# Osteoporosis in anorexia nervosa

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***Anorexia nervosa is a disorder characterized by low body weight and amenorrhoea (in females). These features lead to a risk of osteoporosis, a condition in which bone loss leads to weakening of bone structure and increased fracture risk.***

Although the incidence of anorexia nervosa (AN) has remained stable over time, several strands of evidence suggest that the illness has become more severe over the last 30 years (Moller-Madsen et al, 1996). Rates of admission to hospital have increased (Williams and King, 1987; Munk-Jorgensen et al, 1995), as has the mortality rate (Nielsen et al, 1998). One of the most profound aspects of morbidity is the effect that the illness has upon the skeleton.

Osteoporosis in young women as a result of AN is becoming a significant clinical problem. The causes are not completely understood, although they are likely to include malnutrition and oestrogen deficiency. The management issues are complex, because of the often chronic course of the disorder and the fact that treatment is often resisted. The aim of this article is to describe our current understanding of the pathophysiology and management of osteoporosis in AN.

## PROBLEMS OF CLASSIFICATION

One of the difficulties in describing the pathophysiology of bone in AN is that the clinical spectrum is broad. AN occurs most commonly in women, although around 1 in 10 anorexics are male (Hsu, 1989). Sufferers may present for treatment after 6 months or 26 years of illness. Severity can range from a body mass index (BMI)* of just below 17.5 in which there is little overt disability down to a BMI of less than 12, where all major organ systems are severely affected.

Onset of anorexia can occur at any time from childhood to maturity, although for the majority it occurs within 1–2 years of menarche. The impact on the skeleton is likely to vary considerably depending on these factors. For example, a period of AN during childhood is likely to result in stunted growth, whereas onset of the illness during the late teens and early twenties is likely to result in a failure to attain peak bone mass, leaving the sufferer at a high risk of developing osteoporosis (*Figure 1*). There is, as yet, no standardized way of describing the severity of the disease or the patterns of remission, relapse and recovery which commonly characterize the disorder.

Osteoporosis is most commonly diagnosed by measuring bone density at the femoral neck and lumbar spine using dual energy X-ray absorptiometry (DEXA). World Health Organization (WHO, 1994) guidelines suggest that bone density of 1 standard deviation below the population norm should be described as osteopenia, while bone density of 2.5 standard deviations or more below the norm is described as osteoporosis. Normal bone development does not occur in a linear fashion, but follows an N-shaped curve with a rapid increase in bone density at the time of puberty and a corresponding decrease (in women) at the menopause (*Figure 1*). This means that it is important to compare bone density in any clinical group with an appropriately matched control group. This can be done using age-matched norms (expressed as standardized z-scores).

A further difficulty in the assessment of osteoporosis is that the accuracy of bone density as a predictor of fracture risk has recently been questioned (Marshall et al, 1996). However, most studies of osteoporosis have been carried out in elderly women where the risk of falling because of poor coordination and muscle tone accounts for much of the variance in fracture rates. This is less likely to be an issue among women with a history of AN, which might mean that bone density will be a more accurate predictor of fracture

*Body mass index = weight in kg divided by height in metres squared.

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rate. Measures of bone turnover may have additional utility in this respect (Wilkin, 1999). We would suggest that, wherever possible, all three parameters of bone health, bone density, bone turnover and fracture rate, should be assessed where osteoporosis is suspected.

## DESCRIPTION OF THE PROBLEM

### Fracture rate

Fractures are one of the commonest causes of pain and disability in AN (Herzog et al, 1990). The annual incidence of non-spine fractures has been estimated at 0.05 per person year in AN. This is seven times the rate reported in an age-matched community sample (Rigotti et al, 1991).

### Bone density

There have been many cross-sectional studies of bone density in AN (Serpell and Treasure, 1997). However, it is difficult to get a clear overview of the risk factors because the case mix between series has differed greatly. Some have included patients with bulimia nervosa as well as those with restricting AN and the binge–purge subtype of AN. The ages of patients included also vary widely between studies.

Most studies have small sample sizes, thus the number of factors which can be used in analysis is limited. Nevertheless, a few factors have been found to predict bone density in the majority of studies. These are duration of amenorrhoea (Biller et al, 1989; Hay et al, 1992; Seeman et al, 1992; Herzog et al, 1993; Iketani et al, 1995; Brooks et al, 1998; Hotta et al, 1998) and BMI or some other variable which reflects body composition (Seeman et al, 1992; Iketani et al, 1995; Siemers et al, 1996; Hotta et al, 1998; Goebel et al, 1999). (These two variables are likely to be highly correlated with one another as amenorrhoea and oestrogen status are dependent on body weight.)

