compared to the

	ANOREXIA NERVOSA *Age < 18 years* **Mean (±SD)**	**CONTROL SUBGROUP** *Age < 18 years* **Mean (±SD)**	***P***
Age *years*	**21.0** (±3.2)	**21.0** (±3.3)	*DNS*
Weight *kg*	**40.1** (±3.9)	**55.4** (±5.9)	*0.0000*
Height *cm*	**162.1** (±0.1)	**163.3** (±0.1)	*DNS*
BMI *kg/cm^2*	**15.2** (±1.3)	**20.7** (±1.1)	*0.0000*
Total fat mass *kg*	**7.0** (±3.0)	**16.4** (±4.8)	*0.0000*
Total lean mass *kg*	**32.7** (±3.8)	**38.6** (±5.0)	*0.0000*

BMI = body mass index; NSD = non-significant difference between the means; SD = standard deviation

Table 5. The mean age, weight, height, BMI, total body fat and lean mass in anorexia nervosa and control subgroups (girls aged ≥ 18 years).

respective control subgroup (Table 6), which suggests that this group may have a greater tendency for the development of low BMD or osteoporosis in early adulthood. Grinspoon and others similarly reported that the BMD at the lumbar spine measured by DXA in 23 patients with anorexia nervosa (mean age 23 years) also reduced (Grinspoon et al., 1995). Other investigators also detected reduction of trabecular BMD at the lumbar spine (Bachrach et al., 1991; Klibanski et al., 1995; Karlsson et al., 2000).

This group of patients had a longer duration of amenorrhea, about 2 years on average, and might have a stronger negative effect on the BMD. Low bone mass in anorexia nervosa-related amenorrhea has been reported (Hergenroeder et al., 1991; Bachrach et al., 1991) However, comparison of height, weight, BMI, total body fat, lean mass and BMD measured at various skeletal regions did not show any significant difference between the anorexic subgroups under 18 years old and in patients of more than 18 years old.

In conclusion, it looks like that at an early age (up to 18 years old) there is no difference in BMD of adolescent girls with anorexia nervosa as compared with the normal. However, after the age of 18 years, there is a difference in the mean BMD between the group of patients with anorexia nervosa and the normal group, suggesting that after the age of 18 the amount of bone mineralization is more pronounced which acts as an important predictive factor for the future bone strength.

The duration of anorexic state is one of the most important predictors of reduced BMD at the lumbar spine (Soyka et al., 1999).

Our group carried out a follow-up in 15 patients with anorexia nervosa who attended the Eating Disorders Department of the Hospital de Santa Maria. The average follow-up period was of 7.6 years. The most important variable with negative correlations to bone mass recovery was disease duration (do Carmo et al, 2007). A positive correlation between bone mass recovery and the return of regular menstrual cycle was evident. However, in anorexic patients when body weight improved and menstrual cycles became regular, severe damage to bone structure was still likely to be maintained (do Carmo et al, 2007).

BMD g/cm^2	**ANOREXIA NERVOSA** *Age < 18 years* **Mean (±SD)**	**CONTROL SUBGROUP** *Age < 18 years* **Mean (±SD)**	***P***
L_1 – L_4	**0. 864** (±0.1)	**1.039** (±0.1)	*0.0014*
Hip	**0. 716** (±0.1)	**0. 894** (±0.1)	*0.0028*
Distal foream	**0. 531** (±0.0)	**0. 581** (±0.0)	*0.0098*
Whole body	**1. 061** (±0.1)	**1. 124** (±0.1)	*0.0020*

BMD = bone mineral density; NSD = non-significant difference between the means; SD = standard deviation

Table 6. The mean BMD at the lumbar spine, at the hip, at the distal forearm and at different bones of the body between anorexia nervosa and control subgroups (girls aged ≥ 18 years).

When compared, the mean BMD of 19 girls with anorexia nervosa was found to be similar to the mean BMD of 70 – 80-year-old postmenopausal women (Biller et al., 1991).

Finally, a histomorphometric study of 4 anorexic patients with low body weight showed that estrogen therapy had a very limited benefit in improving BMD and bone mass apposition (Kreipe et al., 1993).
Therefore, the severe impacts of anorexia nervosa in teenagers include retardation of linear growth, decreased bone dimension and reduced stature in adulthood (Soyka et al., 1999; Karlsson et al., 2000).

