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Determinants of Skeletal Loss and Recovery in Anorexia Nervosa

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Context: Anorexia nervosa (AN) is complicated by severe bone loss. The effects of persistent undernutrition and consequent neuroendocrine dysfunction on bone mass and the factors influencing skeletal recovery have not been well characterized.

Objective: The objective of the study was to determine the rate of bone loss at the spine and hip in women with AN and whether resumption of menstrual function and/or improvement in weight are determinants of skeletal recovery in AN.

Design: The study had a longitudinal design.

Setting: The study was conducted at a clinical research center.

Study Participants: Participants included 75 ambulatory women with AN.

Main Outcome Measures: Bone mineral density (BMD) and body composition were measured with dual x-ray absorptiometry.

Results: In women not receiving oral contraceptives, those who did not improve weight or resume menses had a mean annual rate of decline of 2.6% at the spine and 2.4% at the hip. Those who resumed menses and improved weight had a mean annual increase of 3.1% at the posteroanterior spine and 1.8% at the hip. Women who recovered menses demonstrated a mean increase of posteroanterior spine but not hip BMD, independent of weight gain. Women who improved weight, regardless of whether they recovered menstrual function, demonstrated a mean increase of hip, but not spine, BMD. Increase in fat-free mass was a more significant determinant of increased BMD than weight or fat mass gain. In women receiving oral contraceptives, there was no increase in BMD at any site despite a mean 11.7% weight increase.

Conclusions: These data suggest that rapid bone loss, at an average annual rate of about 2.5%, occurs in young women with active AN. Resumption of menstrual function is important for spine BMD recovery, whereas weight gain is critical for hip BMD recovery. We did not observe an increase in BMD with weight gain in women receiving oral contraceptives. Therefore, improvements in reproduction function and weight, with increases in lean body mass a critical component, are both necessary for skeletal recovery in women with AN. **(*J Clin Endocrinol Metab* 91: 2931–2937, 2006)**

ANOREXIA NERVOSA (AN) is a prevalent psychiatric disease, particularly among young women of reproductive age, and is complicated by severe bone loss. We have previously reported that osteopenia is present in 92% and osteoporosis in 38% of young women with AN, with less than 15% of women having normal bone density, despite an average age in the early 20s (1, 2). Our group and others have investigated the determinants of bone loss in this group of patients with AN. However, there are few data regarding the rate of bone loss in women with active AN or factors influencing skeletal recovery in this population. We therefore prospectively studied 75 women with AN with serial bone mineral density (BMD) measurements at the spine and hip to investigate rates of bone loss in active AN and determine whether increases in weight, changes in body composition, and/or resumption of menstrual function are important predictors of skeletal recovery in this population of young women.

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Abbreviations: AN, Anorexia nervosa; ANCOVA, analysis of covariance; BMD, bone mineral density; OCP, oral contraceptive pill; PA, posteroanterior.

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Subjects and Methods

Subjects

Seventy-five women with AN who participated at least twice in screening visits at least 6 months apart for AN bone loss studies in the General Clinical Research Centers at Massachusetts General Hospital and Massachusetts Institute of Technology were included in the analysis. At the time of the first evaluation, all subjects fulfilled all Diagnostic and Statistical Manual of Mental Disorders IV criteria for AN, including percent ideal body weight less than 85%, amenorrhea for at least 3 months (except for those patients receiving oral contraceptives), and all psychiatric manifestations of the disease. The protocol was approved by the Partners Human Research Committee and the Massachusetts Institute of Technology Institutional Review Board, and all subjects gave informed, written consent before study participation.

Protocol

Study participants attended an outpatient visit, during which a medical history, including detailed menstrual history, and physical exams were also performed. Nutritional evaluation included the following: weight was measured, height and frame size were determined, and percent ideal body weight and body mass index were calculated by research dietitians. Percent ideal body weight was calculated based on the 1983 Metropolitan Life Tables (3). A pregnancy test was performed before BMD was measured [dual x-ray absorptiometry (Hologic, Inc., Waltham, MA) at the posteroanterior (PA) spine and hip, with a variation of $< 1\%$ for bone (4), 1.4% for body fat mass, and 1.5% for fat free mass (5)].

