TIME COURSE OF BONE LOSS IN PATIENTS WITH ANOREXIA NERVOSA

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RUNNING HEAD: BMD in anorexia nervosa

Abstract

Objective: To evaluate the time course of bone mineral density (BMD) in women with anorexia nervosa (AN) during two years of follow-up.

Methods: We prospectively studied 51 female with AN aged 18-38 years, and forty age-matched healthy women (19-34 years). BMD was measured in lumbar spine (LS), femoral neck (FN) and total hip (TH) by DXA.

Results: At baseline, weight, body mass index, and lumbar and hip BMD were significantly ($p<0.001$) lower in AN patients than in controls. Patients who gain weight showed a significant increase in BMD at FN (+1.6%; $p<0.05$), and TH (+4.4%; $p<0.05$) and lower non significant changes in LS (+1.3%). Weight at entry, and percent change of weight were significant determinants ($p<0.05$) of the variability in percent change of BMD at FN and TH, whereas weight at entry was the main determinant of bone modifications at lumbar spine.

Conclusions: Our data emphasize the influence of weight gain in recovery of bone mass in AN patients, especially at the hip.

KEY WORDS: Anorexia nervosa; bone mineral density; weight recovery

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Anorexia nervosa (AN) is an eating disorder that usually begins in adolescence and is characterized by patient-induced and maintained weight loss that leads to progressive malnutrition and specific pathophysiological signs (disturbance of body image and fear of obesity) (1). Over the last few years, anorexia nervosa has become a serious public health issue in industrialized countries (2, 3). A recent study of a Spanish female population with ages between 12 and 21 years showed a prevalence of 0.3% for AN, 0.8% for bulimia and 3.1% for non-specified eating disorders (4,5).

On the other hand, this disorder carries a high rate of morbidity, with osteoporosis being one of its major complications (5-7). In fact, osteoporosis and osteopenia may occur in 20-50%, and 50-90% of cases depending of the groups observed (8-14), with bone fracturing occurring in more than 40% of chronic anorexic patients in the poor outcome group at long-term follow-up (8). The mechanism underlying the phenomenon of bone loss observed in AN patients is still unclear, although estrogen deficiency and loss of body weight are probably the major etiological factors (5, 14). On the other hand, the time course of bone loss in AN patients, and the factors influencing skeletal recovery in this population have not been well characterized (14). Prospective studies analyzing recovery from osteoporosis are scarce and have yielded conflicting results. Thus, some authors have concluded that recovery from osteoporosis is possible in some patients, whereas others suggest that only partial BMD improvement is achieved after resumption of menstrual function and weight improvement (3, 15-22).

In this context, the aim of our study was to evaluate the clinical course of bone mineral density in a prospective cohort of 51 individuals with AN to determine how vertebral and hip BMD was affected by weight gain.

METHODS

Participants

This study included 51 Spanish females with anorexia nervosa (AN) with ages ranging between 18 and 38 years, who were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders 4th ed. (DSM IV) (23).

These participants stem from the Eating Disorder Unit, Division of Psychiatry, University Hospital M. Valdecilla from Santander, in the Northern Spain. The diagnosis of AN was made by a psychiatrist. From an initial sample of 64 outpatients with a history of AN consecutively admitted to the Eating Disorder Unit between 2002 and 2004, 60 patients were included at baseline (T1). Four patients had to be excluded due to an additional illness or treatment known to affect bone status (one patient with inflammatory bowel disease, one with co-morbid diabetes mellitus type 1, and two receiving glucocorticoids). After a mean follow-up period of 26±3 months (T2) (range 18-32 months), patients were reassessed at the eating disorder unit. A complete set of data (T1 and T2) could be gathered for 51 patients. Thirty-two (63%) of them had restricting type of AN, and the remaining 19 (37%) had binge-eating/purging type.

All 51 participants were amenorrheic (four of them exhibited primary amenorrhea) and had body weight <85% of expected or BMI<17.5 kg/m^2 at diagnosis. However, during the time period until the initial recruitment (T1), some weight changes occurred so that the BMI at that time of baseline examination ranged from 12-21 kg/m^2 (Table 1). Moreover, sometimes patients also experience resumption of menses. Therefore, the duration of the amenorrhea refers to the time of amenorrhea that the patients were presenting at entry in the study (T1).

