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On Exposure to Anorexia Nervosa, the Temporal Variation in Axial and Appendicular Skeletal Development Predisposes to Site-Specific Deficits in Bone Size and Density: A Cross-Sectional Study

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ABSTRACT

Skeletal development is heterogeneous. Throughout growth, bone size is more maturationally advanced than the mineral being accrued within its periosteal envelope; before puberty, appendicular growth is more rapid than axial growth; during puberty, appendicular growth slows and axial growth accelerates. We studied women with differing age of onset of anorexia nervosa to determine whether this temporal heterogeneity in growth predisposed to the development of deficits in bone size and volumetric bone mineral density (vBMD), which varied by site and severity depending on the age at which anorexia nervosa occurred. Bone size and vBMD of the third lumbar vertebra and femoral neck were measured using dual-energy X-ray absorptiometry in 210 women aged 21 years (range, 12–40 years) with anorexia nervosa. Results were expressed as age-specific SDs (mean ± SEM). Bone width depended on the age of onset of anorexia nervosa; when the onset of anorexia nervosa occurred (1) before 15 years of age, deficits in vertebral body and femoral neck width did not differ (−0.77 ± 0.27 SD and −0.55 ± 0.17 SD, respectively); (2) between 15 and 19 years of age, deficits in vertebral body width (−0.95 ± 0.16 SD) were three times the deficits in femoral neck width (−0.28 ± 0.14 SD; $p < 0.05$ comparing the deficits), (3) after 19 years of age, deficits in the vertebral body width (−0.49 ± 0.26 SD; $p = 0.05$) were half that in women with earlier onset of anorexia nervosa. No deficit in bone width was observed at the femoral neck. Deficits in vBMD at the vertebra and femoral neck were independent of the age of onset of anorexia nervosa but increased as the duration of anorexia nervosa increased, being about 0.5 SD lower at the vertebra than femoral neck. We infer that the maturational development of a region at the time of exposure to disease, and disease duration, determine the site, magnitude, and type of trait deficit in anorexia nervosa. Bone fragility due to reduced bone size and reduced vBMD in adulthood is partly established during growth. (J Bone Miner Res 2000;15:2259–2265)

Key words: anorexia nervosa, growth, osteoporosis, peak bone density, regional specificity

INTRODUCTION

PATIENTS WITH fractures have reduced bone mineral content (BMC) relative to controls. The deficit in BMC may be caused by reduced bone size and reduced volumetric bone mineral density (vBMD).[(1)] These deficits often are site specific; women with spine fractures may have greater deficits in BMC at the spine than hip and women with hip fractures may have greater deficits at the hip than spine, while women with forearm fractures may have the greatest

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deficits at this site.[2–4] These deficits may be caused by excessive bone loss during aging,[5] reduced mineral accrual during growth,[6–10] or reduced bone size.[1,11,12]

Several investigators have reported that growth in bone size is more maturationally advanced throughout childhood and adolescence than the mineral being accrued within its periosteal envelope.[13–16] The rate of growth of one region compared with another also differed.[16–20] We hypothesized that the differing timing of growth from region to region was important in the pathogenesis of bone fragility as it predisposed to the development of site-specific deficits in bone size or BMC depending on the age at which exposure to illness or risk factors occurred.[16] We speculated that the more advanced maturity of a region's size than its mass predisposed to reduced vBMD, and the more maturationally advanced region relative to another region predisposed to greater deficits in bone size and mass in the region further from its adult peak when illness occurs. In this way, exposure to disease or risk factors at different stages of growth may selectively increase fracture risk at the spine or hip or both in adulthood. The purpose of this study was to test the hypothesis that the age of onset of anorexia nervosa will influence the site and severity of structural abnormalities because of the heterogeneity of growth.

