**Psychiatr. Pol. 2016; 50(3): 509–520**
PL ISSN 0033-2674 (PRINT), ISSN 2391-5854 (ONLINE)
www.psychiatriapolska.pl
DOI: http://dx.doi.org/10.12740/PP/59289

# Bone mineralization disorders as a complication of anorexia nervosa – etiology, prevalence, course and treatment

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**Summary**

Anorexia nervosa (AN) most often has its onset in adolescence, which is a crucial period to achieve peak bone mass. The hormonal abnormalities (hypoestrogenism, hypercortisolism, decreased secretion of dehydroepiandrosterone, testosterone, insulin-like growth factor) and malnutrition are associated with profound bone mineralization disorders. Densitomertic bone mineral density (BMD) values for osteopenia and osteoporosis were found respectively in 35–98% and 13–50% of women with AN. Prospective studies indicate a further decline in BMD at the beginning of treatment and a crucial importance of weight gain and return of spontaneous menses for its growth. Due to frequent chronic and relapsing course of AN densitometric assessment of BMD is recommended in all patients with AN and amenorrhea lasting around twelve months. In order to establish standards for the treatment of osteoporosis in AN, studies on pharmacological treatment are conducted. There are promising results indicating the improvement in BMD after treatment with physiologic estrogen replacement treatment and sequential administration of medroxyprogesterone in teenage girls and bisphosphonates in adult women. Supplementation of vitamin D and adequate consumption of calcium from diet are recommended. Further studies on the effectiveness of long-term treatment of osteoporosis with regard to the possibility of increase in BMD and reducing the risk of osteoporotic fractures are needed.

**Key words**: anorexia nervosa, osteoporosis, bone mineral density

The study was not sponsored.

## Introduction

The peak of anorexia nervosa (AN) onset occurs between 14 and 18 years of age. In 85% the onset is before 20 years of age and almost in 100% before 25 years of age [1]. This is a crucial period to achieve peak bone mass. 90% of peak bone mass in healthy women is achieved around 15 years of age, whereas peak bone mass is achieved close to 17–22 years of age [2]. Malnutrition and hormonal disorders related to it in women with AN, as well as often encountered chronic or recurrent nature of the disease lead to the risk of osteopenia or osteoporosis at a young age. This paper presents a review of the literature concerning the etiology, prevalence, course and treatment of bone mineralization disorders in AN.

## Etiology of bone mineralization disorders in anorexia nervosa

Osteoporosis in AN is determined by many factors. Extreme limitation of food intake, low body weight and abnormal secretion of hormones that influence bone metabolism (hypoestrogenism, hypercortisolism, decreased level of insulin-like growth factor (IGF-1), dehydroepiandrosterone (DHEA) and testosterone) are considered to be factors associated with osteoporosis [3–9]. The crucial role in developing bone metabolism disorders in AN is attributed to estrogens deficit, which have antiresorptive effect. Greater degree of bone mineralization disorders in patients with AN compared with women with other causes of hypogonadotropic hypogonadism indicates a significant and independent influence of factors related to malnutrition on bone mineral density (BMD) [10, 11].

One hypothesis concerning the impact of malnutrition on BMD assumes that starvation leads to a decrease secretion of IGF-1, which has a crucial effect on bone metabolism and gonadal axis [12, 13].

Some authors prove that due to a reduction in cortical bone formation and the lack of protective effect on bone metabolism (inhibition of bone resorption), decreased leptin level (associated with low body fat mass in AN) plays a role in the etiology of osteoporosis in AN [14]. Nevertheless, when other factors dependent on nutritional status are taken into account, leptin is no longer considered as a factor directly influencing BMD [9]. Neuropeptide Y can be an independent factor influencing bone metabolism. Its increased secretion is related to low levels of bone formation and resorption markers in adolescents with AN [8, 10]. Ghrelin effect on BMD may be indirect and linked to its effects on the secretion of growth hormone, cortisol and gonadal axis [7].

The mechanism underlying the decrease in BMD in a group of adolescents and adult women with AN may be different. Among girls with AN the growth is inhibited and bone maturation is delayed. Moreover, the rate of bone turnover is decreased and the increase of bone mass is smaller comparing to the group of healthy peers [9, 15]. They have reduced biochemical markers of bone formation and comparable or lower than in the control group resorption markers [15, 16]. In adult women the increase in bone resorption in relation to bone formation is observed [7]. Similarly like in the first years after menopause, in the beginning of AN the bone turnover is high [17].