In addition, an age-matched group of 40 healthy female (19-34 years) recruited among hospital workers served as a control group. None of them had a medical history of eating disorders neither other medical illnesses known to affect bone health. The study was approved by the local Ethical Committee, and written consent was obtained from all participants before participation.

Clinical protocol

Age and weight at diagnosis of AN, menstrual history, calcium, estrogen, and vitamin D intake, and exercise habits were determined by direct interview and review of the medical records. Patients' physical activity was classified in four levels: light (level 1, mainly sedentary activities), moderate (level 2, working in a standing position or without regular walking), heavy (level 3, occasional carrying of heavy burdens and regular walking), very heavy (level 4, regular carrying of heavy burdens or high-level sporting activities) (7, 24). Height and weight were measured with subjects wearing light indoor clothing but without

shoes. Body mass index (BMI) was defined as weight (kg) divided by squared height (m^2).

Bone densitometry

Bone mineral density (BDM) was measured by dual x-ray absorptiometry (DXA, Hologic QDR 4500, Walthman, MA, USA) at the lumbar spine (L2-L4) (LS), femoral neck (FN), and total hip (TH). In vivo precision was 0.4-0.5% at the different measurements sites. Results were expressed as grams per centimeter squared and T-score (defined as the number of standard deviations [SDs] below the mean value of young white Caucasian women), and Z-score (defined as the number of SDs below the mean of women of the same age). Quality control was performed according to the usual standards (25).

Follow-up evaluation

Every 6-12 months, we repeated the measurement of bone mass, and reassessed the clinical characteristics, including weight, height, BMI, menstrual status, use of estrogen, calcium and vitamin D supplements, and type and frequency of regular exercise. Weight improvement was defined as increasing weight to more than 10% of body weight (26, 27). Resumption of menses was defined as having experienced at least one menses in the previous 3 months (22).

Statistical analysis

Differences between AN and controls were analyzed using unpaired Student's t test. Differences between the baseline (T1) and final (T2) bone mineral density measurements were analyzed using Student's t test for paired samples. We used correlation analysis to determine predictors of changes in bone density measures. Multiple backward stepwise linear regression analyses were used to study the association between each of the variables and site specific BMDs (dependent variable). We adjusted for potential confounders by adding them to the regression models. Significance levels less than 5% were considered significant. All analyses were performed using SPSS for Windows (SPSS Inc, Chicago, IL, USA).

RESULTS

Baseline characteristics

Baseline (T1) clinical characteristic of the sample are shown in table 1. As expected, weight and BMI were significantly ($p<0.001$) lower in AN patients than in controls. Moreover, a significant reduction in BMD at lumbar spine and hip was also observed ($p< 0.001$) (Table 1). In fact, osteoporosis (defined by the WHO criteria, T score <2.5) was detected in at least one of the three sites (lumbar spine, femoral neck or total hip) in 10 (20%) patients with AN, and osteopenia (defined as a T score of -1 to -2.5) in 27 of them (52%). Conversely, osteopenia was only observed in 8 of the healthy control women (20%), and none of them had osteoporosis.

Twelve patients were sedentary, 5 had a moderate, 12 heavy, and 22 very heavy physical activity level. Twenty six patients (51%) were taken calcium and vitamin D supplements, and 20 (38%) were on some form of oral contraceptive. There were no significant differences between age, weight, BMI, duration of illness, duration of amenorrhea, and BMD values in AN patients who received estrogens and those who did not (data not shown).

Follow-up evaluation

All 51 AN patients had a complete physical examination between 18 and 36 months (mean ± SD: 26 ± 3 months). During this time, most patients continued her physical activity, and at the end of the study, 14 patients (27%) had weight improvement as previously defined, and 37 (73%) had no significant changes or had lost weight. The average BMI of the group that improved weight (mean 18.8±1.8 kg/m^2) lay within normal range, above the 17.5 kg/m^2 cut-off for anorexia nervosa. Patients who improve weight had at first visit (T1) lower weight and BMI, and shorter duration of amenorrhea than patients who did not (Table 2). The group of AN patients who improve weight showed a significant increase in BMD at femoral neck (+1.6±9.6; $p<0.05$) and total hip (+4.4±10.7%; $p<0.05$), and lower non significant changes in lumbar spine (+1.3±6.7%). In contrast, a decrease in femoral neck (-3.8±5.8%), and total hip BMD (-1.0±6.2%) was observed in patients with unchanged or decreased weight (Table 2). These patients also experienced a slight non significant mean increase in spine BMD (+0.2±6.0%).