We studied anorexia nervosa because it is a chronic disease that begins in adolescence and results in osteoporosis in young adults. It affects 1% of adolescent females and is characterized by a fear of fatness, self-imposed semistarvation, weight loss, and fractures.[21–28] Estrogen deficiency, the result of hypothalamic pituitary dysfunction and reduced body weight, has a central role in the pathogenesis of osteoporosis in this illness, resulting in reduced mineral accrual when anorexia nervosa occurs during growth and bone loss when anorexia nervosa occurs in young adulthood. Estrogen deficiency also may slow growth in bone size, particularly of the axial skeleton, as truncal growth accelerates at puberty.[16–19]

We measured bone size and BMC in women with anorexia nervosa to test the following specific hypotheses: (1) regions further from their adult peak when anorexia nervosa occurs have greater deficits in bone size than regions closer to their peak; (2) anorexia nervosa affects bone size and mineral accrual; because growth in size is more advanced than mineral accrual throughout growth, anorexia nervosa will affect BMC more severely than bone size producing reduced vBMD; (3) appendicular growth decelerates during puberty while axial growth accelerates; thus, anorexia nervosa during puberty will affect axial more than appendicular size; (4) most of the BMC accrued during growth occurs in late puberty, when bone growth is almost complete; anorexia nervosa will have little effect on bone size but will reduce BMC resulting in reduced vBMD; and (5) anorexia nervosa in adulthood will not affect bone size but will reduce vBMD due to bone loss.

MATERIALS AND METHODS

Subjects

We studied 210 women with a mean age of 21 years (range, 12–40 years) with active anorexia nervosa. The diagnosis of anorexia nervosa was based on ICD-10 criteria.[21] Results were compared with those in 370 healthy female volunteers between 7 and 40 years of age who received no drugs and suffered no diseases known to affect bone. To study the effects of anorexia nervosa on bone size, analysis was confined to the 149 women over 18 years of age who completed their growth. Informed consent was obtained from all participants. The study was approved by the Austin and Repatriation Medical Center Ethics Committee.

Measurement of bone mass and bone size

Total body and regional BMC (g) and areal BMD (aBMD; BMC/projected area of the region scanned, g/cm^2) were measured using dual-energy X-ray absorptiometry (DPX-L, version 1.3z; Lunar Corp., Madison, WI, U.S.A.).[29] Height and width of the third lumbar vertebral body were derived from the posteroanterior lumbar scan. Vertebral vBMD (g/cm^3) was calculated by the method of Carter et al. (BMC/volume, where volume = scanned area$^{3/2}$).[30] Femoral neck width was calculated as scanned area/length. Femoral neck vBMD was calculated as BMC/volume [volume = π * (femoral neck width/2)^2 * scanning length].[16,31] CV ranged between 1.5 and 2.4%. Total body fat mass and total lean mass were calculated from total body scan.

Statistical analysis

Results were expressed in absolute terms and as the number of Z scores or SD scores above or below the age predicted mean (of zero) derived by linear regression using data in the controls. Because BMC does not account for size, comparing BMC and bone width required that BMC be adjusted for bone size.[1] Student's *t*-tests were used to determine whether a trait deficit differed from zero and whether regional deficits differed in the same subjects. Trait deficits across groups with differing age of onset of anorexia nervosa were compared by analysis of variance (ANOVA). Data were presented as mean ± SEM.

RESULTS

As shown in Table 1, the mean age of onset of anorexia nervosa in the total sample of 210 patients was 21 years (range, 11–39 years) and the duration of the disease was 37.5 months (range, 2–240 months). As shown in Fig. 1, in healthy controls, BMC and bone width increased as age increased. vBMD at the vertebra, but not femoral neck, increased with age. In patients with anorexia nervosa, vertebral and femoral neck BMC and vBMD decreased as age increased. Deficits in bone width and vBMD were observed in the vertebra and femoral neck (Table 1).

