ABSTRACT. Adolescents with anorexia nervosa (AN) are at risk for low bone mass at multiple sites, associated with decreased bone turnover. Bone microarchitecture is also affected, with a decrease in bone trabecular volume and trabecular thickness, and an increase in trabecular separation. The adolescent years are typically the time when marked increases occur in bone mass accrual towards the attainment of peak bone mass, an important determinant of bone health and fracture risk in later life. AN often begins in the adolescent years, and decreased rates of bone mass accrual at this critical time are therefore also concerning for deficits in peak bone mass. Factors contributing to low bone density and decreased rates of bone accrual include alterations in body composition such as low body mass index and lean body mass, and hormonal alterations such as hypogonadism, a nutritionally acquired resistance to GH and low levels of IGF-I, relative hypercortisolemia, low levels of leptin, and increased adiponectin (for fat mass) and peptide YY.

Therapeutic strategies include optimizing weight and menstrual recovery, and adequate calcium and vitamin D replacement. Oral estrogen-progesterone combination pills are not effective in increasing bone density in adolescents with AN. Recombinant human IGF-I increases levels of bone formation markers in the short term, while long-term effects remain to be determined. Bisphosphonates act by decreasing bone resorption, and are not optimal for use in adolescents with AN, in whom the primary defect is low bone formation. (J. Endocrinol. Invest. 34: 324-332, 2011) ©2011, Editrice Kurtis

INTRODUCTION

The adolescent years are a common time for the onset of anorexia nervosa (AN), a condition characterized by low weight, an intense fear of gaining weight, body image impairment, and in post-menarchal girls, amenorrhea for at least 3 consecutive cycles. As many as 0.2-4% of teenage girls and college aged young women are reported to suffer from this devastating eating disorder (1). Of concern, the onset of AN is often during the adolescent years, when bone mass accrual is maximal and attainment of peak bone mass is normally occurring (2). The condition is associated with alterations in multiple endocrine axes, and many of these hormonal alterations have a deleterious impact on bone metabolism. In this review, we will discuss bone metabolism in adolescents with AN, the pathophysiology underlying low bone mass in this condition, and potential therapeutic strategies.

BONE DENSITY AND MICROARCHITECTURE IN ADOLESCENTS WITH AN

Low bone density is common in adolescent girls and boys with AN compared with healthy adolescents (3-5). In a series of 60 adolescent girls with AN and 58 normal-weight controls, we assessed bone density using dual energy x-ray absorptiometry (DXA), and reported Z-scores of <–1 at one or more sites in 41% of the girls with AN and Z-scores of <–2 in an additional 11% (3). Bone density is lower in AN than in controls at multiple skeletal sites. Both the spine (primarily trabecular bone) and the hip (primarily cortical bone) are affected in girls with AN, although trabecular bone overall seems to be affected more than cortical bone. Measurement of bone density by DXA can underestimate bone mass in children, especially short children. Importantly however, height-adjusted measures of bone density, such as spine bone mineral apparent density (BMAD) and whole body (WB) bone mineral content/height (BMC/Ht) (and corresponding Z-scores) are lower in girls with AN than normal-weight controls, supporting the concept that low bone density measurements in AN are not an artifact of shorter stature (6). In fact, in this cohort, girls with AN did not differ from controls for height or height SD score.

In addition to these worrisome cross-sectional data, prospective data indicate that girls with AN have a reduced rate of bone mass accrual compared with normal-weight controls. Whereas healthy girls continue to accrue bone over time, girls with AN have little or no increase in bone mass, leading to a continuing decrease in bone density Z-scores compared to normal girls (5). The lack of bone accrual in these critical adolescent years can result in permanent deficits in peak bone mass, and adult women who develop AN in their adolescent years have lower bone density than women who develop this disorder in adult life, even after controlling for the duration of amenorrhea or duration of illness (7).

Although AN occurs mainly in females, males also develop AN and studies have shown that bone mass is reduced in boys with this disorder. We examined bone...
density in 17 adolescent boys with AN compared with 17 normal-weight controls, and reported lower bone density at multiple skeletal sites (spine, total hip, femoral neck, and WB) in boys with this eating disorder (4). However, in contrast to girls with AN, bone density appears to be more severely affected in cortical than in trabecular sites in boys with AN, with hip bone mineral density being most affected. In this study, 59% and 65% of boys with AN had Z-scores of <-1 at the hip and the femoral neck respectively, compared with 24% and 18% of normal-weight controls. In contrast, the proportion of boys with low bone density Z-scores at the spine did not differ between the groups. As in girls, height-adjusted measures of bone density (spine BMAD and WB BMC/Ht) and their Z-scores are lower in boys with AN compared with controls. Castro et al. have similarly reported high rates of low bone density in adolescent boys with AN, with 35% of the boys having Z-scores of <-1 at the spine and the femoral neck (8).