Statistical analysis

Statistical analysis was performed using JMP Statistical Discoveries (version 4.0.2, SAS Institute, Inc., Cary, NC). Clinical characteristics were compared by ANOVA. Changes in and predictors of absolute BMD, not T scores, were determined. Analysis of covariance (ANCOVA) was used to determine predictors of change in BMD and control for variables that were different between groups at baseline. To calculate annualized rates of BMD change, data from each study participant were individually annualized, and then aggregate data were analyzed. Stepwise regression models were constructed for determinants of BMD at the spine and hip. Statistical significance was defined as a two-tailed $P \leq 0.05$. Data are reported as mean ± SEM.

Results

Clinical characteristics

Seventy-five ambulatory women with AN were studied. The mean age of the participants was 24.4 ± 0.6 yr (range 18–40 yr), mean percent ideal body weight 75.8 ± 0.8, mean PA spine BMD T score −1.8 ± 0.1 and mean hip T score −1.4 ± 0.1. The mean number of months between the two visits was 13.5 ± 1.0, with a range of 6–69 months. Baseline clinical characteristics of 45 women not receiving oral contraceptives, divided into subgroups for comparison, are shown in Table 1, A–C. In Table 1A, the subset of women who neither improved weight nor resumed menses was compared with those who both improved weight and resumed menses. Weight improvement was defined as increasing weight to more than 85% of ideal body weight and/or by 10% of body weight (6–8). Resumption of menses was defined as having experienced at least one menses in the previous 3 months. In Table 1B, women who did not resume menses were compared with those who resumed menses, regardless of whether their weight also improved. In Table 1C, the subset of women who did not improve weight were compared with those who improved weight, regardless of whether they also resumed menses. Clinical characteristics of women who were receiving oral contraceptives are reported in Table 2. In 17% of patients, oral contraceptives received contained 30 μg ethinyl estradiol, in 70% they contained 35 μg, and in 13% the dose of ethinyl estradiol was not known.

Determinants of skeletal recovery in women not receiving oral contraceptives

In women not receiving oral contraceptives, resumption of menstrual function predicted an increase in BMD at the PA spine but not hip, independent of weight improvement ($P = 0.02$). Weight improvement predicted an increase in BMD at the hip but not PA spine, independent of resumption of menstrual function ($P = 0.05$). Likewise, percent change in weight, analyzed as a continuous variable, predicted an increase in BMD at the hip but not PA spine (percent change weight = 8.0 + 0.76 × percent change hip BMD, R = 0.34, $P = 0.02$). The association between percent change in weight and increase in hip BMD remained significant after controlling for resumption of menses by ANCOVA ($P = 0.03$).

In the subset of women who did not either recover menstrual function or improve weight, as defined above, a decrease of 2.7% in spine and 2.6% in hip BMD was observed over a mean 13.8 months (Table 1A). This is equivalent to an annual decline in bone density of approximately 2.6% at the PA spine and 2.4% at the hip (Fig. 1A). In contrast, women who resumed menses and improved weight experienced a mean increase in PA spine BMD of 3.6% and hip of 2.1% over 22 months (Table 1A). This is equivalent to an annual mean increase of 3.1% at the PA spine and 1.8% at the hip (Fig. 1A).

Change in BMD was significantly different between the groups (those who resumed menses and improved weight *vs.* those who neither resumed menses nor improved weight) at both the PA spine ($P = 0.02$) and hip ($P = 0.02$) and remained significant after controlling for time between visits by ANCOVA but was a trend after annualization ($P = 0.064$) (Fig. 1A).