Bone width depended on the age of onset of anorexia nervosa (Table 1), not disease duration (Fig. 2). When the onset of anorexia nervosa occurred (1) before 15 years of age, deficits in vertebral body and femoral neck width did not differ (−0.77 SD and −0.55 SD, respectively); (2) between 15 and 19 years of age, deficits in vertebral body width (−0.95 SD) were three times the deficits in femoral neck width (−0.28 SD; $p < 0.05$ comparing the deficits); and (3) after 19 years of age, deficits at the vertebral body

TABLE 1. SAMPLE SIZES, AGE, MENARCHE, ONSET OF AMENORRHEA, AND DURATION OF AN, HEIGHT, WEIGHT, BODY MASS INDEX, TOTAL FAT MASS, TOTAL LEAN MASS, BONE SIZE, BMC, aBMD AND vBMD AT THE THIRD LUMBAR VERTEBRA AND FEMORAL NECK ARE SHOWN FOR ALL WOMEN WITH AN (IN ABSOLUTE TERMS AND Z SCORES) AND CONTROLS (IN ABSOLUTE TERMS)

	Women with AN	*Controls*	*Adult women (≥18 years of age) according to age of onset of AN*		
			11.0–15.0 years	*15.1–19.0 years*	*19.1–39.0 years*
Numbers	$n = 210$	$n = 370$	$n = 26$	$n = 74$	$n = 49$
Age (years)	21.2 ± 0.4	21.8 ± 0.4	20.0 ± 0.5	21.8 ± 0.5	28.1 ± 0.8
Menarche (years)	17.0 ± 1.2†	13.3 ± 0.5	23.9 ± 6.1	13.7 ± 0.2	13.5 ± 0.3
Onset of amenorrhea (years)	17.7 ± 0.3	—	14.1 ± 0.3	17.4 ± 0.1	24.3 ± 0.6
Duration of AN (months)	37.5 ± 2.9	—	59.5 ± 6.8	42.7 ± 4.9	35.6 ± 5.3

	Absolute values	Z scores	Absolute values	Z scores		
Height (cm)	163.1 ± 0.5‡	−0.34 ± 0.05§	160.1 ± 0.6	−0.61 ± 0.24‡	−0.32 ± 0.12†	−0.31 ± 0.16*
Weight (kg)	45.5 ± 0.5§	−1.32 ± 0.05§	56.2 ± 0.8	−1.27 ± 0.14§	−1.37 ± 0.08§	−1.74 ± 0.11§
Body mass index (kg/m^2)	17.1 ± 0.2§	−1.38 ± 0.05§	21.5 ± 0.2	−1.09 ± 0.12§	−1.30 ± 0.09§	−1.69 ± 0.12§
Total fat mass (kg)	8.2 ± 0.3§	−1.29 ± 0.05§	17.2 ± 0.5	−1.09 ± 0.10§	−1.17 ± 0.06§	−1.59 ± 0.07§
Total lean mass (kg)	35.2 ± 0.3	−0.80 ± 0.07§	35.9 ± 0.4	−0.67 ± 0.24‡	−0.84 ± 0.13§	−1.05 ± 0.18§
Bone size (cm)						
Vertebral body height	3.45 ± 0.03	−0.04 ± 0.08	3.34 ± 0.02	0.39 ± 0.28	0.08 ± 0.15	−0.02 ± 0.29
Vertebral body width	3.74 ± 0.01§	−0.64 ± 0.09§	3.87 ± 0.02	−0.77 ± 0.27†	−0.95 ± 0.16§	−0.49 ± 0.26*
Femoral neck width	3.03 ± 0.06†	−0.18 ± 0.07‡	3.04 ± 0.02	−0.55 ± 0.17‡	−0.28 ± 0.14*	−0.03 ± 0.14
BMC (g)						
Vertebra	13.81 ± 0.21§	−1.04 ± 0.07§	15.78 ± 0.25	−1.25 ± 0.23§	−1.19 ± 0.13§	−1.30 ± 0.15§
Femoral neck	4.22 ± 0.06§	−0.97 ± 0.09§	4.65 ± 0.04	−1.23 ± 0.26§	−1.16 ± 0.16§	−1.24 ± 0.18§
aBMD (g/cm^2)						
Vertebra	1.07 ± 0.01§	−1.23 ± 0.08§	1.16 ± 0.01	−1.69 ± 0.25§	−1.50 ± 0.15§	−1.72 ± 0.17§
Femoral neck	0.93 ± 0.01§	−1.02 ± 0.09§	1.02 ± 0.01	−1.10 ± 0.26§	−1.14 ± 0.15§	−1.40 ± 0.19§
vBMD (g/cm^3)						
Vertebra	0.30 ± 0.01§	−1.03 ± 0.08§	0.33 ± 0.01	−1.32 ± 0.23§	−1.14 ± 0.13§	−1.48 ± 0.16§
Femoral neck	0.39 ± 0.01§	−0.77 ± 0.08§	0.43 ± 0.01	−0.58 ± 0.20‡	−0.78 ± 0.13§	−1.03 ± 0.17§

Results are expressed as mean ± SEM.