An important new area of investigation in bone biology and fracture-risk prediction has been assessment of bone microarchitectural parameters and bone strength. Studies in adult women with AN using high resolution (HR) peripheral quantitative tomography have reported decreased cortical thickness compared with normal-weight women, and decreased trabecular bone density, trabecular number as well as increased trabecular separation (9). We reported lower bone trabecular volume, lower trabecular thickness and number, and greater trabecular separation in adult women with AN compared with controls, using flat panel ultra HR volume CT (FpVCT) (10). We have also examined bone microarchitecture using FpVCT in adolescent girls with relatively mild AN, and have reported that these girls have lower bone trabecular volume, lower trabecular thickness, and greater trabecular separation than controls (11). The important point made in this study was that abnormalities in bone microarchitectural parameters were found in these girls even though their bone density was still normal. These data suggest that deleterious microarchitectural changes may occur even before bone density decreases can be detected by DXA. Finally, we have used finite element analysis to demonstrate decreased bone strength in women with AN, as indicated by lower failure load and stiffness (12). All these data indicate significant bone impairment in AN.

A few studies have used quantitative ultrasononography (QUS) to assess the impact of AN on bone. One study reported higher speed of sound (SOS) at the radius and tibia in adolescent girls with AN than in controls (13). However, in this study, SOS did not correlate with DXA measures of bone density, height-adjusted measures of bone density (such as spine BMAD), or with anthropometric parameters, leading the authors to conclude that QUS was not an effective measure of bone density in AN. In contrast, a prospective study reported a significant decrease in amplitude-dependent SOS Z-scores of the hand phalanges in girls with AN over a mean of 19 months of follow-up, concerning for a worsening of bone density over time, leading the authors to infer that QUS of the phalanges may be a good method to monitor bone density in AN (14).

BONE TURNOVER IN ADOLESCENTS WITH AN

Normal adolescence is characterized by increased bone turnover with increases in levels of both bone formation and bone resorption markers, particularly in the early pubertal years (15). This increased bone turnover is believed to be consequent to rising levels of GH and IGF-I in puberty. Subsequently, in later puberty, as levels of gonadal steroids increase, bone turnover decreases and approaches adult levels. In contrast to healthy adolescents, teenage girls and boys with AN have lower levels of both bone formation and bone resorption markers than normal-weight controls (4, 5, 16), suggestive of a reduced state of bone turnover contributing to low bone density. This is also in contrast to adults with AN, who have an uncoupling of bone turnover markers, with a decrease in bone formation, and an increase in bone resorption markers (17).

PATHOPHYSIOLOGY UNDERLYING LOW BONE DENSITY IN AN

Alterations in body composition

Body composition is a known important determinant of bone density. In both boys and girls with AN, body mass index (BMI), fat mass, and lean mass are lower compared with healthy controls (3, 4). We have reported that BMI is an important predictor of spine bone density, whereas lean mass is a very strong predictor of bone density at multiple sites, including the spine, hip, femoral neck, and WB in adolescent girls with AN and controls (3). Similarly, in boys with AN and controls, BMI and lean mass are important predictors of bone density at the spine, hip and WB (4). Lean mass is a particularly strong predictor of bone density in both boys and girls at multiple sites, likely because the pull of muscle on bone has bone anabolic effects, and increases in lean mass over time predict increases in bone density over the same period of time (5).

Hormonal alterations

Hypothalamic-pituitary-gonadal axis

Gonadal steroids have important effects on bone metabolism. Estrogen inhibits osteoclastic bone resorption, and may have bone anabolic effects (18, 19). Testosterone is aromatized to estrogen and thus inhibits bone resorption, and may have independent bone anabolic effects (19). AN is associated with hypogonadotropic hypogonadism, and LH pulsatility patterns in females with AN revert to an early pubertal pattern of night-time entrained pulses, or a pre-pubertal pattern of low amplitude pulses (20). Girls with AN have lower estradiol levels than similar age controls, even when the latter are assessed in the early follicular phase of their menstrual cycles, when their gonadal steroid levels are at a nadir (3). Levels of free testosterone are lower in mature girls with AN than controls (5), and lower levels of both total and free testosterone have been reported in adult women with AN compared with controls (21). Similarly, boys with AN have lower levels of testosterone and estradiol and a lower free androgen index than boys of similar age (4). In girls, duration of amenorrhea is an inverse predictor...