

Osteoporosis in Anorexia Nervosa: Prevention and Treatment

Philip S. Mehler

Department of Internal Medicine, Denver Health and The University of Colorado Health Sciences Center, Denver, Colorado

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Abstract: Background: *Osteoporosis is a very prevalent complication of anorexia nervosa. In contrast to the many other medical complications of anorexia, osteoporosis and its sequelae of fractures, kyphosis, and pain may persist regardless of the overall treatment outcome. Discussion:* *Traditional well-proven therapies for postmenopausal osteoporosis are not as effective against osteoporosis in anorexia nervosa. Therefore, clinicians who treat these patients must become increasingly vigilant about osteoporosis in regards to preventive, diagnostic, and treatment strategies.* © 2003 by Wiley Periodicals, Inc. *Int J Eat Disord* 33: 113–126, 2003.

Key words: *osteoporosis; anorexia nervosa; treatment strategies; mortality risks*

INTRODUCTION

The hallmark of anorexia nervosa is the marked emaciation among patients. Most of the medical complications of anorexia are a direct result of this weight loss and malnutrition (Mehler, 2001). Although many of the medical complications of anorexia nervosa are reversed by timely restoration of body weight, osteoporosis is one serious complication that often persists even after weight restoration and resumption of menses (Hartman, Crisp, & Rooney, 2000; Klibanski, Biller, Schoenfeld, Herzog, & Saxe, 1995). Therefore, clinicians who participate in the care of these patients must become familiar with the preventive, diagnostic, and therapeutic strategies available for osteoporosis associated with anorexia nervosa.

SCOPE OF THE PROBLEM

Osteoporosis is a major health problem associated with significant morbidity and mortality risks. In the United States, the annual health care cost for osteoporosis patients

Correspondence to: Dr. Philip S. Mehler, Denver Health, 660 Bannock Street, MC1914, Denver, CO 80204, E-mail: Pmehler@dhha.org

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is estimated to be between \$15 and \$20 billion. Anorexia nervosa patients and their predisposition to osteoporosis contribute to this large expenditure (Hamdy, 2001). More than 50% of female patients with anorexia nervosa develop osteoporosis (Powers, 1999; Treasure & Serpell, 2001). Similarly, more than 50% of men with anorexia nervosa have lumbar spine and femoral neck bone densities that are more than 2 *SDs* below age-matched controls (Andersen, Watson, & Schlechte, 2000).

It was once believed that amenorrhea, which is experienced by more than 95% of patients with anorexia nervosa, was devoid of adverse consequences. This thinking has changed radically. Amenorrhea predisposes women to low bone density and osteoporosis (Ayers, Gidwani, Schmidt, & Gross, 1984; Biller et al., 1989). Because osteoporosis is asymptomatic until a fracture occurs, the majority of patients are not even aware of having the disease. This is concerning because anorexia nervosa generally has its onset in adolescence, the same time as that in which peak bone mass is being acquired.

The peak bone mass achieved as a young adult is the major determinant of final bone density and fracture risk. Anorexia nervosa is associated with markedly reduced bone density, especially at the lumbar spine, but also at the proximal femur and distal radius (Bachrach, Guido, Katzman, Litt, & Marcus, 1990; Davies et al., 1990). Many of these patients will never reach their peak bone mass. As a result of this state of reduced bone density, anorectic adolescents experience diminished growth and an increased risk of painful fractures, disfiguring kyphosis, loss of height, and morbidity. The bone density of these patients does not increase to the normal range even several years after the recovery from anorexia nervosa. Consequently, they remain at high risk for osteoporosis in the future. Lucas, Melton, Crowson, and O'Fallon (1999) showed that the risk of any fracture in patients with anorexia nervosa increased almost threefold compared with age-matched controls. These authors also reported that the cumulative incidence of fractures among women 20 years after the diagnosis of anorexia nervosa was 57%. An older study (Rigotti, Neer, & Skates, 1991) reported that the risk for nonspine fractures is elevated 7.1-fold in anorectic patients. Therefore, there is a pressing need for clinicians who treat anorexia nervosa to increase their awareness of osteoporosis prevention and management before a significant problem occurs. A transient episode of anorexia in youth may permanently impair skeletal integrity. It is also important to educate the patient about the many serious bone-related risks associated with anorexia nervosa and to reassure them that clinically significant bone loss does not usually occur within the first 12 months of anorexia nervosa. Early and aggressive successful interventions for anorexia nervosa may prevent bone loss (Wong, Lewindon, Mortimer, & Shepherd, 2000).