Results are expressed only as Z scores for women aged ≥18 years stratified according to differing ages of onset of AN.

AN, anorexia nervosa.

* $p = 0.05$; † $p < 0.05$; ‡ $p < 0.01$; § $p < 0.001$ comparing women with AN with age- and gender-matched healthy controls.

(−0.49 SD; $p = 0.05$) were half that in women with earlier onset of anorexia nervosa. No deficit was observed at the femoral neck.

The deficit in vBMD was independent of the age of onset but correlated with the duration of anorexia nervosa (vertebra, $r = -0.31$ and slope is −0.0003 g/cm^3 per month; femoral neck, $r = -0.39$ and slope is −0.0007 g/cm^3 per month; for both, $p < 0.001$; Fig. 2). The deficit in vBMD was greater at the vertebra than femoral neck irrespective of age of onset of anorexia nervosa ($p < 0.01$; Table 1).

The differing combinations of BMC and bone sizes forming vBMD at the vertebra and femoral neck are shown in Fig. 3. Reduced vBMD occurred in all cases occupying the lower right panel because BMC Z scores were always lower than bone width Z scores. Increased vBMD occurred in all cases occupying the upper left panel because BMC Z scores were always higher than bone width Z scores. For most patients with anorexia nervosa, the values for the vertebra occupied the bottom left panel formed by reduced vertebral BMC and reduced vertebral body width Z scores. However, vertebral BMC Z scores were more negative than vertebral body width Z scores producing reduced vBMD. Most values for the femoral neck occupied the bottom two panels (i.e., reduced BMC) but deficits in femoral neck width were modest with values distributed around the mean of zero. For example, boxed values A, B, and C all had reduced vBMD. In each example, BMC is relatively lower than bone size.

DISCUSSION

We report that women with anorexia nervosa had reduced bone width. The location of the deficit depended on the age of onset of anorexia nervosa. Onset of anorexia nervosa before 15 years of age was associated with deficits in vertebral body and femoral neck width. Later onset was associated with greater deficits in vertebral body than femoral neck width. Adult onset was associated with a modest deficit confined to the vertebral body. Women with anorexia