3.2 Adulthood

In 18 anorexic women (mean age: 25 years, ranging from 19 to 36 years) with amenorrhea for at least one year, a lower BMD was detected as compared with the BMD of control group. It was moreover recorded that physically inactive anorexic women had a lower BMD compared with the physically active group, suggesting that physical activity may have a protective effect (Rigotti et al., 1991).
Other studies have detected bone mass loss in the majority of women with anorexia nervosa and in 50% of those women the Z-score was 2.0 SD below the mean BMD; although both cortical and trabecular bone tissues are affected, the loss of trabecular bone is found to be more severe (Bachrach et al., 1991).
In adult women with anorexia nervosa, the mean spinal BMD had decreased about 32%, while distal radius BMD was reduced to about 18%, as compared with the control group (Bachrach et al., 1991).

4. Bone metabolism

Studies in adults with anorexia nervosa have detected a severe imbalance in bone turnover with a decrease in bone formation and an increase in bone resorption (Grinspoon et al., 1999). However, the data obtained in the adult anorexic women cannot be extrapolated to the anorexic adolescents where the rate of bone growth and mineral apposition remains active.
Bone metabolism is understudied and not fully understood in this adolescent population (Abrams et al., 1993). Most studies in adolescents with anorexia nervosa have included a small number of patients and without specific information about the markers of bone turnover, including simultaneous measurements of the bone formation/resorption markers. Other studies have included subjects with a broad age spectrum, which is from the early adolescence until early adulthood. However, the bone mass was not measured through the stages of puberty. BMD is more related to the stages of sex maturation and the bone age than the chronological age (Rubin et al., 1993).
Nutrition or calcium supplementation is directly associated with BMD, however, its impact depends on the stages of puberty (Rubin et al., 1993)
Abrams and colleagues conversely found that an increased intake of isolated calcium did not raise the BMD of adolescent girls with anorexia nervosa due to a decrease in calcium absorption with a corresponding increase in calcium excretion (Abrams et al., 1993). However, the bone markers were not evaluated in this study.
Malnutrition is associated with calcium and vitamin D deficiency (Soyka et al., 1999; Martin et al., 1997).
Saggese and colleagues demonstrated that there were changes in markers of bone formation in six adolescent patients (aged 11 to 21 years) with anorexia nervosa, but they

did not investigate other bone formation or resorption markers in these patients (Saggese et al., 1992).

The reduction of bone formation markers in anorexia nervosa is consistent with the proposed hypothesis that severe malnutrition may have a pronounced deleterious effect on functioning of the osteoblasts (Table 1). An increase in markers of bone resorption may represent increased osteoclast activity (Hotta et al., 1998; Grinspoon et al., 1999).

The biochemical markers of bone formation (osteocalcin and bone-specific alkaline phosphatase) were significantly reduced in 19 girls with anorexia nervosa. Most of the variation of bone formation in anorexia nervosa was due to the levels of IGF-1, which was found to be reduced in young women with anorexia nervosa (Soyka et al., 1999). The IGF-1 acts as an osteotrophic hormone, which affects bone growth and bone turnover by stimulating osteoblasts, collagen synthesis and longitudinal bone growth. Thus, a reduction of IGF-1 during the critical period of bone mineralization at puberty may be an important factor in the development of a low BMD in adolescents with anorexia nervosa.

The low IGF-1 plasma concentration in anorexia nervosa is correlated with reduced BMI. Therefore, IGF-1 deficicency associated with malnutrition may substantially contributes to the decrease in bone formation in the adolescents with anorexia nervosa (Golden et al., 1997; Grinspoon et al., 1999).

IGF binding proteins 2 and 3 (IGF-BP2 and IGF-BP3) plasma concentrations, the indicators of nutritional status of the individual are modified in anorexia nervosa. IGF-BP2 is increased where as IGF-BP3 is decreased in association with reduced IGF-1 as compared with the normal subjects. Moreover, the BMI correlates positively with the free IGF-1 and negatively with the IGF-BP2 (Argente et al., 1997).

Hotta and others have performed a study in Japanese anorexic youth submitted to intra-venous nutrition. The results revealed that the improvement of nutritional status was associated with rapid and marked increase in plasma levels of osteocalcin and IGF-1 (Hotta et al., 1998).