NORMAL BONE METABOLISM

Remodeling of the skeletal structure continues even after growth has stopped. Bone is in a constant state of turnover with bony matrix being continually resorbed and reformed. Osteoblasts are the bone-forming cells and osteoclasts are the cells responsible for resorption of bone. Under normal circumstances, there is a dynamic and balanced coupling of osteoblast and osteoclast function. Thus, bone formation and bone resorption are linked.

These cells are in turn controlled by systemic hormones, cytokines, and trophic growth factors. One of the key hormones is parathyroid hormone (PTH). It stimulates osteoblastic recruitment and osteoclast-mediated bone resorption. Calcitonin, another endogenous hormone, directly inhibits osteoclast function. Similarly, estrogen decreases the recruitment

and responsiveness of osteoclast precursor cells. Therefore, in states of estrogen deficiency (e.g., menopause, anorexia nervosa), osteoclasts are activated by specific circulating cytokines, such as interleukin-1 and tumor necrosis factor (TNF). These cytokines, which are otherwise normally inhibited by the presence of estrogen (Jilka, Hangol, & Girasole, 1992), promote bone resorption, resulting in reduced bone mineral density. The majority of bone mass is acquired during adolescence through the complex interplay of these hormonal-cytokine factors together with the bone osteoblast and osteoclast cells (Bonjour, Theintz, Buchs, Slosman, & Rizzoli, 1991).

Decreases in bone density and the resultant state of osteoporosis occur either because bone resorption occurs at a faster rate than bone formation, there is overall decreased bone formation, or there is a combination of these abnormalities that results in excess resorption. By measuring serum and urine markers of bone formation (osteocalcin, bone-specific alkaline phosphatase) and bone resorption (urine deoxypyridinoline and serum carboxyterminal type 1N-telopeptide), the specific mechanism responsible for a particular case of bone mineral loss can be determined. Specifically, in postmenopausal osteoporosis, the main precipitant is an increase in bone resorption. In contrast, patients with anorexia nervosa may have reduced bone mineral density due to both an increase in resorption along with a decrease, or at a minimum, no concomitant increase in the rate of bone formation, and an uncoupling of this normally well-coordinated process (Grinspoon et al., 1999; Lennkh et al., 1999; Soyka, Grinspoon, Levitsk, Herzog, & Klibanski, 1999). The aforementioned markers of bone resorption are elevated in anorexia nervosa patients and the markers of bone formation are reduced (Stefanis, Mackintosh, Abraha, Treasure, & Moniz, 1998).

ETIOPATHOGENESIS

A number of putative factors may be involved with the severe and often irreversible state of low bone density in anorexia nervosa. Estrogen has been used for many years to prevent bone loss in postmenopausal women. This practice is supported by both observational and randomized trials (Cauley et al., 1995; Grady & Cummings, 2001). It seems logical to surmise that the estrogen deficiency and resultant amenorrhea, which define anorexia nervosa, are involved with the heightened osteoporosis risk (Anderson, Woodward, & La France, 1995). Studies have demonstrated that a longer duration of amenorrhea correlates with a greater reduction in bone mineral density (Herzog et al., 1993; Iketani, Kiriike, Nakanishi, & Nakasuji., 1995; Seeman, Szmukler, Formica, Tsalamadris, & Mestrovic, 1992). When amenorrhea begins before the age of 18 years, the deleterious effects on spinal bone density are even more severe (Biller et al., 1989). Similarly, in male anorectics, the physiologic effects of testosterone deficiency may affect bone density because testosterone is a major substrate for estrogen production (Swerdloff & Wong, 2000). However, some studies fail to support the correlation between reduced bone density and low levels of sex hormones (Bachrach et al., 1990; Hergenroeder, 1995). Because of the inconsistencies among reports, it is believed that other factors are involved because patients with anorexia nervosa have more profound bone loss than amenorrheic athletes without anorexia nervosa (Grinspoon, Gulick, Askari, & Landt, 1996).

