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Editorial

Long-term Skeletal Consequences of Anorexia Nervosa: A "Wake up Call"

Bone health in the setting of nutritional deficiency from anorexia nervosa (AN) has been intensely studied over the past two decades. Unfortunately, the peak incidence of eating disorders and time for acquisition of peak bone mass coincide during adolescence. Given that over one-half of the adult skeleton is accrued during this developmental period [1], there is understandable concern that AN threatens genetic peak bone mass attainment and causes lasting skeletal deficits into adulthood. The mechanisms behind AN's impact on the skeleton are multifactorial. These skeletal deficits are associated with low weight, low lean body mass, low fat intake, and hormonal perturbations [2–4]. Bone anabolic hormones such as insulin-like growth factor-1 (IGF-1), dehydroepiandrosterone, leptin, amylin, and insulin are reduced in adolescents with anorexia, whereas cortisol, a hormone known to be deleterious to bone, is elevated [5]. Understanding the contribution of numerous pathophysiological contributors to the low bone mass seen continues to drive research in this area.

An important and unresolved question is whether bone insults suffered during adolescence due to AN persist and have clinical implications during the adult years. Previous data have frequently been conflicting, with some studies suggesting restoration of normal bone mass with psychological and weight recovery [6–8] and others demonstrating no change or only partial improvement [9–12]. In an observational study, Rigotti et al. [13] followed a cohort of 27 women with AN for a mean duration of 6.7 years to determine how cortical bone density was affected by weight gain, resumption of menses, treatment with estrogen, or vigorous exercise. They observed no significant changes in cortical bone density over a median of 25 months of follow-up; at the end of the study, the mean bone density did not differ between patients who remained underweight or those who recovered [13]. No differences in the spine, hip, or whole body were observed in 36 women with adolescent-onset AN who were followed up for 11 years [8]. In contrast, adolescents followed up for 12–16 months showed gains in total body bone mineral density (BMD) but no change in the lumbar spine [9]. Another longitudinal cohort was followed up for an average of 11.7 years after the first admission for AN [14]. Patients with a "poor outcome," defined as persistent menstrual abnormality and body weight reduction >15%, showed a marked reduction in lumbar and radial BMD [14]. In patients exhibiting recovery, BMD remained lower than in a comparison control group.

In this issue of the *Journal of Adolescent Health*, Mumford et al. [15] explore the long-term impact of AN on skeletal health after weight recovery, including measures of BMD, as well as bone geometry and strength. The authors studied 41 young adults (mean age 21.2 ± 2.9 years) with a history of AN during adolescence, who then completed a bone health assessment in follow-up at 5 and then 10 years. Twenty-eight participants completed the 5-year assessment, and 13 participants, the 10-year assessment, each defined as the duration of time after their first AN-related hospitalization. The skeletal assessments were performed using dual-energy x-ray absorptiometry (DXA) which provides an evaluation of the central or axial skeletal and peripheral quantitative computed tomography (pQCT) which provides bone density and skeletal strength assessments of the peripheral or appendicular skeleton. The latter tool provides a three-dimensional or volumetric measurement so is thus less confounded by small bone size, as will be discussed in greater detail. In addition, assessments of the peripheral skeleton are more informative as adolescents tend to fracture bones of the extremities (vs. those of the central skeleton). Anthropometric measures, biochemical outcomes, and fracture history were also examined. The results from this longitudinal protocol showed persistent negative effects of the disease on bone health, including reductions at the femoral neck and radius (each site rich in cortical bone), as well as cortical thinning at the weight-bearing tibia. Serum IGF-1, a nutrition-dependent factor, was positively correlated with total BMD. IGF-1 appears to be an important physiological regular of bone density as a link between IGF-1 and DXA measures of BMD has been noted previously in adolescent girls with AN [2,16], as well as in adolescent boys and girls with inflammatory bowel disease (IBD) [17] and cystic fibrosis [18]. While fracture risk was not increased in the current study, a subset of patients (n = 3 or 8% of the sample) sustained >4 fractures, raising concerns for underlying skeletal fragility.