5. Bone mass during the recovery of anorexia nervosa

Therapeutic strategies to stimulate bone mass recovery in patients with anorexia nervosa need to be carefully formulated. A study conducted in New York showed that just a mean weight of approximately 90% of the desirable body weight, spontaneous menses return in 86% of patients within the next 6 months (Golden et al., 1997). Therefore, 90% of desirable weight seems to be a reasonable target for weight gain therapy. Resumption of menses was obviously associated with the activation of the hypothalamic-pituitary-ovarian axis (also associated with total body fat mass). It was concluded that plasma levels of 17β-estradiol is the best marker for determining the resumption of menstrual cycle (Golden et al., 1997).

Studies conducted up to 8 years after the onset of anorexia nervosa showed that only 48% of patients recovered normal body weight and showed regular menstrual cycles (Herzog et al., 1993).

However, the BMD at the lumber spine of 69 women at various stages of recovery from anorexia nervosa showed a decrease in BMD compared to controls. Even exercise did not show any protective effect on the skeleton in these patients. BMD in these women was moreover associated with the duration of amenorrhea (Hay et al., in 1992).

A group of 51 women with anorexia nervosa was investigated during 11.7 years. In these patients measurements of BMD were made at the lumbar spine and forearm. Groups were divided into three according to their stages of recovery:

a. a good recovery - women who had regular cycles and not weighed less than 85% of their expected body weight,
b. a poor recovery - the patients who had not reached regular cycles and weighed less than 85%,
c. an intermediate stage of recovery - the patients had not yet achieved regular cycles but their body weight was found to be higher than 85% of expected body weight.

The group of patients with good recovery had a significantly increased BMD at the lumbar spine and at the forearm as compared with the other two groups. The group with an intermediate recovery type had a higher BMD at the lumbar spine than the group with a poor recovery. It was concluded from this study that the recovery of trabecular bone mass is achieved by a successful treatment of anorexia, but the recovery of cortical bone mass is comparatively slow and gradual. (Herzog et al., 1993).

Independent effect of weight gain in improving BMD and in the absence of estrogen therapy have also been reported(Bachrach et al., 1991; Rigotti et al., 1991; Herzog et al., 1993).

A Canadian study in Toronto showed that bone mass was strongly correlated with lean tissue in anorexia nervosa while its relation with the body fat mass was weaker. However, the follow-up of anorexic patients for 7 to 26 months showed a modest increase in weight (average 4.9 kg), which was due primarily to an increase in body fat mass with a slight and insignificant increase in lean body mass. Bone mass remained almost unchanged or even decreased in some cases. Only 4 patients gained normal body weight (BMI > 20 kg/m^2) and had normal menstrual cycles, but the bone mass in these four responders did not increase. In this study the authors demonstrated that the adolescent girls with anorexia nervosa restore bone mass following an increment of the soft body mass/tissue. (Kooh et al., 1996).

A swiss study showed that bone mass decreased 6 to 28% despite nutritional and body weight recovery (Ruegsegger et al., 1988).

According to Hotta and colleagues, an increase in BMD and normalization of bone formation and resorption markers occur if the BMI is above 16.5 kg/m^2. The yearly BMD increment is BMI dependent in young patients recovering from anorexia nervosa (Hotta et al., 1998). The retrospective data of Valla and his colleagues showed a recovery of BMD in those who regained body weight and regular menstrual cycles and suggested that in addition to body weight other factors, such as menstrual disorders and hypoestrogenism are independent and additive risk factors causing loss of bone mass in patients with anorexia nervosa (Valla et al., 2000).

In hypoestrogenism, the impact of hormone therapy on bone mass depends on pathogenesis, hormone administration route and the dosage used (Bruni et al., 2000).

A survey of Robinson and his colleagues revealed that most of the clinicians dealing with anorexia nervosa prescribe contraceptive pills for the treatment of low BMD despite its poor effectiveness in preventing or reversing anorexia-associated conditions (Karlsson et al., 2000; Kreipe et al., 1993; Bruni et al., 2000).

Klibanski et al. studied 48 women with anorexia nervosa (mean age 23.7 years old) and reported that the BMD at the lumbar spine did not change after 1.5 years of estrogen therapy. However, about 4% increase in BMD was evident in the treated patients who had

less than 70% of the desirable body weight. In contrast, in women not receiving estrogen therapy, the BMD decreased by 20%. The patients who regained spontaneous menstrual cycles had a 19.3% increase in bone mass (Klibanski et al., 1995). Other authors, however, found that the oral contraceptives used in anorexia nervosa were associated with an increased BMD all over the body including at the lumbar spine (Seeman et al, 1992).