Other putative factors may include different cytokines and hormones. Several studies of anorexia patients found decreased levels of insulin growth factor-1 (IGF-1), a hormone that is naturally trophic to bone and stimulates its growth via osteoblast function (Grinspoon et al., 1996). There is a direct correlation between lower body weight and

reduced levels of IGF-1 in anorexia nervosa patients, which leads to ongoing bone resorption without concomitant bone formation. Conversely, serum levels of IGF-1 increase with weight restoration (Counts, Gwirtsman, & Carlsson, 1992).

Elevated serum cortisol and urinary free cortisol levels are also potential causative factors of osteoporosis in anorexia nervosa patients (Biller et al., 1989; Boyar, Hellman, & Roffuarg, 1997). This is due to increased hypothalamic-pituitary secretion along with diminished renal clearance of cortisol (Gold, Guirstman, & Augerinus, 1986; Newman, & Halmi, 1989). Carmicheal and Carmichael (1995) showed a relationship between urinary and serum cortisol levels and a reduction in bone formation and density, especially in trabecular bone.

However, Soyka et al. (1999) found little correlation between cortisol levels and bone density in anorexia nervosa patients. Elevated cortisol levels did not explain the lower bone densities found in patients with anorexia nervosa compared with hypothalamic amenorrheic patients (Grinspoon et al., 1999). Hypercortisolism would be a plausible explanation for the marked osteoporosis found in anorexia nervosa. Elevated levels of cortisol decrease bone formation and hasten bone resorption, which promote trabecular bone loss. However, there are no definitive data to implicate cortisol (Biller et al., 1989).

Another hormone that may be involved is leptin because low levels are found consistently in patients with anorexia nervosa (Grinspoon et al., 1999; Mehler, Donahue, & Eckel, 1999). Leptin may have an effect on IGF-1, especially in low body weight states (Mundy, 1999). Additional clarification of leptin's exact role is needed.

Rates of bone formation increase when overall nutritional intake improves (Hotta et al., 2000). Nutritional intake and dietary habits also have a direct relationship with exercise-related menstrual irregularities (DeCree, 1998). However the strength of this association is weakened because bone biopsies in patients with anorexia nervosa do not demonstrate evidence of osteomalacia, or abnormal bone mineralization. As a result, the specific mechanisms that underlie the bone damage in anorexia nervosa patients have not been elucidated fully.

DIAGNOSIS

Patients with anorexia nervosa have a much greater degree of osteopenia compared with estrogen-deficient patients with amenorrhea but without malnutrition (Grinspoon, Thomas, Pitts, & Gross, 2000). Because of the long-term severe consequences of osteoporosis in this relatively young population of patients, and the potential irreversibility of the reduction in bone density, timely diagnosis and screening strategies are of utmost importance. The National Osteoporosis Foundation (1998) recommends a bone densitometry test for women younger than 65 years of age who have one or more risk factors for the development of osteoporosis. Low body weight qualifies as one such risk factor. In addition, these guidelines specifically mention the amenorrhea of anorexia nervosa as an additional risk factor (National Osteoporosis Foundation, 1998; Osteoporosis, 1998). The main goals of the diagnostic approach are to establish the diagnosis of osteoporosis in anorexia nervosa, to quantify the severity of the disease, and to monitor the patient's progress in response to therapy.

Dual-energy x-ray absorptiometry (DEXA) is the most commonly used technique for measuring bone density and is currently viewed as the gold standard. During this relatively short procedure (less than 30 min), two energy beams are directed at the patient. The radiation risk associated with the DEXA scan is very low and is estimated to be less than 10% of that of a chest x-ray.