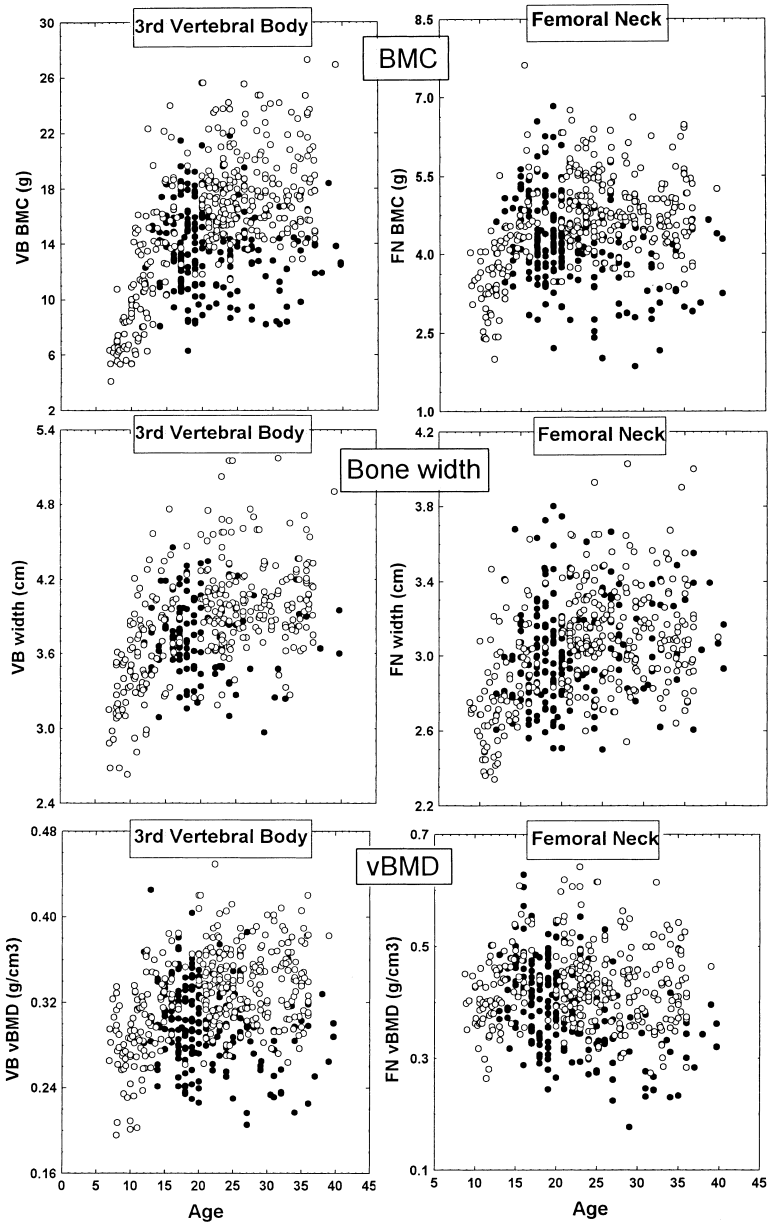

FIG. 1. BMC (g), bone width (cm), and vBMD at the third lumbar vertebra and femoral neck (g/cm^3) in healthy controls (open circles) and female patients with anorexia nervosa (closed circles) as a function of age.

nervosa had reduced vertebral and femoral neck vBMD. Deficits were greater at the vertebra than femoral neck; deficits in vBMD increased at both sites as the duration of anorexia nervosa increased but were independent of the age of onset of anorexia nervosa.

Bone width

Deficits in bone size occurred at both axial and appendicular sites in women with early onset of anorexia nervosa because both are distant from their adult peak. When the onset of anorexia nervosa occurred in adulthood, femoral neck width was unaffected and vertebral body width was affected minimally because growth at both sites was complete, or nearly so. Greater deficits at the vertebral body than femoral neck probably reflect the differing growth pattern of the axial and appendicular skeleton. Growth of the legs proceeds more rapidly than growth of the trunk before puberty, it decelerates in puberty whereas trunk length accelerates and continues when leg length has virtually ceased.[16] Thus, anorexia nervosa occurring in the peripubertal period delays the pubertal growth spurt of the trunk affecting vertebral size more than femoral neck size.

We infer that the maturational stage of development of a trait at the time of exposure to disease influences the size of the deficit produced by that illness. Disease occurring in early development results in reduced bone size increasing fracture risk at the vertebra and femoral neck; disease occurring around puberty may result in reduced vertebral body width only, selectively increasing vertebral fracture risk in adulthood.