To investigate the independent effects of resumption of menstrual function on skeletal recovery, women who did not receive oral contraceptives were divided into the following two subsets: 1) those who resumed menses, and 2) those who did not resume menses between the two visits. Study participants were categorized without regard to changes in weight. The group of women who resumed menses also increased weight by a mean of 9.2 ± 2.4%, compared with 6.6 ± 1.8% in those who remained amenorrheic (difference between groups nonsignificant). Thirty-six percent of women who resumed menses did not also increase their body weight by at least 10% or to more than 85% ideal body weight. Of the women who did not resume menses, BMD decreased −2.4 ± 0.8% at the PA spine and −1.6 ± 0.7% at the hip during a mean 14.1 ± 1.0 months (Table 1B). This is equivalent to an annual decrease in BMD at the PA spine of 2.2 ± 0.8% and at the hip of 1.6 ± 0.7% (Fig. 1B). In contrast, women who resumed menses demonstrated a mean increase in BMD at the PA spine of 3.1 ± 1.9% ($P = 0.02$) *vs.* nonmenstrual function recovered (Table 1B). This remained significantly different after controlling for baseline PA spine BMD, which differed between the groups, and after annualization (Fig. 1B). However, there was no statistically significant increase in BMD at the hip in those who resumed menses *vs.* those who did not (0.9 ± 1.5 *vs.* −1.6 ± 0.7%, $P = 0.10$).

To investigate the independent effects of weight improvement on skeletal recovery, women who were not receiving oral contraceptives were divided into the following two subsets: 1) those who improved weight, and 2) those who did not improve weight. Study participants were categorized without regard to their menstrual status, and 68% of women who improved weight did not also resume menses. BMD decreased −1.8 ± 1.0% at the PA spine and −2.9 ± 1.0% at the hip during a mean 13.3 ± 1.1 months in women who did not improve weight, compared with those who improved weight (Table 1C). This is equivalent to an annual decrease in BMD at the PA spine of 1.8 ± 0.9% and at the hip of 2.1 ± 0.8% (Fig. 1C). In contrast, women who improved weight, regardless of whether menstrual function recovered, demonstrated an increase in BMD at the hip of 0.6 ± 1.0%, $P = 0.05$ *vs.* nonweight improved (Table 1C). This remained significantly different after controlling for age of menarche, which differed in the groups at baseline, and after annualization (Fig. 1C). However, there was no statistically significant increase in BMD at the PA spine in those who improved weight *vs.* those who did not (−0.2 ± 1.4 *vs.* −1.8 ± 1.0%, $P = 0.33$).

TABLE 1. A. Clinical characteristics of women with AN not receiving oral contraceptives, categorized by presence or absence of weight improvement and resumption of menstrual function at subsequent visits

	Improved weight and resumed menstrual function (n = 7)			Neither improved weight nor resumed menstrual function (n = 19)		
	First visit	Second visit	% Change between visits	First visit	Second visit	% Change between visits
Age (yr)	21.9 ± 1.9			25.5 ± 1.6		
Age of menarche (yr)	13.5 ± 0.6			12.7 ± 0.4		
Weight (kg)	42.6 ± 2.4	47.5 ± 2.3	12.2 ± 3.2[a]	44.0 ± 1.5	44.2 ± 1.6	0.4 ± 1.3
Ideal body weight (%)	75.0 ± 2.9	83.3 ± 2.7[a]		74.9 ± 1.5	75.1 ± 1.5	
Body mass index (kg/m^2)	16.1 ± 0.69	18.2 ± 0.7[a]		16.3 ± 0.39	16.4 ± 0.37	
Mean PA spine T score	−1.3 ± 0.5	−1.1 ± 0.4[a]		−1.9 ± 0.2	−2.2 ± 0.2	
PA spine BMD	0.90 ± 0.05	0.92 ± 0.04[a]	3.6 ± 2.9[a]	0.83 ± 0.03	0.81 ± 0.03	−2.7 ± 1.1
Mean hip T score	−1.4 ± 0.5	−1.3 ± 0.5		−1.4 ± 0.3	−1.6 ± 0.3	
Hip BMD	0.78 ± 0.06	0.80 ± 0.06	2.1 ± 1.9[a]	0.78 ± 0.03	0.76 ± 0.03	−2.6 ± 0.9
Mean length of follow-up visit (months) [range]		22.0 ± 8.2 (7–69)			13.8 ± 1.3 (7–29)	

Improved weight: at subsequent visit, increased body weight by at least 10% or to more than 85% of ideal body weight.
[a] $P \leq 0.05$ *vs.* non-weight-improved and nonmenstrual function-resumed group.