Table 1. World Health Organization *t*-score and diagnostic guidelines for osteoporosis

Diagnosis	<i>t</i> Score
Normal bone density	+1.0 to -1.0
Osteopenia	+1.0 to -2.5
Osteoporosis	-2.5 and lower

An x-ray radiograph, such as a spine film, is not precise enough to determine the presence of osteoporosis even though it may show reduced bone density. Bone mineral density is a calculated value ascertained by dividing the bone mineral content by the surface area of the bone scanned. The patient's bone mineral density is then compared with that of a reference population of the same gender. The *t* score represents the number of standard deviations from normal, when a patient's bone mineral density is compared with that of a young, healthy reference population. The World Health Organization has issued guidelines to help define the degree of bone demineralization by using the *t* score (Table 1). The normal range is above -1.0. Patients with osteopenia or reduced bone mineral density have *t* scores that range from -1.0 to -2.5. This is the extent of what can be diagnosed from a simple x-ray. Patients with full-blown osteoporosis have *t* scores below -2.5 (Kanis, Melton, Christiansen, Johnston, & Khaltaev, 1994). Of note, this classification is intended only for the lumbar vertebrae, proximal femur, radius, and ulna of postmenopausal women. However, for clinical purposes, these guidelines are extended to other populations given the absence of other specific guidelines. There is a good correlation between the *t* score and the risk of a bony fracture (Marshall, Johnell, & Wedel, 1996). As the *t* score becomes more negative, there is an exponential rise in the risk of osteoporotic fractures. Siris et al. (2001) demonstrated that women with clinically significant low bone mineral density have an increased risk of incident fracture within 1 year.

Technology that measures the bone mineral density of peripheral bones (e.g., the heel and fingers) is being used to diagnose osteoporosis because of the potential diagnostic cost savings. However, possible drawbacks include the lack of normalized data for test comparison and there are no therapeutic or standardized guidelines for the new tests. Ultrasound of the heel bone has been used as a new modality for diagnosing osteoporosis (Resch et al., 2000). This method of diagnosis is affordable, radiation is not a factor, and performance time is minimal. However, there is limited information to validate and universally endorse its role. DEXA remains the recommended method for diagnosing osteoporosis, monitoring therapy, and assessing fracture risk (Genant, Cooper, & Poor, 1999; Kanis, & Gluer, 2000).

There are no specific laboratory tests to diagnose osteoporosis. Blood tests are used to exclude secondary and unrelated causes of osteoporosis and to monitor patient response to therapy.

Likewise, there are no definitive data with regard to the proper time to obtain the initial DEXA scan in anorexia nervosa patients. Prudence would suggest that DEXA has an important role in the ongoing care of these patients in view of their high risk for the development of severe osteoporosis. Some experts have recommended a DEXA scan for all anorectic patients with a history of 2 years or more of anorexia nervosa (Treasure & Serpell, 2001). This is a reasonable recommendation because the discovery of a significantly reduced bone density measurement has important treatment and clinical management implications. Moreover, the DEXA results provide graphic visual evidence that the anorectic patient has a serious medical problem. It is easy to share the DEXA results with

these young patients and to advise them that they are progressing toward having the same bone mineral density as an 80-year-old woman (Mehler & Andersen, 2000). This information may be used successfully in psychotherapy to promote change and encourage restoration of full body weight.

There is an emerging consensus that follow-up DEXA scans should be performed regularly until there is resumption of menses and substantial weight restoration. The exact interval for these follow-up scans has not been defined. However, serial DEXA scans are indicated for individuals who are being monitored to assess the efficacy of osteoporosis therapy. They are also recommended in other clinical situations associated with progressive bone mineral loss. Waiting at least 1–2 years after the initial scan is reasonable because most successful treatment regimens for osteoporosis will not result in detectable improvements in bone density in less than 2 years.

TREATMENT

Anorexia nervosa is often a protracted illness with onset in adolescence (Sullivan, Bulik, Fear, & Pickering, 1998; Zipfel, Lowe, Peter, & Herzog, 2000). The adolescent years represent a critical period for bone mineral deposition. Failure to achieve peak bone mass during this time is an important risk factor for the subsequent development of osteoporosis. Clinicians should know the main predictors of low bone density in anorexia nervosa patients to help guide the diagnostic and therapeutic approaches to osteoporosis prevention and treatment in this population.

