



# The role of *anorexia nervosa* in secondary osteoporosis development with the risk for low energy fractures

Rola *anorexia nervosa* w rozwoju wtórnej osteoporozy z uwzględnieniem ryzyka złamań kości

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## Abstract

*Anorexia nervosa* (AN) has in recent years become considerably more common. The disease primarily affects girls and young women, and also boys and young men. AN is a risk factor for secondary osteoporosis. AN-related metabolic disturbances lead to diminished bone quality and increased risk of fractures. The consequences of low energy fractures are the main causes of death in women with AN. Hormonal disturbances (e.g. hypogonadism, increased levels of ghrelin and Y peptide, changes in leptin and endocannabinoid levels), as well as the mechanisms involved in bone resorption (RANK/RANKL/OPG), are considered to be of great importance for anorectic bone quality. The risk of osteoporotic, non-vertebral fractures in AN patients is significantly higher than in healthy women. An improvement of bone mineral density is possible after substantial body mass increase. Weight loss, in conjunction with a well-balanced, controlled diet, is the key to correct peak bone mass levels, and diminishes the risk of osteoporosis with its consequence of low energy bone fractures.

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**Key words:** *anorexia nervosa*, risk of fracture, secondary osteoporosis

## Streszczenie

W ostatnich latach obserwuje się znaczny wzrost częstości występowania jadłowstrętu psychicznego (AN, *anorexia nervosa*). Problem dotyczy zwłaszcza dziewcząt i młodych kobiet, ale coraz częściej dotyka także chłopców i młodych mężczyzn. *Anorexia nervosa* jest czynnikiem ryzyka rozwoju osteoporozy wtórnej. Zaburzenia metaboliczne, występujące u pacjentów z AN doprowadzają do pogorszenia jakości kości i w konsekwencji do zwiększenia ryzyka złamań. Ich następstwa są główną przyczyną śmiertelności chorych z AN. U podstaw zmian jakości kości wymienia się zaburzenia hormonalne (m.in. hypogonadizm, wzrost greliny i peptydu Y, nieprawidłowe stężenia leptyny i endokannabinoidów) oraz wynikające z tego faktu zakłócenia mechanizmu regulacji resorpcji kostnej (układ RANK/RANKL/OPG). Ryzyko pozakręgowych osteoporotycznych złamań kości u kobiet z AN jest znacząco wyższe niż u zdrowych rówieśniczek. Poprawa gęstości mineralnej kości następuje dopiero po uzyskaniu znaczącego wzrostu masy ciała. Przeciwdziałanie utracie wagi, nadzór nad prawidłowym odżywianiem są kluczem do osiągnięcia prawidłowej szczytowej masy kostnej, zmniejszenia ryzyka osteoporozy i złamań niskoenergetycznych kości. (Endokrynol Pol 2011; 62 (1): 45-47)

**Słowa kluczowe:** jadłowstręt psychiczny, ryzyko złamań, wtórna osteoporoza

Nutritional disorders such as *anorexia nervosa* (AN) and bulimia are considered to be psychosomatic disturbances, the incidence of which has grown over recent years. Girls and young women predominate in the general, AN-affected population. However, the disease is increasingly being diagnosed in boys and young men. AN is manifested by obsessive self-control of body shape, associated with grossly distorted perception of the sufferer's own body and a morbid fear of fatness. Affected patients refuse meals, while hiding the fact that food and eating restrictions are often combined with self-induced vomiting. Their attention is focused on meals,

weight control and a general concentration on eating and foods. Patients' weight plunges dramatically, while they impose more and more extreme dietary limitations on themselves.

Subjective symptoms of anorectic patients are scarce. Patients are convinced that a slim body shape is the key to a successful life, thus positively perceiving any weight control possibilities. They are unable to perceive their true emaciation, while evaluating their body shape with shame as all the time being too fat. Secondary amenorrhoea is a characteristic feature in such women. Patients also complain of dizziness and headaches, while mete-



orism and constipation are other frequent symptoms. Patients are often of above average intelligence, with high scores at school/university being obvious manifestations of a demand for success.

Medical examination of patients with anorexia finds a total disappearance of adipose tissue bordering on cachexia, together with bradycardia and low arterial blood pressure. The skin is cool and pale grey, often with very fine hair, and head hair is thinning. Hands are cold and sweaty. In advanced forms of the disease, lipoprotein oedemas of hands and feet are observed. The preserved tissue of mammary glands is a common feature, in contrast to the loss of adipose tissue in other body regions. Features of dehydration are simultaneously observed. Metabolic disorders, which occur in anorectic patients, lead to bone quality deterioration and, in consequence, to low energy bone fractures.

Studies have found that 40% of anorectic females experience periods of overeating and bulimia. In cases when a non-anorectic subject demonstrates such behaviour more often than twice a week, over a period longer than three months, bulimia would be diagnosed. Bulimia is characterised by paroxysmal overeating, followed by compensatory behaviour such as self-induced vomiting, fasting, the use of diuretics and laxatives, enemas and excessive physical exercise.

Anorexia nervosa is a dangerous disease which, despite treatment, carries a high risk of death. According to the literature, the consequences of osteoporotic bone fractures are at the base of disease complications and death among patients with anorexia. Therefore, osteoporosis should be acknowledged as one of the more serious, anorexia-related threats [1].

The aetiopathogenesis of the disease has yet to be fully understood. Some role in appetite distortion can be played by the disturbed synthesis of leptin and endocannabinoid, as well as of ghrelin, IGF-1 and melatonin [2–4]. Identified disorders of hormone and cytokine secretion can, however, be of secondary importance and they should thus be treated as a consequence of the disease, rather than its direct cause. This thesis is supported by the fact that, even if hormonal supplementation can induce menstruation, it does not mean a simultaneous withdrawal of the metabolic consequences of anorexia, for example those concerning mineral bone density, which improves only after a gain in body weight and better nutrition.