B. Clinical characteristics of women with AN not receiving oral contraceptives, categorized by presence or absence of resumed menstrual function at subsequent visits

	Resumed menstrual function (n = 11)			Did not resume menstrual function (n = 34)		
	First visit	Second visit	% Change between visits	First visit	Second visit	% Change between visits
Age (yr)	23.2 ± 1.4			25.0 ± 1.0		
Age of menarche (yr)	13.3 ± 0.52			13.0 ± 0.31		
Baseline weight (kg)	43.7 ± 1.7	47.5 ± 1.5	9.2 ± 2.4	43.6 ± 1.3	46.3 ± 1.3	6.6 ± 1.8
Ideal body weight (%)	75.4 ± 2.3	81.2 ± 2.2		74.8 ± 1.2	78.4 ± 1.2	
Body mass index (kg/m^2)	16.5 ± 0.6	17.9 ± 0.5		16.3 ± 0.3	17.2 ± 0.3	
Total fat (kg)	8.0 ± 1.1	10.3 ± 0.8	37.5 ± 10.8	7.6 ± 0.7	9.5 ± 0.7	41.2 ± 11.8
Fat-free mass (kg)	32.3 ± 1.2	34.4 ± 1.0	6.9 ± 2.1	33.7 ± 0.9	34.4 ± 0.9	3.5 ± 1.4
Baseline mean PA spine T score	−1.4 ± 0.4	−1.2 ± 0.2[a]		−2.1 ± 0.2	−2.3 ± 0.2	
PA spine BMD	0.89 ± 0.04	0.91 ± 0.03[a]	3.1 ± 1.9[a]	0.82 ± 0.02	0.80 ± 0.02	−2.4 ± 0.8
Baseline mean hip T score	−1.6 ± 0.3	−1.4 ± 0.3		−1.5 ± 0.2	−1.6 ± 0.2	
Hip BMD	0.78 ± 0.04	0.78 ± 0.04	0.9 ± 1.5	0.77 ± 0.02	0.76 ± 0.02	−1.6 ± 0.7
Mean length of follow-up visit (months) [range]		18.1 ± 5.4 (7–69)			14.1 ± 1.0 (6–29)	

Improved weight: at subsequent visit, increased body weight by at least 10% or to more than 85% of ideal body weight.
[a] $P \leq 0.05$ *vs.* nonmenstrual function-resumed group.

C. Clinical characteristics of women with AN not receiving oral contraceptives, categorized by the presence or absence of improved weight at subsequent visits

	Improved weight (n = 22)			Did not improve weight (n = 23)		
	First visit	Second visit	% Change between visits	First visit	Second visit	% Change between visits
Age (yr)	23.6 ± 1.0			25.5 ± 1.3		
Age of menarche (yr)	13.4 ± 0.3			12.7 ± 0.38		
Weight (kg)	42.9 ± 1.6	48.5 ± 1.5	13.7 ± 1.9[a]	44.3 ± 1.3	44.7 ± 1.3	1.0 ± 1.2
Ideal body weight (%)	74.7 ± 1.6	83.1 ± 1.3[a]		75.1 ± 1.4	75.5 ± 1.3	
Body mass index (kg/m^2)	16.2 ± 0.4	18.2 ± 0.4[a]		16.5 ± 0.4	16.6 ± 0.3	
Total fat (kg)	7.9 ± 0.9	11.1 ± 0.8[a]	57.7 ± 10.2[a]	7.5 ± 0.7	8.5 ± 0.7	24.8 ± 14.7
Fat-free mass (kg)	32.4 ± 1.0	34.1 ± 0.9	8.4 ± 1.5[a]	34.3 ± 1.2	34.7 ± 1.1	0.5 ± 1.4
Mean PA spine T score	−2.0 ± 0.2	−2.1 ± 0.2		−1.8 ± 0.2	−2.0 ± 0.2	
PA spine BMD	0.82 ± 0.02	0.82 ± 0.02	−0.2 ± 1.4	0.84 ± 0.02	0.8 ± 0.02	−1.8 ± 1.0
Mean hip T score	−1.5 ± 0.2	−1.5 ± 0.2		−1.5 ± 0.2	−1.6 ± 0.2	
Hip BMD	0.76 ± 0.03	0.77 ± 0.03	0.6 ± 1.0[a]	0.78 ± 0.03	0.76 ± 0.03	−2.9 ± 1.0
Resumption of menstrual function (%)		31.8			17.4	
Mean length of follow-up visit (months) [range]		16.9 ± 2.8 (6–69)			13.3 ± 1.1 (7–29)	