The duration of anorexia nervosa is a predictor of low bone mineral density. The longer the duration of the illness, the greater the reduction in bone mineral density. There is a significant correlation between spinal bone mineral density and the duration of emaciation below a body mass index (BMI) of 15 kg/m² (Hotta, Shibasaki, Sato, & Demura, 1998). A longer duration of amenorrhea is also associated with a greater reduction in bone density (Bachrach et al., 1990). It is not surprising that low serum estrogen levels are correlated with low bone density (Turner et al., 2001). Yet, studies have shown that estrogen supplementation does not improve bone density in anorexia nervosa patients. A possible way to explain this dichotomy is that current estrogen level is not the issue. Rather, cumulative estrogen exposure is the key determinant of bone density. Lean body mass is also a predictor of bone mineral density (Grinspoon et al., 1999). This and other markers of body composition such as BMI correlate with bone density (Siemers, Chakmakjian, & Gench, 1996). Presumably, this is due to the passive mechanical loading on bone (Heaney, 1998). Normalized present and past weight may be the best predictor of lumbar bone density (Goebel, Schweiger, Kruger, & Fichter, 1999). Clinicians should heighten their vigilance of the patient with anorexia nervosa who has profound weight loss and a longer duration of amenorrhea.

THERAPEUTIC OPTIONS

There is a dearth of prospective randomized trials to definitively guide the prevention, treatment, and management of osteoporosis in patients with anorexia nervosa. The emphasis must be placed on aggressive multidisciplinary treatments to facilitate early restoration of body weight and return of menses before significant bone loss occurs.

Weight restoration is a safe and effective way to attenuate the rate of loss of bone mineral density. It is a safe and effective means to increase bone mass (Bachrach, Katzman, & Litt, 1991; Stefanis et al., 1998), although it is imprudent to conclude that bone density will return to preillness levels with weight gain (Baker, Roberts, & Towell, 2000; Carmicheal, & Carmicheal, 1995; Rigotti et al., 1991). One study suggested that more than 50% of women with a previous history of anorexia nervosa will suffer at least one bony fracture by age 40 and that fracture risk among these women is about triple that of women without a history of anorexia nervosa (Lucas et al., 1999). Although the full extent of the benefit from weight gain on bone density may not be known, its effect to at least prevent additional bone loss lends credence to its overall importance.

The role of physical activity in anorexia-related osteoporosis is again somewhat nebulous in contrast to the general population where it has a beneficial effect on bone mineral density. Physical activity is necessary for bone mineral acquisition and maintenance throughout adult life. High impact exercise such as running and weight lifting stimulate the accrual of bone mineral content in the skeleton. However, physical activity has both a protective and a harmful effect on bone density in anorexia nervosa patients. Higher levels of physical activity in anorectic women are associated with higher mean cortical bone density than in less active patients (Rigotti, Nussbaum, Herzog, & Neer, 1984). This association remained significant in multivariate analyses that accounted for confounders such as age, weight, and duration of amenorrhea and disease. In this study, however, the bone density of active anorectics did not differ from sedentary controls. Bachrach et al. (1990) compared the bone mineral density in anorectic patients with low, moderate, and high activity levels and found no correlation with exercise patterns. Soyka et al. (1999) and Hay et al. (1989) did not find a relationship between the amount of physical activity and bone mineral density in patients with anorexia nervosa. Others have found moderate exercise to have a protective effect and strenuous exercise to be detrimental (Joyce, Warren, Humpries, Smith, & Coon, 1990). Sundgot-Borgen, Bahr, Falch, and Schneider (1998) examined bulimic and anorectic women and discovered that bulimics who exercised regularly had a higher bone mineral density in weight-bearing areas but anorectic patients did not. Of the 13 anorectics in the study, 9 had osteoporosis despite excessive exercise. An explanation may be that excessive exercise in patients with anorexia nervosa contributes to further weight loss with the overall net result being detrimental to bone density. In estrogen-deficient and underweight anorectics, endurance training is insufficient to decrease the rate of bone turnover and increase bone formation (Dalsky, 1992).