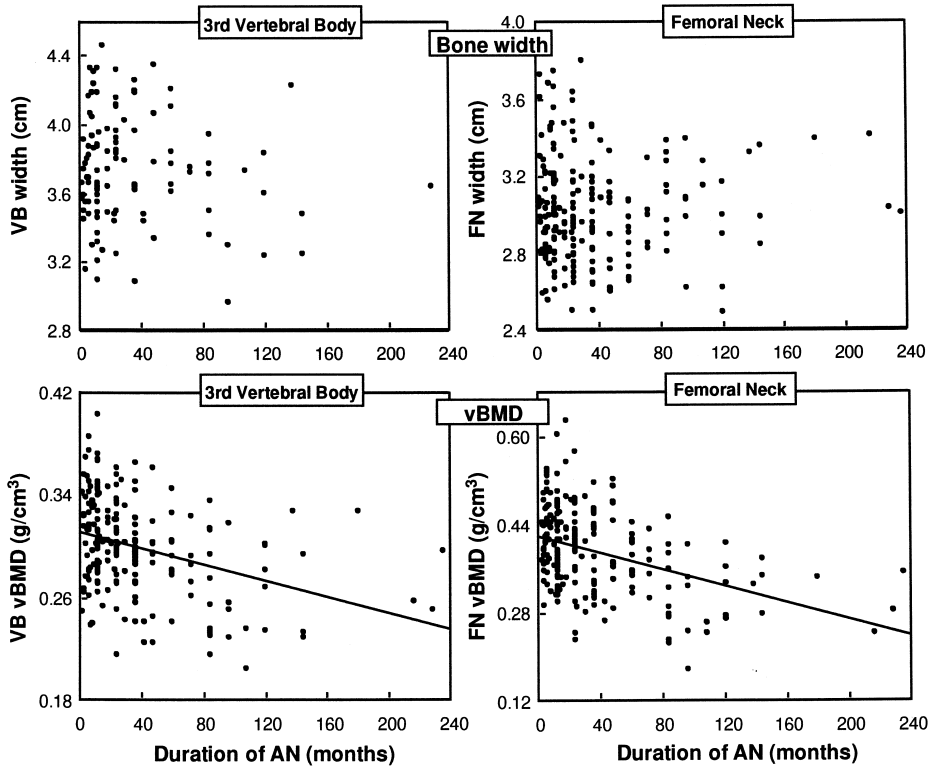

FIG. 2. Bone width (cm) and vBMD (g/cm^3) of the third lumbar vertebra and femoral neck in female patients with anorexia nervosa as a function of duration of anorexia nervosa (months).

vBMD

During growth, vBMD is a function of the relationship between growth in bone size and growth in mass contained within the periosteal envelope of the bone.[16] vBMD at the cortical site is constant during prepubertal growth in healthy persons because the increase in bone size is matched by a proportional increase in bone mass.[16,31–33] When a disease occurs during growth, both bone size and mineral accrual may be reduced but vBMD may be unaffected if the reduction in bone size and mineral accrual are proportional. Reduced vBMD will result if the deficit in mineral accrual is relatively more severe than the deficit in bone size, because bone size is always nearer its adult peak than its mass[13–16]; this temporal difference in growth of bone size versus mass predisposes to the development of reduced vBMD should illness intervene.[16] Thus, illness such as anorexia nervosa interrupts mineral accrual and growth in bone size but interrupts mineral accrual proportionately more resulting in reduced vBMD. The greater deficit in vertebral vBMD and vertebral body width may confer a greater fracture risk at the vertebra than femoral neck.

There are many examples supporting the notion that vBMD during growth depends on the relationship between the growth in size of bone and mineral accrual within it (not just the absolute change in either). Gonadectomy in male rats reduces mineral accrual more than it reduces bone size,

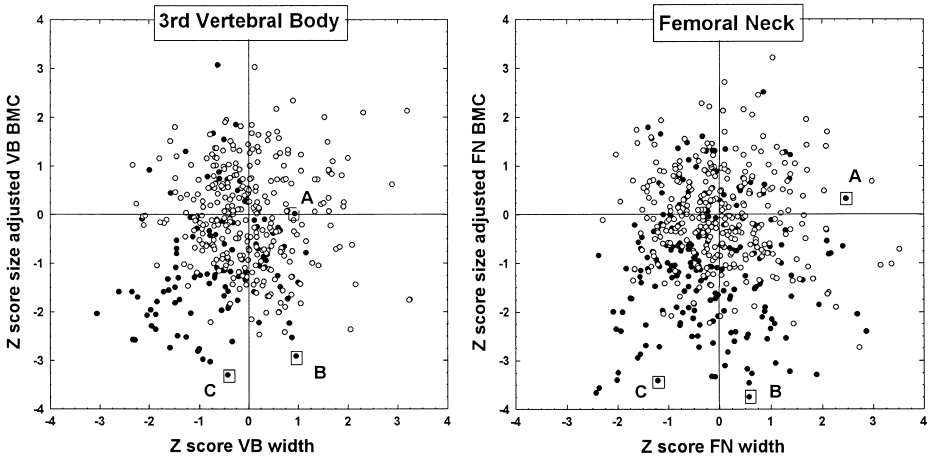

FIG. 3. Distribution of values for BMC (adjusted for bone size) and bone size Z scores at the vertebral body (VB) and femoral neck (FN) in healthy controls (open circles) and patients with anorexia nervosa (closed circles). Boxed values (A, B, and C) are examples of low vBMD (see text).