## Prevalence of bone mineralization disorder among women with anorexia nervosa

The first reports on osteoporosis in AN were based on assessment of radiological examinations of the wrist [18] and spine [19], in which thinning of the bone structure and the presence of vertebral compression fractures were observed. Development, increasing precision and availability of densitometry have demonstrated that decrease in BMD in AN occurs early, and it is a common complication of the disease. Decrease of bone mineralization is observed earlier in trabecular bone, which is more metabolically active [20–22], within which a demineralization is deeper [23].

BMD depends on duration of AN [4, 21, 24–26]. There was no significant reduction in BMD in adolescent girls with a short duration of AN (from 2.5 to 12 months) regarding entire skeleton and lumbar spine [27]. However, in another study in a group of adolescent girls with AN diagnosed within previous 12 months lumbar spine BMD was lower in comparison to their age-matched controls [28].

The persistence of secondary amenorrhea also has a significant effect on BMD in AN [16, 18, 21–23, 25, 29–32]. In one study, amenorrhea lasting more than 20 months was associated with BMD values range for osteopenia in almost all of the patients with AN, whereas in patients with amenorrhea lasting shorter than 20 months, in 50% of cases [24]. In another studies BMD values corresponding to densitometric criteria for osteoporosis were found in 38% of women with amenorrhea lasting for 24 months [33, 34].

Studies have shown that 50% of adult women with AN have significantly decreased BMD (T-score < – 2SD) and BMD is lower in patients with onset of AN in adolescence (comparable duration of disease) [35]. In studies regarding larger groups of young women [3, 13, 33, 36–38] BMD values corresponding to osteopenia were found (in various locations) in 48–92% of women and those corresponding to osteoporosis in 21–38%. In the group of 214 women who suffered from AN (recruited from the general population; 50% had never been hospitalized), BMD values for osteopenia in any of the studied locations (lumbar spine, femur, the entire skeleton) was found in 52% of women, for osteoporosis in 34%, and the results within normal range were found in only 13.8% of patients [38]. Among patients with a chronic course of the disease, BMD in the lumbar spine and femoral neck at the border and below the threshold of bones fragility was found respectively in 45% and 75% of participants [39].

## The course of bone mineralization in patients with anorexia nervosa

Most of the studies regarding bone mineralization are one-time survey carried out during the course of disease or short-term observations of BMD changes during AN treatment.

In a prospective study of adolescent girls with AN [40] there was an increase in the proportion of patients with reduced BMD in the initial period of treatment. With regard to the lumbar spine it was caused by the actual decline, whereas as for entire skeleton it was caused by the lack of increase in BMD ($g/cm^2$). Similar results were

obtained in other studies [9, 41]. During the 12 month observation Soyka et al. found the increase in the percentage of girls with reduced BMD of lumbar spine from 37% to 71% despite the fact that 65% of patients at that time reached a normal weight [9].

Studies indicate that the rate of bone mass loss in women with AN is higher than in postmenopausal osteoporosis [26, 30, 42, 43]. The annual rate of decline in BMD in women with AN was determined to be 2.6% at the lumbar spine and 2.4% at the hip [42]. Ruegsegger et al. [43] found that within one year a loss of trabecular bone reaches approx. 3%. One study has shown that a sharp decline in BMD finishes after 4 months of realimentation [26].

Improvement in BMD is dependent on weight gain and resumption of menses [21, 26, 31, 36, 42, 44–51]. Within 6 months after the restoration of normal body weight in women with AN increase in the lumbar spine BMD by 1.8% and 3.3% in the femoral neck BMD was observed [30].

Miller et al. [42] have shown positive effect of restoration of menses on lumbar spine BMD independently of other factors and independent effect of weight gain on hip BMD. In adults, the critical value of BMI (body mass index) for the increase in BMD is 16.4 ± 0.3 kg/m$^2$, and the degree of decrease in BMD is associated with the persistence of BMI on the level lower than 15 and 16 kg/m$^2$ [52]. Halvorsen et al. [36] have shown that during around 8-year follow-up lumbar spine and hip BMD were closely related to current BMI and amenorrhea lasting more than 2 years had a negative impact on BMD. Improvement in BMD in terms of cortical bone is slower in relation to the trabelcular bone [32, 49].

It has been demonstrated that after recovery a greater increase in BMD is expected in girls under 18 years of age [29], and that in adolescence higher BMD increases can be expected in younger girls with primary amenorrhea [40]. Castro et al. [53] showed that in girls with good outcomes of AN treatment who had BMD at the level of densitometric criteria for osteoporosis at the baseline, annual increases in the lumbar spine and femoral neck BMD were respectively 9.1%, and 4.5%. It was three times higher than in the control group. This study indicates that girls with an episode of AN who recover during adolescence can catch up with their healthy counterparts in terms of bone mineralization.