Improved weight: at subsequent visit, increased body weight by at least 10% or to more than 85% of ideal body weight.
[a] $P \leq 0.05$ *vs.* non-weight-improved group.

TABLE 2. Clinical characteristics of women with AN receiving oral contraceptives, categorized by presence or absence of improved weight at subsequent visits

	Improved weight (n = 13)			Did not improve weight (n = 17)		
	First visit	Second visit	% Change between visits	First visit	Second visit	% Change between visits
Age (yr)	24.3 ± 1.5			23.0 ± 1.1		
Age of menarche (yr)	13.3 ± 0.6			13.9 ± 0.3		
Weight (kg)	47.4 ± 1.7	52.7 ± 1.4[a]	11.7 ± 1.9[a]	45.7 ± 1.3	46.5 ± 1.5	1.6 ± 1.1
Ideal body weight (%)	77.7 ± 1.9	86.6 ± 1.4[a]		76.6 ± 1.5	76.8 ± 1.6	
Body mass index (kg/m^2)	17.1 ± 0.4	19.0 ± 0.4[a]		16.8 ± 0.3	17.1 ± 0.3	
Total fat (kg)	8.3 ± 1.7	12.9 ± 1.7[a]	111.4 ± 52.3	8.6 ± 0.9	9.2 ± 0.8	18.4 ± 8.5
Fat-free mass (kg)	37.8 ± 1.1[a]	40.2 ± 1.0[a]	7.8 ± 2.7[a]	35.6 ± 1.1	35.6 ± 1.2	0.6 ± 1.3
Mean PA spine T score	−1.1 ± 0.2[a]	−1.1 ± 0.2[a]		−2.0 ± 0.2	−1.9 ± 0.2	
PA spine BMD	0.94 ± 0.02[a]	0.94 ± 0.03[a]	−0.0 ± 1.2	0.85 ± 0.03	0.85 ± 0.02	0.3 ± 0.9
Mean hip T score	−0.9 ± 0.3	−0.8 ± 0.3		−1.3 ± 0.3	−1.4 ± 0.3	
Hip BMD	0.85 ± 0.03	0.85 ± 0.04	−0.6 ± 1.5	0.81 ± 0.03	0.8 ± 0.0	−0.9 ± 1.0
Mean length of follow-up visit (months) [range]		10.4 ± 1.1 (5.4–18.0)			12.4 ± 1.2 (5.3–20.7)	

Improved weight: at subsequent visit, increased body weight by at least 10% or to more than 85% of ideal body weight.
[a] $P \leq 0.05$ *vs.* non-weight-improved group.

When percent change in fat-free mass, percent change in fat mass, and percent change in weight were entered into a stepwise regression model, only percent change in fat-free mass was a significant determinant of the variability in percent change in BMD in women not receiving oral contraceptives (PA spine: $r^2 = 0.18$, $P = 0.01$; hip: $r^2 = 0.24$, $P = 0.003$), suggesting that increase in fat-free mass was a more important predictor of skeletal recovery than gain in weight or fat mass.