Nonpharmacologic treatment (i.e., weight restoration) of osteoporosis is beneficial. The benefits of pharmacologic treatment are less definite. Physicians have believed for many years that estrogen products, either in the form of oral contraceptives or estrogen replacement therapy, would prevent bone density loss in anorectic women as they have in postmenopausal women. Estrogen therapy initiated soon after menopause prevents further bone loss and improves bone mineral density (Bore et al., 2000; Speroff, Rowan, Symons, Genant, & Wilborn, 1996). It was logical to surmise that this benefit would extend to anorectic women based on the fact that estrogen and progesterone levels are low in anorectic and postmenopausal women. Once a patient with anorexia nervosa regains 90% of her total body weight, there will generally be resumption of menses within 6 months (Golden et al., 1997).

Observational studies consistently demonstrate that estrogen-based hormone therapy reduces the risk of hip and other types of fractures in postmenopausal women and randomized trials show that estrogen prevents postmenopausal bone loss (Grady &

Cummings, 2001). Villareal et al. (2001) reported that estrogen improved bone mineral density and had a significant osteogenic effect with an increase of bone mineral density of 4.3% in elderly frail women. It has been both surprising and disappointing to learn that exogenous estrogen did not preserve or restore bone mass in anorexia nervosa patients (Grinspoon et al., 2000; Iketani et al., 1995; Klibanski et al., 1995). Very early studies also raised doubts about the ultimate efficacy of estrogen for improving bone density in anorectic patients (Rigotti et al., 1984). In addition, there is also some concern about using estrogen in adolescent anorectics because it might accelerate fusion of the epiphyses, thereby compromising final adult height.

Conversely, evidence suggests that estrogen may still have a beneficial role in the treatment and prevention of osteoporosis associated with anorexia nervosa. In some studies, resumption of menses correlated with improvements in bone mineral density (Iketani et al., 1995; Klibanski et al., 1995). In others, a longer duration of amenorrhea in anorexia nervosa patients was associated with more severe bone loss (Baker et al., 2000; Grinspoon et al., 2000). Contraceptive use among patients with anorexia nervosa was associated with greater bone mineral density at the lumbar spine than in patients who did not use contraceptives, although bone mineral density was still lower than in controls (Seeman et al., 1992).

It is imperative that clinicians be cognizant of the concern that hormonal therapy is not, as initially believed, the panacea for the possibly irreversible osteoporosis of anorexia nervosa. However, estrogen replacement therapy should not be abandoned completely at this time. There is only one randomized controlled trial involving estrogen in anorexia nervosa patients. It comprised a relatively small number of patients with an average follow-up of only 18 months (Klibanski et al., 1995). The quartile of patients followed for the longest period of time did show a 4% increase in bone density. Although it appears that the benefits of estrogen are at best equivocal in anorexia nervosa, estrogen therapy should be evaluated further as a treatment modality. The ideal hormone replacement agent should be safe, effective, inexpensive, and acceptable to patients. Unfortunately, this ideal agent has not been identified yet.

In view of the less than convincing evidence for estrogen's efficacy with regard to osteoporosis in anorexia nervosa, hormonal medications, if utilized, should contain low levels of estrogen to minimize potential adverse effects. These pills, which contain on average 30–35 μm of estrogen, are referred to as low-dose pills. Some representative medications from this class are shown in Table 2. Side effects may include nausea, breast tenderness, and breakthrough bleeding (menstrual bleeding at a time other than the normal cycle). All of these agents also have a mild procoagulant effect among users and increase the risk of blood clots. These medications should be avoided by women with a previous history or strong family history of thromboembolism. Smoking has a synergistic effect with hormonal therapy to increase the risk of clotting. Additional contraindications to the usage of estrogen include active liver disease, undiagnosed abnormal