Long-term prospective studies provide inconsistent results regarding the possibility of restoring normal BMD in women who suffered from AN. Some studies indicate the accretion and normalization of BMD after the restoration of normal body weight [24, 46]; the other ones indicate maintenance of decreased BMD despite recovery [9, 47, 48, 54–57].

Studies of adult women with AN [52, 58] indicate that the normalization of indicators of bone resorption and formation follows after reaching a BMI greater than 16.4 ± 0.3 kg/m$^2$, and that the marker of bone formation positively correlates with BMI and IGF-1, whereas the marker of bone resorption correlates negatively with BMI. Interestingly, after few days of complete intravenous hyperalimentation an increase bone formation and no changes in bone resorption marker were observed. The authors suggest that the reduction in bone formation in AN results from malnutrition, and an increase in bone resorption may be associated with estrogens [58].

## Bone mineralization and abnormal bone microarchitecture in patients with anorexia nervosa

In a group of young people who have not reached a peak bone mass yet predictive value of BMD as the indicator of the fracture risk is questionable, in contrast to BMD among older people with osteoporosis. During adolescence reduced BMD may be related to the delaying of puberty and inhibiting bone growth. There is a systematic error in the assessment of BMD by DXA (dual-energy X-ray absorptiometry) through adolescence, which results from differences between age at which puberty and growth spurt begins in individuals and from the fact that shorter children have lower BMD values. Therefore reduced BMD during adolescence may be not related to the quality of bone and bone microarchitecture abnormalities and in women who recovered from AN in late adolescence an improvement in BMD can be expected within few years after recovery [59]. Therefore, it is proposed that in adolescents, unlike adults, we should not use a term osteopenia (T-score between – 1 and – 2.5SD) and osteoporosis (T-score < – 2.5SD) but rather reduced bone mass and poor bone mass accumulation [60].

Despite these doubts, studies using flat panel volume CT in young women with AN indicate bone microarchitecture disorders associated with reduced values of BMD [61]. Similar microarchitecture abnormalities have been demonstrated in a group of adolescent girls suffering from AN with BMD comparable to those found in healthy girls [59].

In bone biopsy studies in patients with AN with profound bone mineralization disorders a picture typical for osteoporosis was obtained: the presence of thinner trabeculae with minimal activity of osteoblasts and osteoclasts [62] or an increase in resorption surface with a slightly increased number of osteoclasts [63].

## Bone fractures in patient with anorexia nervosa

The consequences of osteoporosis are atraumatic or low energy fractures. Predominatingly fractures occur in locations typical for osteoporosis (spine, radial bone, femoral neck). Fractures of pelvic bones, humerus, sternum, ribs, clavicle and metatarsal have also been reported [18, 23, 62, 64–66].

In the Genant's semiquantitative grading system study, in a group of young women with AN, during the 18-month follow-up, asymptomatic vertebral fractures were suspected in 12.5% of participants [67].

Fracture risk is particularly high in patients suffering from chronic AN when disease lasts more than 7–10 years, and osteoporotic fractures can occur in women even in the 3$^{rd}$ decade of life [30].

Among the 214 young and middle-aged women recruited from the entire population (50% had never been hospitalized) with approx. 5.5 years of duration of AN, fractures occurred in 30% (in 36% of cases there were multiple fractures and in 42% atraumatic fractures) [38].

In a population-based retrospective study [68] in 57% of patients with AN fractures of the spine, femoral or radial bone were found in the period of 40 years after diagnosis,

and standardized incidence ratio (defined as the number of fractures compared with those expected in the population) was 2.9. In another similar study, incidence ratio was 1.98 (for fractures of the femoral neck – 7.17, and for the spine – 3.49). A significant increase in the risk of fractures was observed in particular after more than one year from initial diagnosis, and the increased risk was present for more than 10 years after diagnosis [69].

## Management of bone mineralization disorders in patients with anorexia nervosa

An early diagnosis of the disease plays a crucial role in the prevention of osteoporosis in AN. Informing patients about AN complications or the risk of them (including the reduction of bone mineral density, osteoporosis, increased risk of fractures), motivation for treatment, normalization of diet and the fastest as possible restoration of normal body weight and spontaneous menses are also very important.

Densitometry is recommended in patients with eating disorders and amenorrhea lasting around twelve months [70].