producing a smaller bone with reduced vBMD; in female rats gonadectomy results in increased growth in femur length with disproportionately lower mineral accrual, producing reduced vBMD in a bigger bone.[34] Growth hormone administration in growing rats produces a greater increase in bone size than the increase in mineral accrual, resulting in reduced vBMD in the larger bone.[35] In Turners syndrome, vBMD is normal because reduced accrual is matched by reduced bone growth.[36]

Thus, reduced vBMD is the result of a "mismatch" in mass and size independent of the absolute value of either trait. This is the point made in Fig. 3; reduced vertebral vBMD was the result of reduced BMC and size but more greatly reduced BMC than size. Reduced femoral neck vBMD was the result of reduced BMC and normal or only modestly reduced bone size. Thus, reduced vBMD may occur in small, normal, or large bones if the BMC is relatively more reduced than its size. The relative contributions of reduced mineral accrual, bone loss, or both to the level of BMC cannot be identified in a cross-sectional study. The deficit in vBMD correlated with the duration of disease reflecting the likely involvement of bone loss.

There have been many studies reporting reduced bone mass in patients with anorexia nervosa.[22–27] Deficit in bone mass at the spine was greater than at the proximal femur.[24,27,28] We confirm these studies and extend the work by suggesting that the site specificity and magnitude of the deficits in BMC are likely to be a function of the age of onset of anorexia nervosa and the duration of disease. The deficits in BMC are a result of reduced bone size as well as reduced vBMD, particularly at the lumbar spine. Apportioning the deficit in vBMD to reduced accrual and bone loss is not possible in a cross-sectional study. The correlation between the duration of anorexia nervosa and vBMD is consistent with the role of bone loss.[27] Although we did not measure biochemical markers of bone formation, there is evidence that bone loss may be caused by both reduced bone formation and increased bone resorption.[37,38] Reduced estrogen, testosterone, insulin-like growth factor 1 (IGF-1), and hypercortisolemia may contribute to bone loss as well as reduced growth in size and mineral accrual in patients with anorexia nervosa.[38]

There have been several retrospective and prospective studies reporting the effect of recovery from anorexia nervosa on BMD.[39–46] Investigators report increased BMD in subjects who increased their body weight,[47] have persistent deficits in BMD, or have continued bone loss despite recovery.[39,42–45] Hay et al. reported a 14% higher spine aBMD in 21 women recovered from anorexia nervosa compared with those with ongoing anorexia nervosa[46]; aBMD was 7% lower than healthy controls. These disparate reports are likely to be the result of variable definitions of recovery, differences in disease severity before recovery, differences in the duration of disease and recovery, and failure to account for differences in bone size.

In conclusion, reduced bone size and reduced vBMD in adults with secondary osteoporosis have their origin in growth as well as aging. Patients with primary osteoporosis also have reduced bone size and reduced vBMD, deficits that also are likely to have their origins in growth and aging.[2,5–7] Thus, growth-related factors (reduced peak mineral accrual and reduced bone growth) and age-related factors (excess bone loss and impaired periosteal apposition) are each likely to contribute to structural abnormalities in adults with primary and secondary osteoporosis. The size of the contributions may vary from site to site in an individual and at a given site from individual to individual. This variability in part will be caused by the differing age of onset of the disease (affecting bone size and mineral accrual) and the duration of the disease (causing bone loss). A better understanding of the diversity in the pathogenesis of primary and secondary osteoporosis may be obtained by recognition that bone fragility in old age is the result of both growth-related and age-related factors influencing the skeletal size, its architecture, and mass.

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