Determinants of skeletal recovery in women receiving oral contraceptives

To investigate the effects of weight improvement on skeletal recovery in women with AN receiving oral contraceptives, this group (n = 30) was divided into the following two subsets: 1) those who improved weight, and 2) those who did not improve weight. BMD did not increase significantly at either skeletal site in women who had improved weight, compared with those who did not experience weight improvements (Table 2 and Fig. 2). This remained true after controlling for all variables that differed between the two groups at baseline. There was no significant difference in time between visits for women receiving and not receiving oral contraceptives.

Discussion

AN is a psychiatric disease that affects young women of reproductive age disproportionately and is complicated by severe bone loss (1, 2), which we demonstrate in this study to be rapid, at an average annual rate of about 2.5%. Because there are no effective therapies available, it is particularly important to identify endogenous factors that contribute to skeletal gain during recovery from AN. Although we and other groups have investigated mechanisms of bone loss in women with AN, there are few published data regarding the determinants of skeletal recovery in this population. Our data suggest that resumption of menstrual function is a critical factor in recovery of lumbar spine bone density, independent of weight gain. In contrast, weight gain is an important determinant of hip bone density recovery. Importantly, our data also suggest that recovery of lean body mass may be a particularly important component of weight gain to achieve skeletal recovery in women who are recovering from AN.

We have previously established that AN is complicated by osteopenia in 92% and osteoporosis in 38% of women with AN, with fewer than 15% of women having normal bone density at all skeletal sites (1, 2). However, the rate of bone loss in women with active AN has not been well characterized. In this study, we demonstrate rapid bone loss, at an average annual rate of about 2.5%, in women with active AN. These data provide additional evidence supporting the importance of early intervention for women with AN, a psychiatric disease with serious medical consequences, including bone loss.

Data regarding skeletal recovery during weight recovery in women with AN are scant, and most published papers report fewer than 30 cases of women with AN (9–14). Some of these reports suggest that weight recovery results in increases in BMD, whereas others are not able to demonstrate increases in bone density in women recovering from AN. Most studies suggest that residual bone loss is common after recovery from AN. The two largest studies, each of 51 women with AN, demonstrated increases in BMD in weight-recovering patients, although not to normal, even after several years of weight recovery (15, 16). One of these studies, by Hotta *et al.* (15), reported that BMD did not increase in the Japanese cohort studied, unless body mass index was greater than 16.4 ± 0.3 kg/m^2. To our knowledge, no published studies have investigated the differential effects of weight increase, menstrual function resumption, and changes in body composition on skeletal recovery.

The data reported in this manuscript regarding determinants of skeletal recovery in women with AN are consistent