In patients with reduced BMD calcium and vitamin D supplementation is recommended, however it does not affect significantly BMD in patients with persistent malnutrition and amenorrhea [9, 45]. In Poland vitamin D supplementation is recommended between September and April with a dose of 600 to 1,000 IU/day for children and adolescents and 800–2,000 IU/day for adults. If skin synthesis of Vitamin D is insufficient supplementation is recommended throughout the whole year (it is assumed that exposition to the sun of 18% of the body surface (i.e. uncovered forearms and partially exposed legs) without sunscreen in the period from April to September 2–3 times a week between 10 a.m. and 3 p.m. is sufficient for skin synthesis of Vitamin D). Test of serum concentration of 25(OH)D should be recommended for all patients with osteoporosis. If its concentration indicates deficiency or suboptimal level (respectively below 20 ng/mL and between 20–30 ng/mL) therapeutic doses of Vitamin D should be recommended (in severe depletion 1,000–10,000 IU/day, depending on patient's age and body weight; treatment duration 1–3months). Reevaluation of 25(OH)D concentration should be performed after 3–4 months and then semi-annually [71]. Calcium supplementation appears to have a negative risk-benefit effect, and so that it should not be used routinely in the prevention or treatment of osteoporosis. At present obtaining of calcium requirement from diet in preference to supplements is recommended [72].

Physical activity can be recommended in patients who gained weight. In the case of a significantly reduced BMD patients should be warned against practicing dangerous sports due to the risk of osteoporotic fractures. Excessive exercise can cause persistent amenorrhea and may have a negative impact on BMD. Walking, jogging and dancing have more beneficial effect on bone mineralization comparing to swimming or cycling [4].

Extrapolating the experience of the osteoporosis treatment in hypogonadotropin hypogonadism with a different etiology than AN and postmenopausal osteoporosis many gynecologists recommend hormone replacement therapy to older adolescent

female patients [73]. Such treatment has weak scientific evidence and estrogen treatment appears to be ineffective due to the multifactorial determinants of osteoporosis in AN [74, 75]. Meta-analysis of estrogen therapy studies in young women with AN indicates weak evidence of the effectiveness of such therapy on lumbar spine BMD, and the lack of evidence of its effect on femoral neck BMD [76]. However, promising results were obtained in the group of teenage girls after physiologic estrogen replacement [6]. In girls with a skeletal age ≥ 15 years estradiol were administered transdermally with sequential administration of medroxyprogesterone, and in younger girls gradually increasing doses of oral estradiol, mimicking its secretion during puberty. The treatment group had significantly higher spine and femur BMD, despite the lack of differences in body weight and body composition changes between the treatment group and the group receiving placebo. BMD changes were comparable in the control group and in the group treated with estrogens [6]. Another study [21] showed that despite the lack of differences in BMD changes in the group receiving estrogen-progesterone therapy or placebo, women with the greatest deficiency of body weight (deficiency of body weight > 30%) benefited in terms of trabecular bone BMD changes.

In an open study in which DHEA or estrogen-progesterone therapy was provided, after controlling for weight gain no influence on the BMD was observed. In both groups decrease of bone resorption markers was found and in the group receiving DHEA there was an increase in bone formation markers and IGF-1. During the study there was a significant increase in body weight (greater in the group receiving DHEA) [5]. Gordon et al. [77] showed the beneficial effects of DHEA on bone metabolism and normalization of estradiol, testosterone and IGF-1 levels in adolescent girls with AN. However, due to the lack of long-term studies regarding the efficacy and safety of anabolic hormones treatment currently their use is not recommended. Therefore, decisions concerning the possible hormonal therapy and hormone dose should be individualized.

It is believed that in patients with AN and in healthy young women high doses of estrogens (e.g. contained in contraceptives) can inhibit the secretion of IGF-1 and testosterone, which cause an unfavorable effects on BMD [6, 21]. In addition, such treatment may give patients a false sense of health, contribute to reduced motivation to undertake psychotherapy and may diminish efforts to normalize diet and achieve weight sufficient for recovery of spontaneous menses.

The use of bisphosphonates in adult women with AN was associated with an increase in lumbar spine BMD after 6 and 9 months [78]. However, the results of 3–12 months bisphosphonate treatment show limited effectiveness of such treatment comparing to BMD changes as a result of improvement in nutritional status [79]. Bisphosphonate therapy in young women is questioned because of the lack of long-term studies and the possibility of teratogenic effects on the fetus [79].

For now the possibility of combined treatment with contraceptives and IGF-1 requires further research. Randomized study showed no increase in BMD in women receiving oral contraceptives, favorable changes after addition of IGF-1, and the greatest changes in the group receiving both oral contraceptives and IGF-1 [74].

## Conclusion

AN is associated with a high risk of osteoporosis and osteoporotic fractures at a young age. Restoring normal body weight and return of spontaneous menses are crucial for improving bone mineral density in women. Despite the promising results indicating the improvement in BMD after treatment with physiologic estrogen replacement in teenagers or bisphosphonates in adult women, further studies are needed to establish standards for the treatment of osteoporosis in AN.

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