6. Bone complications in anorexia nervosa

The persistent low bone mass often a common complication of anorexia nervosa in the adolescent population may cause increased risk of spontaneous and/or clinical fractures (Kooh et al., 1996 ; Bachrach et al., 1991; Brotman & Stern, 1985; Herzog et al., 1993).
The degree of reduced bone mass may cause severe complications. Women with anorexia nervosa and one year of amenorrhea had multiple crash vertebral fractures (Rigotti et al., 1991).
A study revealed collapse of the femoral head in a short stature 20 year-old anorexic dancer. This patient had delayed bone age (13 years), primary amenorrhea and hypoestrogenism. The possible osteonecrosis mechanisms included repeated micro-traumas (Warren et al., 1990).
However, a study performed by Hartman and colleagues in 19 women who recovered from anorexia nervosa for more than 20 years showed that recovery from clinical disease did not confer a normal bone mass (Hartman et al., 2000).
Marked osteoporosis can develop in young adult women with persistent amenorrhea and anorexia nervosa. Unlike other forms of pre-menopausal osteoporosis, fractures in these patients at the various regions of the skeleton are common, with a 7-fold increased risk for nonvertebral fractures as compared with women of the same age (Steelman & Zeitler, 2001; Heaney R., 1998; Rigotti et al., 1991).

7. Thin postmenopausal women

Aging in both sexes is accompanied by loss of muscle mass and strength. Muscle weakness may harm the quality of life and autonomy of elderly people.
The decline of lean body mass that occurs with aging probably includes a decrease in somatotropin (GH) synthesis and secretion due to decreased pituitary response to GHRH, loss of muscle fibers, neuromuscular changes, sedentary lifestyle and other changes intrinsically associated with aging (Douchi et al., 1998).
In the pre-menopausal women, the response to GHRH is increased which is not found in the post-menopausal women, suggesting that the age-related decline in GH results in the loss of muscle mass (Douchi et al., 1998). Bone loss accelerates substantially in the late perimenopause and continues at a similar pace in the first postmenopausal years (Gillette-Guyonnet et al., 2000; Finkelstein J. et al, 2008).
In the post-menopause, the lean mass of the trunk, lower limb and of the total body, measured by DXA, is lower than in the premenopausal women and is inversely related to age and menopause duration. In postmenopausal women the loss of lean body mass is independent of the age and bodyweight. The lean body mass of the trunk declines more quickly than other areas of the body (Finkelstein J. et al, 2008). Addition of androgen to estrogen therapy increases lean body mass in postmenopausal women (Davis, S., 1999).

A study of 129 women aged between 75 to 89 years showed that muscle mass was significantly reduced along with the incidence of osteoporosis and reduced BMD at the hip. It was concluded that the lean body mass has a protective effect on BMD at the femoral neck (Gillette-Guyonnet et al., 2000). So far, it is unclear whether lean mass regulates the bone mass in the postmenopausal women. The importance of lean mass or muscle mass in controlling the bone mass is supported by in vitro and in vivo studies. The results of autopsies after adjusting body weight, age and height showed that there was a significant relation between the weight of the ashes of the third vertebra of the spine and the left psoas weight; another investigation revealed the existence of a correlation between the lumbar spine extensor muscles strength and BMD at the lumbar spine (Aloia et al., 1991). A study in women of more than 60 years old revealed that the lean body mass contributed significantly to predict the cancellous BMD (Aloia et al., 1991). However, no correlation between the whole body potassium and the BMD at the trochanter or Ward's triangle was evident (Aloia et al., 1991). The duration of fertility period but not the age at menarche or at menopause may affect osteoporosis?. The obstetric history of previous childbirths and/or miscarriages, independent of the number, is not a risk factor for osteopenia or osteoporosis?

8. Contribution of lean and fat mass to bone mass

The body fat tends to increase with age. Most of the studies match the importantance of the body weight in determining the BMD, especially in the axial skeleton. However, the relative contribution of both the lean and fat body masses in BMD is not evident. In the transition to menopause, the BMI and the total body fat mass are increased. Also the lean body mass and bone mass are decreased, while the fat mass increases in postmenopausal women (android distribution). It however, remains unclear whether the changes are due to age or to menopause (Tremollieres et al., 1996; Douchi et al., 1998; Ijuin H et al., 1999; Wang Q et al., 1994).