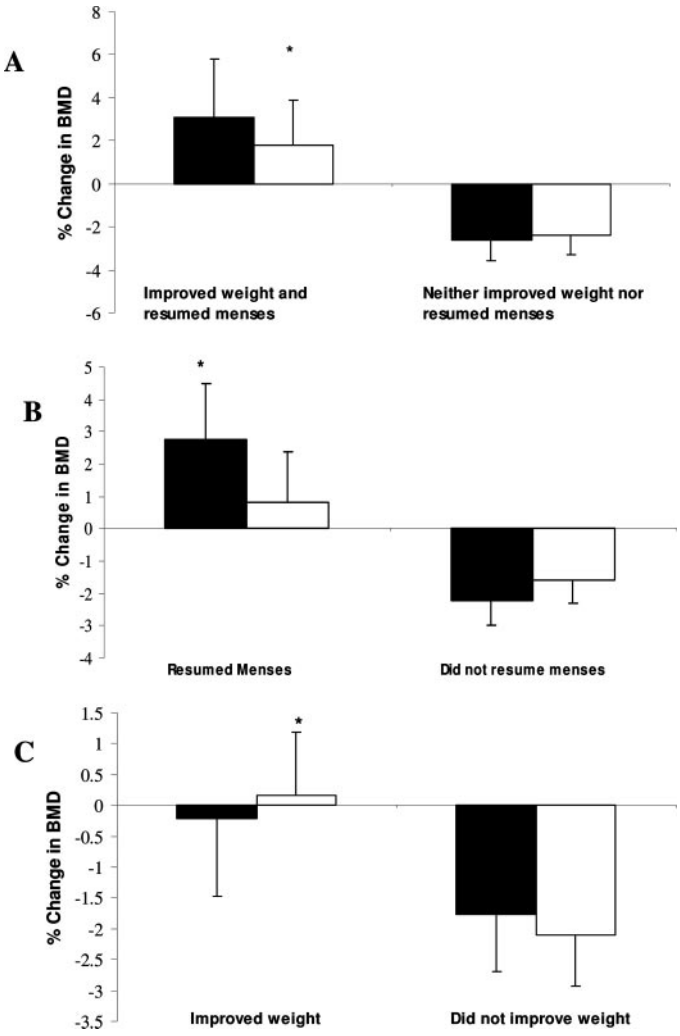

FIG. 1. Annualized percent change in BMD at the PA spine and hip in women not receiving oral contraceptives. A, Women who both improved weight and resumed menses increased BMD at the PA spine and hip, compared with those who neither improved weight nor resumed menses (PA spine, 3.1 ± 2.7 *vs.* $-2.6 \pm 1.0\%$, $P = 0.064$; hip, 1.8 ± 2.1 *vs.* $-2.4 \pm 0.9\%$, $P = 0.045$). B, Women who resumed menses increased PA spine BMD, compared with those who did not improve menstrual function (2.7 ± 1.7 *vs.* $-2.2 \pm 0.8\%$, $P = 0.018$). However, there was no increase in hip BMD. C, Women who improved weight increased hip BMD, compared with those who did not improve weight (0.15 ± 1.0 *vs.* $-2.1 \pm 0.8\%$, $P = 0.038$). However, there was no increase in PA spine BMD. *Black bars*, PA spine BMD; *white bars*, hip BMD. Improved weight, at subsequent visit, increased body weight by at least 10% or to more than 85% of ideal body weight. *, $P < 0.05$.

with our previous data regarding determinants of bone loss in this population. We have demonstrated that duration of amenorrhea (1, 17, 18) and weight (1) are both important determinants of BMD. When we specifically investigated body composition, lean body mass has been shown to be a particularly important determinant of BMD (18, 19). Therefore, interventions aimed at increasing muscle as part of a program designed to increase weight may also be effective at increasing BMD in women with AN. We have also demonstrated that endocrine predictors of bone loss in AN include IGF-I (17–20) and testosterone (20). Further studies to

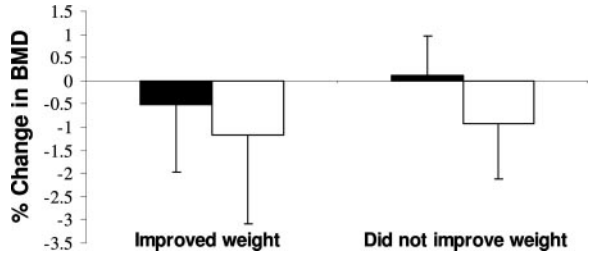

FIG. 2. Annualized percent change in BMD at the PA spine and hip in women receiving oral contraceptives. Women who improved weight did not experience an increase in PA spine or hip BMD. *Black bars*, PA spine BMD; *white bars*, hip BMD. Improved weight: at subsequent visit, increased body weight by at least 10% or to more than 85% of ideal body weight.

determine the role of these endocrine factors, if any, in skeletal recovery in women recovering from AN are merited.