At visit two, when individuals with anorexia nervosa were divided according to their menstrual status, those 10 females (20%) who resumed

menses experienced a slight but non significant increase (+0.8±5.9%) in lumbar BMD, with minor changes in the hip measurements (data not shown).

Regarding the type of AN, patients with restrictive anorexia and patients with the binge-purge type did not differ in terms of weight, BMI or BMD at any localization, neither at baseline nor in the follow-up assessments (data not shown).

To identify the contribution of several confounders to BMD, a stepwise multiple regression analysis was performed with lumbar spine, femoral neck and total hip BMD as dependent variable, and age, weight, height, BMI, duration of illness, amenorrhea, use of estrogens and percent change in weight, as independent variables. When corrected for these factors, weight at entry and percent change of weight remained as significant determinants of the variability in percent change of BMD at hip, whereas baseline weight was the main determinant of BMD in lumbar spine (Table 4).

DISCUSSION

Here we report a longitudinal study with more than 2-year of follow-up (26 ± 3 months), involving 51 patients with AN with a mean duration illness of more than seven years. At baseline, we found a significant reduction in BMD in participants with anorexia nervosa, and a high prevalence of osteopenia (51%) and osteoporosis (20%) when BMD values were considered in at least one of the three usual sites (lumbar spine, femoral neck and total hip). This was an expected result, since osteopenia and osteoporosis may occur in 50-90% and 20-50% of AN patients, respectively (8-14). In our prospective study we also found that participants who gained weight showed a significant increase of BMD at the femoral neck (+1.6%) and total hip (+4.4%) compared with non-weight gainers, and lower non significant increase at lumbar spine (+1.3%) after two years of follow-up. Conversely, BMD decreased near 4% at the femoral neck and around 1% at the total hip in patients who did not improved weight. Spine bone density experienced minor changes in both groups of patients. Moreover, a residual deficit in BMD persisted in all localizations in AN patients, even after weight is recovered. Our results are partially in accordance with Miller et al (22) who observed that rapid hip bone loss, at an average annual rate of about 2.5%, occurs in young women who did not improve weight. Similar results have

been also published by others, (although these studies involved a small number of patients) (15,17,21) and, thus, emphasize the importance of the AN as an osteoporotic risk factor in young women.

Data regarding skeletal improvement during weight recovery in women with AN are scant, and most published papers have analyzed fewer than 30 cases (8,15,16,18,19,20,21,22,28,29). In these studies, some authors reported a BMD recovery in line with gain weight (15,16,19,28,29), while others have mentioned a persistently low bone mass even after weight and menstrual cycles recovery (8,18,20,21,22). In our study we observed a 20% increase in weight in the group of patients who gained weight, but only a 4.4% increase in BMD at the hip. In fact, at the second visit, mean values of lumbar, femoral neck and total hip BMD, were 16%, 13%, and 9%, respectively lower in these patients than in the age-matched controls. Thus, instead the favorable impact of weight gain on BMD at the hip, it was not sufficient to reverse the bone loss process.

At the spine, patients that improve weight and those with unchanged or decreased weight, showed no changes in bone density over 2 years. This would be in accordance with previous studies in which minor modifications (22) or no changes (20,27,30) were found in lumbar BMD over time. In fact, Hotta et al. (20) analyzed the time course of BMD in 29 AN patients over a period of 11-46 months, and found an increase in hip BMD, but not in spine, in patients who had BMI>16.4±0.3kg/m^2, even when they were amenorrheic. Milos et al. (27) showed that of the three DXA localizations, only the total hip measurement showed a significant change over time, with an average annual increase of 1.2% (equivalent to 0.009 g/cm^2) in patients with AN. Finally, Miller et al (22) observed that women who improve weight, regardless of whether they recovered menstrual function, had a mean increase of hip, but not lumbar BMD. Conversely, in this study, those women who resumed menses and improved weight had a significant increase in spine and hip BMD (22). Similar results were also observed by these authors when spine bone mineral density, and whole body bone mineral content adjusted for height were evaluated (30). This was not the situation for our patients. As a matter of fact, when anorexic women were divided according to menstrual status, we found that women who resumed menses experienced a slight but non significant increase in spinal bone density and minor changes in the hip. However, although we elicited menstrual status at