A longitudinal study showed that a rapid increase in visceral fat mass generally attributed to the aging process (Tchernof et al., 1998). Moreover, a total body fat mass assessed by DXA in postmenopausal women could predict BMD at the spine and at the hip.

The decreased fat mass is a risk factor for osteoporotic fractures, because 11% to 15% of patients with fragility fractures showed low fat mass, whereas the lean body mass in the same patients remained the same compared to controls; in women aged more than 75 years, a protective effect of body weight and fat mass on BMD at several skeletal sites was positively correlated with the weight and the fat mass (Gillette-Guyonnet et al., 2000).

A swedish study, on the other hand, compared urban and rural populations and found that the incidence of osteoporotic fractures was higher only in a group of women more than 70 years old with reduced muscle mass, which highlighted the importance of the muscle mass as a primary agent influencing the bone mass changes and the fracture risk in elderly women (Elmstahl et al., 1993).

We have evaluated a group of 53 thin postmenopausal women (BMI < 18.5 kg/m^2). The BMD measurements at the lumbar spine, at the femoral neck and at other parts of the body and the total lean and fat body masses were also accessed. The Z-scores and the T-scores were also determined. Our results revealed that in the post-menopausal patients, osteoporosis was associated with low BMI. The mean Z-scores of the BMD were at the lumbar spine -1.1 SD, at the femoral neck -1.2 SD and at the total hip -1.3 SD, respectively (Mascarenhas M et al., 2003). These data may suggest that low body weight and reduced

BMI in the postmenopausal women may also exacerbate the loss of bone mass as well as enhance the development of osteoporosis. The results are also consistent with the previous data presented on the protective effects of both the total fat mass and body weight on BMD. (Mascarenhas M et al., 2003; Mascarenhas M et al., 2004).
A study in postmenopausal Chinese women with type 2 diabetes mellitus (T2DM) showed a higher osteoporosis risk for the hipbone compared to the lumbar spine, especially in those with a BMI below 18kg/m^2. (Peng-Fei S et al, 2009).

9. Conclusion

In anorexia nervosa and control adolescent women, the mean BMD were similar, but the BMD at the femoral neck and at the lumbar spine showed a tendency to decrease between 8.5% to 9% in the anorexic patients. However, secondary amenorrhea of about 10 months duration may be short in exerting any significant difference in BMD at several skeletal sites.
The anorectic patients were found to be lighter with low total body fat and lean body mass compared to controls of the same age. In these adolescents with or without anorexia nervosa, total body fat and lean mass do not contribute to BMD at the diverse regions of the skeleton.
In the patients of anorexia nervosa aged over 18 years, the BMD at the lumbar spine, femoral neck, distal forearm and at different bone of the body were significantly reduced, suggesting that these girls may have higher tendency to develop low BMD or osteoporosis in their early adulthood. These patients also showed a longer duration of amenorrhea (about 2 years on average), which might have a greater impact on the BMD. In the anorexic patients aged more than 18 years, a positive correlation between the total body fat to the BMD at the femoral neck and at different regions of the bones were observed. The data suggest a direct link between the nutritional status and BMD in patients with anorexia nervosa.
The current consensus on the relative contribution of the total body fat and lean mass to BMD at different bones of the body in the postmenopausal patients comes from the evidence of the most cross-sectional studies.
Longitudinal studies to assess BMD in postmenopausal women are essential to know whether the changes in BMD are sensitive to changes in body composition and to delineate the mechanism involved.
Finally, it seems to be very important to know that young women with anorexia nervosa and the thin postmenopausal women should be identified in advance in order to modify their behavior and consequent reduction in the future risk of osteoporosis and the fragility fractures.

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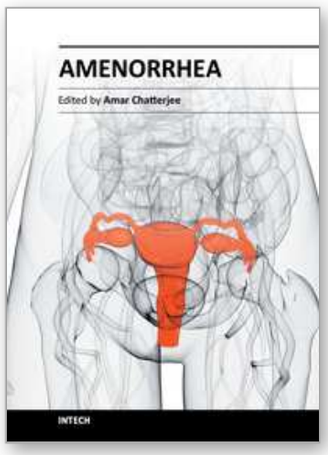

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This book on "Amenorrhea" is a wonderful collection of updated reviews dealing mostly with the aphysiological aspects of secondary amenorrhea. The book represents a collection of eight chapters, each chapter in the book is written by the international experts with extensive experience in the areas covered. We hope that readers will find this book interesting, helpful and inspiring.

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