Other variables have been found to be significant predictors in one or two studies, for example levels of free cortisol (Biller et al, 1989) or relative oestrogen exposure (Herzog et al, 1993). The overall conclusion from these studies is that bone mineral density in eating disorders is related to the severity of the illness in terms of degree of weight loss and duration of illness. Although it is probable that intermediate metabolic and hormonal mediators such as cortisol, insulin, growth hormone and oestrogen are involved, one-off measurements of these variables are unlikely to adequately reflect long-term pathological processes. Similarly, the failure of measures of environmental factors such as exercise and dietary calcium intake to predict bone density in these studies may be because such variables are likely to influence bone density over many years, but are often assessed over much shorter periods of time.

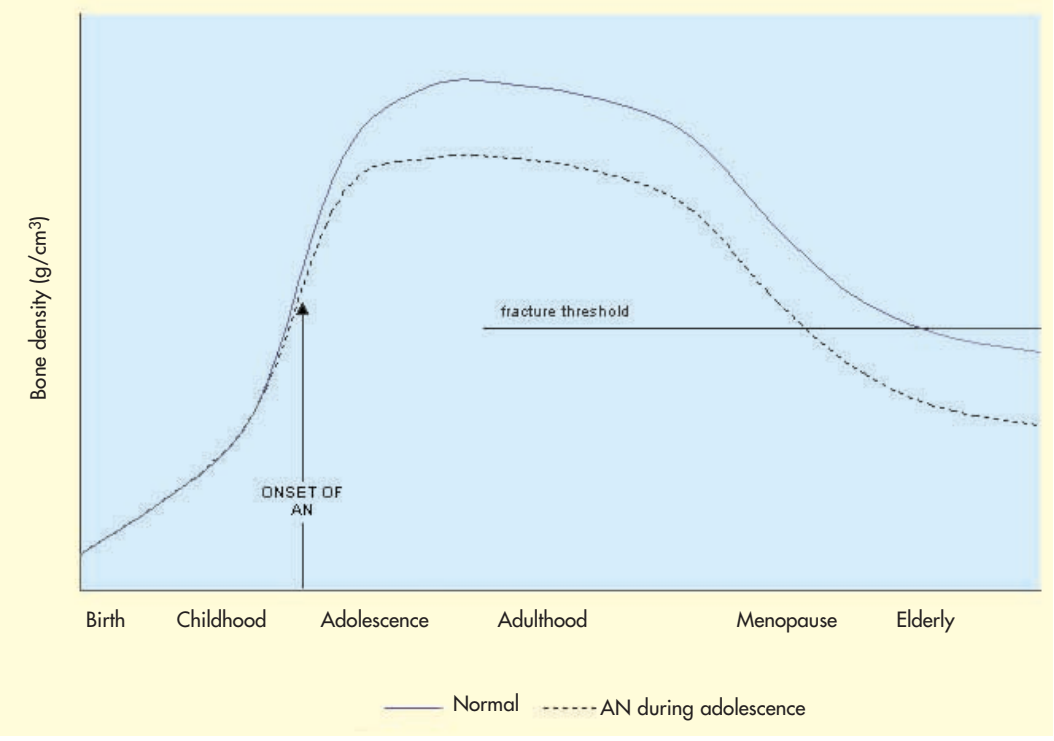


*Figure 1. Schematic representation of changes in bone density over the life cycle in normal women and women with adolescent onset of anorexia nervosa (AN).*

**Biochemical bone markers in AN**

The measurement of biochemical bone markers is a non-invasive, dynamic way of measuring changes in rates of bone formation and resorption (Delmas, 1993). Markers of bone resorption are increased in AN, suggesting active breakdown of bone tissue (Grinspoon et al, 1996). At the same time, markers of bone formation are within the normal range or somewhat reduced (Stefanis et al, 1998). Thus bone formation and resorption are decoupled and there is an overall depletion of bone minerals.

This differs from the high turnover state observed in postmenopausal women. In a cross-sectional study (Hotta et al, 1998), a relationship was found between BMI and markers of bone formation in AN. Patients with a BMI less than 15 showed little evidence of bone formation in the context of high resorption, suggesting that these patients will be at particularly high risk of rapid bone loss.

Our group has found that rapid changes in bone turnover occur once patients are re-fed (Stefanis et al, 1998). Twenty-one patients were followed over 8 weeks of refeeding. Bone markers were measured every 2 weeks, during which time weight increased from an average BMI of 13.0 to 16.7. Markers of bone formation had increased within 2 weeks and remained high over the remaining 6 weeks of the study. Levels of the resorption marker Type 1 carboxyterminal telopetide decreased after the first 2 weeks and remained at this lower level, while levels of urinary deoxypyridinoline remained above normal throughout the study. In a previous study (Treasure et al, 1987) we measured DEXA bone density in 15 patients on admission to our unit and also at the time of discharge 3–4 months later. In all but one case there had been an increase in bone density.