baseline and at the second visit, we did not have detailed information about menstrual function, such as number of menstrual cycles and ovulations, hormone levels, etc, that could be involved in the course of bone loss in the period between both visits. Moreover, 38% of our patients have been taken some form of oral contraceptives, and although hormone replacement therapy has not consistently demonstrated benefit on BMD in anorexic women (31,32), it could ameliorate the bone mass gains in AN patients who improve weight (22).

We also found that weight at baseline was an important determinant of the percent change in lumbar spine and hip BMD. However, our data also indicate that weight gain might play an important role in the process of bone recovery. Thus, the percent change of weight was a strong predictor of bone recovery, and remained in the linear regression analysis as a significant determinant of the variability in the percent change of BMD at the hip, but not at the lumbar spine. This would be again in agreement with Miller et al (22) who suggested that menstrual function was a critical factor in lumbar BMD recovery, independent of weight gain, whereas weight gain was an important determinant of hip bone mass recovery.

We found no differences in BMD between patients with restrictive or binge/purge types of AN. These results are in disagreement with the data of Zipfel et al (21) but in accordance with those described by Milos et al. (27). These authors suggests that because bone density deficits depend on the severity of AN, and restrictive or binge/purge symptoms are not associated with the severity of underweight condition, one can assume that this sub classification does not differentiated the severity of bone deficit. Furthermore, changes in behavioral symptomatology during the course of the eating disorder can be observed (33), so that a sub classification based on the AN subtypes appears not to be related to the subgroups classified on the basis of weight gain.

Our study has some limitations. The sample size was small, which might limit the representativity of the data. Furthermore, the range of age of participants was quite large (18-38 years) including young and adult women, and it is supposable that bone regenerative potential in younger subjects could be different than in older subjects. We used relatively arbitrary definitions of

weight gain, although standard. Therefore we performed linear regression analyses to study the association between each of the variables and site specific BMDs, and found that weight at entry and percent change of weight were important determinants of BMD. Finally, another limitation of the study was the use of areal BMDs, which are influenced by bone size and other factors. However, as previously stated, similar results has been described in these patients when spine bone mineral apparent density, and whole body bone mineral content adjusted for height were evaluated (30).

In conclusion, our data indicate that patients with anorexia nervosa who improved weight experienced a significant increase in BMD at femoral neck and total hip. Weight at entry and percent change of weight were important determinants of BMD at this level, whereas weight at entry was the main determinants of bone modifications at lumbar spine. Thus, our results corroborate findings of other studies that emphasize the influence of weight gain in recovery of bone mass, especially at the hip.

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Table 1. Baseline (T1) characteristics of patients with anorexia nervosa (AN) and controls

	AN (N: 51) *Mean ± SD (range)*	**Controls (N: 40)** *Mean ± SD (range)*
Age (yr)	25.4± 5.3 (18-38)	24.7±4.0(19-34)
Age of menarche (yr)	13.0±1.4 (11-17)	13.0±1.4 (10-16)
Duration of amenorrhea (yr)	1.8 ± 2.2 (0-10)	-
Duration of illness (yr)	7.2±5.1 (0.3-19)	-
Weight at diagnosis (kg)	42±7 (29-54)	-
BMI at diagnosis (kg/cm^2)	16.2±1.2 (12-17.5)	-
Weight at entry (kg)	45±7 (31-63)	61±9 (48-80)*
Height at entry (cm)	161±6 (146-172)	166±6 (150-180)*
BMI at entry (kg/cm^2)	17.3±2.4 (12-21)	21.8±2.7 (17-29)*
Lumbar spine BMD (g/cm^2)	0.877±0.114	1.047±0.113*
Lumbar spine T score	-1.44±1.01	-0.24± 1.0*
Lumbar spine Z score	-1.30±1.03	-0.21±1.0*
Femoral neck BMD (g/cm^2)	0.768±0.131	0.824±0.139*
Femoral neck T score	-1.26±1.34	0.16±1.28*
Femoral neck Z score	-1.34±1.19	-0.01±1.26*
Total hip BMD	0.824±0.156	0.912±0,139*
Total hip T score	-1.10±1.32	0.12±1.10*
Total hip Z score	-1.19±1.30	-0.06±1.11*