Predictors of skeletal recovery (or persistence of skeletal deficits) have been previously explored. The early study of

See Related Article on p. 305

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Bachrach et al. [9] raised awareness about a "critical window" for bone acquisition among adolescents, including both healthy youth and ones with a chronic disease. Recovery of menses has been shown to be a consistent positive predictor of bone density, independent of weight gain [19], supporting the observation of trabecular bone (the most metabolically active component of the skeleton) improving following recovery from AN. In contrast, weight gain, particularly an increase in lean body mass, is an important determinant of hip bone density recovery [19]. Another study sought to understand the clinical implications of body composition measures by DXA (i.e., assessments of percentage body fat) in adolescent girls recovering from AN by examining the association between this measure and return of menses [20]. The ultimate implication of this association would be the benefit on bone health with the return of spontaneous menses.

Initial investigations have been limited to the assessment of bone density in one or two dimensions by DXA. While DXA remains the most widely available method for clinical bone density testing, its measurements can be confounded by height and bone size. [21] In the cohort of Mumford et al. [15] clinical improvement was seen at the time of follow-up (5–10 years after initial evaluation), with body weight and body mass index Z-scores similar to normative standards. Total body and lumbar spine BMD Z-scores remained significantly lower than average ($p = .001$ and $p = .01$, respectively). However, in a clinical context (outside of research), the results would not be considered to be low for gender and age (mean total body BMD Z-score $= -.6 \pm .9$ and mean lumbar spine BMD Z-score $-.4 \pm .8$). The DXA thresholds that raise clinical concern include a BMD Z-score of -2 for all adolescents and -1 for an adolescent athlete [21,22]. Three-dimensional techniques such as pQCT circumvent the influence of bone size on bone density measures, discriminate between trabecular and cortical bone, and provide estimates of bone strength. The authors utilized pQCT in the present study, representing a unique contribution to the existing literature. The radius was particularly affected with epiphyseal bone mineral content and bone mineral density being significantly below average normative values. However, similar to the DXA results, clinically these Z-scores were all ≥ -1.0.

To evaluate, perhaps, the most clinically meaningful measure, Mumford et al. [15] also explored fracture history as a study outcome. By age 18, approximately one-third of girls have sustained a fracture [23]. In a small study, the annual incidence of nonspine fracture was seven-fold higher than the rate reported for a community sample of similar aged women (relative risk 7.1; 95% confidence interval 3.2–18.5) [13]. A larger, community-based study of women with AN demonstrated that their overall fracture risk was significantly increased (standardized incidence ratio 2.9, 95% confidence interval 2.0–3.0) compared with the general population [24]. The actual mechanism behind the increased fracture risk remains unclear. Based on the "clinically normal" BMD values observed in the current cohort, it does not appear to be related to only bone density.

The development of AN during the adolescent years interrupts optimal bone mass attainment. Although bone density appears to improve with recovery of menses and weight restoration, bone deficits may persist into adulthood, increasing the risk of fracture. For women who continue to struggle with this chronic disease, bone health appears to worsen. Overall, clinicians agree that resumption of menses and weight improvement are essential goals of treatment for adolescents with AN. Prevention of skeletal deficits is the optimal strategy for bone health to promote the ability to pursue an active lifestyle throughout the adult years. Ongoing improvements in clinical monitoring tools and research into treatment modalities that optimize bone health remain important parts of care for these patients. If adolescents are receptive to the news of a low bone mass, discussions about this health outcome could serve as a "wake up call" on their road to recovery. The findings of Mumford et al. [15] provide compelling data on the long-term skeletal implications of AN that could be cited in these conversations with patients and families. These data are another reminder of the importance of the adolescent years for bone health and beyond (i.e., peak bone mass attainment and other health outcomes). They are another reminder of why we want our teenagers with eating disorders to get on the road to recovery just as soon as possible.

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