Thus it appears that nutrition alone can rapidly reverse bone loss in AN. However, although it is possible to correct the nutritional deficit in the short term by inpatient refeeding, the changes are not always maintained and over 50% of patients relapse. New forms of outpatient treatment are also being developed but often involve slower rates of weight gain and a proportion still fail to respond. Therefore additional supplementary treatments may need to be considered while therapeutic work is ongoing.

## LONGITUDINAL CHANGES IN BONE DENSITY

Several studies have examined changes in bone density longitudinally among patients undergoing treatment for AN. The success of the treatments in terms of weight gain varies between centres (and between individuals within centres) and the use of supplementary therapies such as calcium, vitamins or oestrogen also varies. The amount of bone change over time also depends upon which site is examined.

Rigotti and colleagues (1991) found no changes in radial bone density in a group of 27 adults patients with AN followed for over 6 months. However, most studies which have examined the lumbar spine have found an increase in bone density in patients who have gained weight (Bachrach et al, 1991; Iketani et al, 1995; Klibanski et al, 1995; Hotta et al 1998).

The relationship between change in BMI and increase in bone density is linear. Furthermore, among those who attain a weight within the normal range, the restoration of menstruation is associated with a further stepwise increase in bone density (Iketani et al, 1995).

## TREATMENT OF OSTEOPOROSIS

Not only is the response to treatment poor in AN, but it is also difficult to predict who will respond well. This makes planning the management of osteoporosis difficult. For example, most studies show that 30–50% of sufferers make a good recovery from AN. These women may not require additional treatment for their bones (although they may be at increased risk for the development of osteoporosis after menopause). The group who fail to respond to treatment for their AN are likely to be at greatest risk, particularly where onset occurs during childhood or adolescence.

Only one randomized controlled trial of the treatment of osteoporosis in AN has been published to date (Klibanski et al, 1995). This study examined the effect of oestrogen/progestin replacement with calcium supplementation. The treatment was well tolerated with only two dropouts from the oestrogen group.

However, after a mean follow-up time of 1.5 years, women with AN showed no significant change in bone density compared with unmedicated controls, although stratification of the data suggested that oestrogen/progestin replacement may prevent further bone loss in women with severe low weight (<70% ideal body weight). This is in marked contrast to the success of oestrogen therapy in the treatment of postmenopausal women.

Several further treatment studies are currently in progress. For example, our group are currently conducting a randomized controlled trial to assess the efficacy of calcium supplementation (with or without vitamin D) in a group of 86

women with a history of AN. Grinspoon and colleagues have shown a dose-dependent response to the short-term administration of insulin-like growth factor (IGF)-1 to women with AN (Grinspoon et al, 1996). The levels of bone formation markers doubled with a high dose but markers of bone resorption were also increased. With a lower dose, formation marker levels increased but resorption marker levels remained unchanged. However, this type of intervention is not likely to be useful in treatment, because of the requirement of constant glucose monitoring to prevent hypoglycaemia.

Other potential therapies under consideration include dehydroepiandrosterone (DHEA) (Gordon et al, 1999). The use of biphosphonates such as alendronate are not recommended in women of childbearing age, hence are unlikely to be suitable for these patients.

## CONCLUSIONS

Osteoporosis is a relatively common complication of AN. Much progress has been made towards understanding the epidemiology and pathogenesis of the problem, but further research in the form of randomized controlled trials is urgently needed to assess the efficacy of treatments of low bone density among patients with current or past AN. There is also a paucity of research concerning osteoporosis among male sufferers or those with onset during childhood. HM

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## KEY POINTS

- Osteoporosis is a common and serious complication of anorexia nervosa.
- Fracture risk is increased approximately seven-fold.
- Major causes are likely to include poor nutrition (including deficiencies in calcium and protein) and hypo-oestrogenaemia.
- Contributory factors are likely to include over-exercise, hypercortisolaemia, smoking and vitamin D deficiency caused by lack of sunlight exposure.
- Nutritional rehabilitation should be the primary aim of treatment. However, anorexia nervosa often follows a chronic course, meaning that alternative treatments should be considered.
- Research is currently in progress to establish the preferred treatment for the condition.
- There is little evidence for efficacy of oestrogen therapy in patients with anorexia nervosa, in contrast to its well established efficacy in postmenopausal women.

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