* p<0.001

Table 2: Baseline (T1) clinical characteristics of women with anorexia nervosa, categorized by presence or absence of improved weight at subsequent visits.

	Improved weight* (N: 14) *Mean ± SD*	Did not improve weight (N: 37) *Mean ± SD*	p
Age (yr)	24 ± 5	25± 5	NS
Age of menarche (yr)	12.6 ± 1.2	13.2 ± 1.5	NS
Duration of amenorrhea (yr)	1.0 ± 0.7	2.0 ± 2.7	0.008
Duration of illness (yr)	5.8 ± 5.0	7.8 ± 5.1	NS
Weight at entry (kg)	41 ± 6	46 ± 7	0.001
BMI at entry (kg/cm^2)	15.6±1.8	17.9 ± 2.4	0.002
Lumbar spine BMD (g/cm^2)	0.869 ± 0.118	0.880 ± 0.114	NS
Lumbar spine T score	-1.57 ±1.08	-1.39±1.00	NS
Lumbar spine Z score	-1.43 ± 1.13	-1.26±1.00	NS
Femoral neck BMD (g/cm^2)	0.760 ± 0.158	0.771± 0.123	NS
Femoral neck T score	-1.36 ± 1.61	-1.22±1.25	NS
Femoral neck Z score	-1.63 ± 1.31	-1.25±1.17	NS
Total hip BMD	0.799 ± 0.161	0.834 ± 0.154	NS
Total hip T score	-1.23 ± 1.43	-1.05±1.30	NS
Total hip Z score	-1.57 ± 1.26	-1.07±1.32	NS

*Improved weight: at subsequent visit, increased body weight by at least 10%

NS: not significant

Table 3: Changes in bone mineral density (BMD) of women with anorexia nervosa, categorized by presence or absence of improved weight at subsequent visits.

	Improved weight			Did not improved weight		
	First visit (T1)	Second visit (T2)	% changes	First visit (T1)	Second visit (T2)	% changes
Weight at entry (kg)	41 ± 6	50 ± 6	20±8	46±7	47±6	1.3±4.3
BMI at entry (kg/cm^2)	15.6±1.8	18.8±1.8	13.1±1.0	17.9±2.4	18.1±2.1	0.2±1.0
Lumbar spine BMD (g/cm^2)	0.869 ± 0.118	0.880±0.118	1.3±6.7	0.880 ± 0.114	0.880±0.104	0.2±6.0
Femoral neck BMD (g/cm^2)	0.760 ± 0.158	0.753±0.115	1.6±9.6*	0.771± 0.123	0.738±0.122	-3.8±5.8
Total hip BMD (g/cm^2)	0.799 ± 0.161	0.826±0.137	4.4±10.7*	0.834 ± 0.154	0.820±0.147	-1.0±6.2

Improved weight: at subsequent visit, increased body weight by at least 10%

* $p<0.05$ vs. non-weight-improved group

Table 4. Multivariate linear regression analysis (percent change bone mineral density as a dependent variable)

	% Change at LS		% Change at FN		% Change at TH	
	β-Coefficient	***p***	***β-Coefficient***	***p***	***β-Coefficient***	***p***
Age at entry	0.13	0.58	0.16	0.52	0.16	0.46
Weight at entry	0.51	0.009	0.32	0.09	0.50	0.005
Duration of illness	-0.06	0.77	-0.07	0.77	-0.43	0.84
Duration of amenorrhea	0.21	0.22	0.12	0.46	0.26	0.08
Estrogen use	0.09	0.52	0.01	0.94	-0.05	0.68
Weight change	0.52	0.07	0.57	0.005	0.82	<0.001

LS: Lumbar spine; FN: Femoral neck; TH: Total hip