Table 2. Common oral contraceptives available in the United States

Name	Estrogen Content (μg)
Norethindrone acetate (Loestrin) (Parke Davis, Morris Plains, NJ)	20
Desogestrel (Desogen) (Organon, West Orange, NJ)	30
DL-norgestrel (lo/Ovral) (Wyeth-Ayerst, Philadelphia, PA)	30
Norgestimate (Ortho-Cyclen) (Ortho-McNeil, Raritan, NJ)	35
Norethindrone (Ortho-Novum) (Ortho-McNeil, Raritan, NJ)	35

uterine bleeding, age older than 35, and smoking more than 10 cigarettes per day (Jelley, 2001). Depot medroxyprogesterone acetate ("Depo") may cause or accelerate bone loss in young women, and therefore should be avoided as a contraceptive choice by patients with anorexia nervosa (Berenson, Radecki, Grady, Rickert, & Thomas, 2001). Interestingly, dehydroepiandrosterone (DHEA), an adrenal hormone, normalizes bone turnover in young women with anorexia nervosa (Gordon et al., 1999).

The data regarding calcium, the single most important nutrient for attaining peak bone mass, are at best tenuous (Barr, Petit, Vigna, & Prior, 2001). In one study, 1,500 mg of calcium per day did not preserve bone density in anorexic patients (Rock, 1999), although it may help to lessen bone loss (Spear, 2001). A recent prospective study of calcium supplementation in women with anorexia nervosa also showed that calcium was unable to reverse bone loss (Treasure & Serpell, 2001). This finding was disappointing because calcium and vitamin D supplementation prevented bone loss in patients with rheumatoid arthritis who were also being treated with corticosteroids (Buckley, Leib, Cartularo, Vacek, & Cooper, 1996). Some authors implicated cortisol excess in the pathogenesis of osteoporosis in anorexia nervosa (Billier et al., 1989; Lucas et al., 1999). Despite this lack of definitive evidence, daily calcium (1,500 mg/d) and vitamin D (400 IU/d) supplementation are the standard of care for amenorrheic patients with anorexia nervosa. Calcium is best absorbed with food. Therefore, patients should take calcium supplements with their meals to optimize absorption of the nutrient (Singh, Singh, & Hershman, 2000).

Other potential pharmacologic modalities for treatment include calcitonin, bisphosphonates, and selective estrogen receptor modulators (SERMs; Table 3). Alendronate and risedronate, the two available oral bisphosphonates, are effective and approved for preventing and treating osteoporosis. They both have similar pharmacokinetics, drug interactions, adverse side effect profiles, and efficacy. Currently, they are only indicated and approved by the Food and Drug Administration for preventing and treating postmenopausal and steroid-induced osteoporosis (Fogelman, Ribot, & Smith, 2000; McClung, Clemmesen, & Daifotis, 1998). Alendronate and risedronate increase bone mineral density by 5%–10% over 2–4 years and reduce fracture risk by 30%–50% (Lieberman et al., 1995). The exact mechanism of action of these bisphosphonates has not been elucidated fully. Their unequivocal efficacy in some conditions is related to their ability to inhibit bone resorption without suppressing bone formation, resulting in increased bone mass and mineralization. For example, oral bisphosphonates have positively transformed the management and prognosis of steroid-induced osteoporosis. Given the possible role of excess cortisol in the osteoporosis of anorexia nervosa as described above, together with the proven efficacy of bisphosphonates for treating glucocorticoid-induced osteoporosis, there is added reason to hope for their potential efficacy in anorexia nervosa (Adachi et al., 1997).

Bisphosphonates must be used with caution. They have not been tested in people younger than 18 years old. Both alendronate and risedronate have been rated as risk