Although in the current study weight improvement resulted in an increased mean hip BMD, compared with nonweight gainers among women not receiving oral contraceptives, weight gainers who were receiving oral contraceptives demonstrated no such skeletal gains. It is important to note that this study was not a randomized, placebo-controlled study and that the results could have been influenced by factors leading to the prescribing of oral contraceptives for some women and not others. Therefore, our data cannot prove or disprove that oral contraceptives inhibit skeletal recovery. They are consistent with the results of our published randomized trials demonstrating no effect of exogenous estrogens to increase BMD in women with AN (21, 22). It could be hypothesized that the effect of oral contraceptives to decrease both endogenous IGF-I and testosterone might play a role in preventing an increase in BMD. We did not have sufficient blood samples or numbers of patients to test this hypothesis. Our results are also consistent with those of Polatti *et al.* (23), who compared change in BMD over 5 yr among 200 healthy women, aged 19–22 yr, who received either oral contraceptive pills (OCP) containing 20 μg of ethinyl estradiol or no treatment. Women who received no treatment demonstrated a 7.8% increase in BMD over the 5-yr period, in contrast to women in the OCP group, who did not experience any increase in BMD at all. The authors postulated that the lack of BMD increase was attributable to suppression of endogenous gonadal steroids plus an insufficient replacement dose for achievement of peak bone mass. In contrast, studies using higher-dose OCPs (containing 30–40 μg of ethinyl estradiol) in healthy women (24–27) and women with hypothalamic amenorrhea (28, 29) have not demonstrated detrimental effects on BMD, and some have even reported increases in BMD. Of note, none of these studies was placebo controlled.

Our data demonstrate that resumption of menstrual function may be particularly important for improvement of spinal bone mass. Although most women who resumed menses had also experienced an increase in weight, we demonstrated an independent effect of resumption of menstrual function on spinal bone density improvement. Spinal bone loss is more prevalent than hip bone loss in AN (1). Our findings are consistent with the known effects of estrogens on bone and may also reflect increases in other gonadal steroids, includ-

ing testosterone, in ovulating women. Our two previous randomized trials, which do not demonstrate an effect of estrogen to improve BMD in AN (21, 22), do not contradict these findings. Exogenous estrogens may exert different effects on bone in women of reproductive age with undernutrition from endogenous estrogens by decreasing endogenous IGF-I and testosterone levels or from exogenous gonadal steroids in postmenopausal women. An alternative explanation for our findings might be that resumption of menses reflects nutritional recovery, whereas oral contraceptive use clearly does not. However, it is important to note that effects of resumption of menstrual function to increase spine BMD remained significant after controlling for increases in weight. Therefore, a hormonal effect independent of nutritional recovery is likely.

Limitations of this study include its relatively small numbers, relatively arbitrary definitions of recovery, use of two-dimensional aereal BMDs, and lack of long-term menstrual history information. It is important to acknowledge that criteria used for recovery in this manuscript, although standard, are arbitrary. Therefore, in addition to the dichotomous statistical analysis, we also performed univariate analyses and ANCOVAs, with percent weight change as a continuous variable, to investigate the robustness of our analyses. Such analyses yielded similar results to those using recovery cutoffs. Specifically, changes in weight predicted changes in hip, although not spine, BMD. Although we elicited the number of months since the last menstrual period, we did not have detailed information about menstrual function in the years before the bone density measurement. We therefore could not determine whether there was a dose-response effect of number of menstrual cycles, or more importantly ovulations, which would require hormone data, on increases in BMD. Another limitation of the study was the use of aereal BMDs, which are influenced by bone size and other factors. Further studies to confirm our findings and determine the mechanisms (endocrine and other) of skeletal recovery in recovering women with AN will be important.

In summary, resumption of menstrual function was an important predictor of spinal skeletal recovery, whereas weight improvement was an important predictor of hip BMD recovery. Whether the importance of menstrual function resumption primarily reflects nutritional recovery or the direct effects of endogenous gonadal steroids on bone mass cannot be determined from this study. However, our data clearly demonstrate an effect on bone density independent of weight gain. Lean body mass appears to be the most important component of weight gain for skeletal recovery. Therefore, improvements in weight, with increases in lean body mass a critical component, and reproductive function are both needed for skeletal recovery in women with AN.

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