A diagnosis of anorexia is obtained from BMI values and when a patient demonstrates compulsive concentration on her/his body weight. Amenorrhoea is a characteristic feature of the disease in women.

In 20–50% of patients with anorexia, secondary osteoporosis is diagnosed, associated with elevated bone

fracture risks, especially in extravertebral locations [5]. Hormonal disorders, mainly hypoestrogenism, hypogonadism and hypercortisolemia, are at the base of anorexia accompanying bone quality changes [1, 6]. Moreover, anorectic patients present with decreased insulin-like growth factor 1 (IGF-1) concentrations and elevated levels of the growth hormone, ghrelin and peptide YY. In consequence of the above-mentioned hormonal disorders, young girls do not achieve age-optimal bone mass. It is assumed that it is the disturbed control of bone resorption activity which plays a significant role in the aetiopathogenesis of osteoporosis in anorectic patients. Some reduction of 17 beta oestradiol levels in the blood serum of patients reduces the synthesis of osteoprotegerin (OPG), a protein which suppresses the RANK/RANKL link (NK- $\kappa$ B, nuclear kappa-beta factor). This link plays an important role in the activation of osteoclasts. The connection of the TANK receptor with the kappa-beta factor induces a differentiation process of cells in the lines of macrophages and monocytes into preosteoclasts. The disturbed, mutual RANK/RANKL/OPG system shifts the trend of bone changes towards an excessive activation of osteoclasts, resulting in excessive bone resorption and bone mineral mass reduction [7].

The role of leptin in the aetiopathogenesis of anorexia is still not entirely explained. Leptin concentration is thought to play a certain role in cyclic oestrogen secretion control. Disorders of its secretion can be an additional factor affecting hypothalamic control of the menstrual cycle. Some anorectic patients present with secretion disorders of melatonin, especially in its nocturnal phase, which may additionally impair the mutual balance mechanism of the RANK/RANKL/OPG system [6, 7].

The lack of vitamins and mineral compounds, normally supplied via food, is also very important in the mechanism of bone mass loss, as observed in the course of anorexia. The deficits of food, vitamins (including vitamin D<sub>3</sub>), calcium and other mineral compounds, additionally disturb bone metabolism. Calcium assimilation from foods is more effective than from pharmacological agents. Also dietary calcium is better incorporated into bones. No intake of dietary supplements can be certain to provide comparable effects [8].

Abnormal concentrations of the biochemical markers of bone metabolism confirm the occurrence of bone metabolism disturbances in anorectic patients: an increased level of resorption markers (CTX-C, the terminal, cross-linked telopeptide of type I collagen alpha chain), with no simultaneous increase of bone-formation marker levels (P1NP, N-terminal propeptide of type I procollagen) [9]. Interesting observations concern the

differences, identified in the course of bone metabolism disorders, between young girls and more mature women. In the former, the total rate of bone metabolism cycles decreases, unlike in young women who demonstrate a growth of bone resorption intensity with a simultaneous lack of the compensatory acceleration of bone-formation process dynamics [10].

In girls with anorexia who are diagnosed before the age of 14, total bone mineral density may still remain within the range of values regarded as normal. However, BMD values, measured in vertebral bodies and in the proximal femoral bone, are already lower in that period of life as opposed to those in their healthy peers [11]. Also in boys, BMD reductions have been observed in various regions of the skeleton, with a distinctive slowdown of bone metabolism rate (confirmed by studied concentrations of the biochemical markers of bone metabolism), observed at the age in which the largest bone mass increase is but a physiological standard [10].

The younger the patient with anorexia, the lower the so-called peak bone mass they achieve. Optimal bone mass levels, obtained in young age, are of key significance for alleviating a later, age-related, gradual BMD decrease, especially that experienced after the menopause.

Metabolic disorders, which accompany anorexia, result in bone quality deterioration and BMD reduction, in particular, within the cortical bone, including impaired bone strength. Studies have demonstrated a distinctly higher risk of low energy bone fractures [12]. A meta-analysis, performed by Rigotti in anorectic women, confirmed the relationship between BMD reduction and increased fracture risk. In fact, the incidence of extravertebral, osteoporotic bone fractures in women with anorexia is statistically significantly higher than that in their normally-eating peers. In other nutritional disorders, such as bulimia nervosa, neither the BMD drop nor the fracture risk rise is so distinctive or attains the level of statistical significance [5].

An abnormal course of bone transformations, which accompany anorexia nervosa in contrast to bone metabolism disorders, which accompany amenorrhoea, does not respond to standard therapeutic management. In cases of menstrual disorders of hypothalamic origin, the standard oestrogen-progesterone therapy improves bone mass, but it fails to induce the same effect in girls with anorexia. BMD improvement can be expected only after a considerable increase of BMI [11, 13].

Similarly, studies performed for therapy efficiency evaluation in cases of secondary osteoporosis in anorectic patients do not provide results which can be com-

pared to therapy effects of other forms of osteoporosis. Clinical trials, including alendronate administration in AN patients, have provided very ambiguous results, ranging from reports which confirm the favourable effects of the therapy to others which claim no improvement at all [14].

Anorexia nervosa is now identified also in boys and young men. Keeping in mind the obvious differences, such as the lack of secondary amenorrhoea, the other symptoms are fairly similar. Changes in the bone system include BMD reduction in many regions of the skeleton. A slower rate of bone metabolism and reduced levels of achieved peak bone mass are the observed features [3].

Studies into the efficacy of applied therapy modes indicate, as with women, that the earliest possible diagnosis and high levels of persuasion to induce proper nutrition and effective body weight loss prevention are of key importance for the therapeutic prognosis [15].

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