Table 3. Therapeutic modalities for osteoporosis in anorexia nervosa

Treatment	Level of evidence for efficacy
Weight restoration	Strong
Calcium-vitamin D	Moderate
Estrogen	Weak
Bisphosphonates	Unproven
Exercise	Unproven

category C, which means that adverse fetal effects have been shown in animals, but no human data are available. They bind to the surface of bone and remain there for many years. There is the theoretical concern that during pregnancy they may be released from maternal bone and transferred to the fetal skeleton (Dawson-Hughes, 2001). In addition, they have been associated with localized irritative effects on the linings of the esophagus and stomach. The absolute risk of esophageal problems is overstated. However, alendronate and risedronate should be avoided if the patient cannot stand or sit upright for at least 30 min after administration or if the patient has known abnormalities of the esophagus that delay esophageal emptying, such as a stricture for which bulimic patients may be at risk (Peters, Leonared, & Licata, 2001). Alendronate has been approved for once-weekly therapy at a dose of 35 mg for prevention and 70 mg for treatment of osteoporosis. The improved patient compliance and tolerability of the once-weekly formulation may offset the slight increase in cost (Schnitzer et al., 2000).

It is also important to be aware that bisphosphonate therapy, which has been so successful in treating and preventing postmenopausal osteoporosis, is of unproven efficacy in anorexia nervosa patients. Given the facts that anorexia nervosa is characterized by a low bone turnover and that these medications reduce bone resorption and increase bone formation, they may have a place in the overall treatment program. However, there are lingering concerns about the long-term safety of these medications if initiated during adolescence and about the possible teratogenic effects during subsequent pregnancies. At this time, they cannot be endorsed universally for anorexia nervosa patients. They might be prescribed on a case-by-case basis if, for example, a DEXA scan shows progressive osteoporosis despite therapy in patients with chronic and protracted anorexia nervosa. With additional study, bisphosphonate therapy may ultimately be proven to benefit patients with anorexia nervosa.

Raloxifene, in a dosage of 60 mg/d, is a relatively new medication from the class of SERMS. These medications were developed as a substitute for estrogen in postmenopausal women in whom estrogen is contraindicated. Raloxifene reduces spine fractures by 5% and improves bone mineral density by suppressing bone turnover (Ettinger, Black, & Mitlak, 1999; Johnston, Bjarnason, & Cohen, 2000). However, there are no data regarding their efficacy in anorexia nervosa patients. It is unlikely that SERMs would be more effective than estrogen. The data are at best equivocal as described above.

Calcitonin, both the inhaled and subcutaneous preparations, is effective in postmenopausal osteoporosis. It is used as a substitute for bisphosphonates. Significant reductions in vertebral fracture risk can be achieved with salmon calcitonin because it increases bone mineral density at the lumbar spine. There is no evidence supporting its use in anorexia nervosa patients. Of note, calcitonin has no associated significant adverse effects, which ultimately might enhance its utility.

The currently available therapies are antiresorptive, which limits the magnitude of the ultimate increase in bone mass. Future research should focus on agents that also stimulate bone formation and have the potential for larger bone mineral density increases (Altkorn & Vokes, 2001).

MALES WITH ANOREXIA NERVOSA

Although anorexia nervosa predominantly affects females, the bone injury found in male anorectics is at least as severe or may be even more severe than in females with anorexia nervosa. Andersen et al. (2000) reported that almost one half of the male

patients with anorexia nervosa had substantial reductions in their bone mineral density. Low testosterone levels may be potentially responsible for the osteoporosis found in males. The optimal treatment regimen for osteoporosis in males with anorexia nervosa is not known. Testosterone replacement might be a logical therapeutic approach. However, there are no definitive data regarding this type of therapy (Scurlock, Timini, & Robinson, 1997).

CONCLUSION

There is an unexpectedly high prevalence of osteoporosis among anorexia nervosa patients. Because of clinically low bone mineral density, they are at increased risk for permanent reduced bone density and for incident fractures and associated morbidity. It is important that clinicians know the proper strategies to identify, manage, and successfully treat osteoporosis in anorexia nervosa. Weight restoration is key along with adequate calcium supplementation and bisphosphonate and SERM therapy. Calcitonin should be used with caution on a case-by-case basis. The latter therapeutic regimens, including bisphosphonates, SERMs, and calcitonin, have not been studied adequately in patients with anorexia nervosa and thus must still be considered experimental. Successful management to prevent osteoporosis and/or restore bone mass must be a high priority to prevent serious long-term complications from bone loss in young patients with anorexia nervosa.

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