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# Effects of the two types of anorexia nervosa (binge eating/purging and restrictive) on bone metabolism in female patients

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## Summary

**Objective**: This study compared the profiles of the two types of anorexia nervosa (AN; restrictive: AN-R, and binge eating/purging: AN-BP) in terms of body composition, gynaecological status, disease history and the potential effects on bone metabolism.

**Design**: Two hundred and eighty-six women with AN (21.8 ± 6.5 years; 204 AN-R and 82 AN-BP) and 130 age-matched controls (CON; 22.6 ± 6.8 years) were enrolled. Areal bone mineral density (aBMD) was determined using DXA and resting energy expenditure (REE) was indirectly assessed using calorimetry. Markers of bone formation (osteocalcin [OC], procollagen type I N-terminal propeptide [PINP] and resorption (type I-C telopeptide breakdown products [CTX]) and leptin were concomitantly evaluated.

**Results**: Anorexia nervosa patients presented an alteration in aBMD and bone turnover. When compared according to type, AN-BP were older than AN-R and showed less severe undernutrition, lower CTx levels, longer duration of AN, and higher REE levels and aBMD at radius and lumbar spine. After adjustment for age, weight and hormonal contraceptive use, the aBMD and CTx differences disappeared. In both AN groups, aBMD was positively correlated with anthropometric parameters and negatively correlated with durations of AN and amenorrhoea, the bone formation markers

  

(OC and PINP) and the leptin/fat mass ratio. REE was positively correlated with aBMD in AN-R patients only.

**Conclusions**: This study shows the profiles of AN patients according to AN type. However, the impact of the profile characteristics on bone status, although significant, was minor and disappeared after multiple adjustments. The positive correlation between REE and aBMD reinforces the concept that energy disposal and bone metabolism are strongly interdependent.

**KEYWORDS**

anorexia nervosa, areal bone mineral density, binge eating/purging, resting energy expenditure, restrictive

## 1 | INTRODUCTION

Anorexia nervosa (AN) is an eating disorder of multifactorial origin. Its prevalence in young females is approximately 0.4% (DSM-5) per year. This disease is characterized by an intense fear of becoming fat despite obvious thinness and extreme behaviours for weight loss, including food restriction with or without self-induced vomiting or use of laxatives. The result is massive weight loss and/or dramatic thinness. AN strongly affects the quality of life of both patients and their relatives.[1] According to current classifications, AN is clinically dichotomized into two types: restrictive (AN-R: presentations in which weight loss is accomplished primarily through dieting, fasting, and/or excessive exercise) and purging (AN-BP: characterized by binge eating and/or purge behaviours). A number of studies have found that patients with restrictive AN are different from those with the purging type in terms of clinical presentation,[2] impulsivity,[3] neurocognitive functioning,[4] emotion regulation and self-regulatory behaviour[5] and brain activation.[6]

It is now well established that women suffering from AN exhibit impaired bone remodelling due to the uncoupling of bone formation and bone resorption,[7-10] which reduces areal bone mineral density (aBMD) at the appendicular and axial bone sites.[8-11] The kinetics of bone loss in AN patients is specific and characterized by intense and very early bone loss.[9,12,13] Demineralization may be detected in adolescent girls in as little as 6-12 months after disease onset [12] and osteoporosis can then occur within 24 months.[9,13] The cumulative alteration in bone mass and bone microarchitecture appears to be a risk factor for fracture not only in adults but also in adolescents suffering from AN.[14-16]

In addition to weight loss, numerous factors such as age of AN onset, durations of AN and amenorrhoea have been reported to influence a BMD at various bone sites in a dependent manner.[9,11] Recently, we demonstrated in patients with AN-R that the more resting energy expenditure (REE) is reduced, the more bone turnover is altered in favour of bone resorption, which may have a deleterious effect on bone mass at term.[10] AN-BP patients are more likely to partially compensate their nutritional intake deficit, as demonstrated by the systematically higher body mass index (BMI)[17] and less disturbed endocrine profile. Therefore, they may have better REE compared with AN-R patients. If energy and bone status are indeed related, we can hypothesize that AN-BP patients will have better preserved bone mass than AN-R patients.

The first aim of the study was to compare the profiles of patients with AN-R and AN-BP in terms of body composition, gynaecological status, metabolic markers and history of the disease. The second aim was to assess the potential impacts of these specificities on bone metabolism.

## 2 | METHODS

### 2.1 | Study design

This study included 286 females with AN (age, 14.4-50.1 years). Among them, 204 had pure AN-R and the remaining 82 had AN-BP. They were consecutively recruited from the Endocrinology Department of Montpellier University Hospital (France) in 2011-2015, and all met the criteria for AN diagnosis as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5, that is, fear of gaining weight and alteration in body size perception). On the basis of the DSM-5 classification, patients were considered to have AN-BP when they were currently binge eating and/or when they purged through self-induced vomiting or the misuse of laxatives, diuretics, or enemas. Patients with no current binge eating and/or purge were classified as AN-R. Clinical assessments were carried out by experienced psychiatrists and nutritionists. The diagnoses and subtypes were established by consensus using the best-estimated procedure through medical records and information from relatives, the nonstandardized clinical assessments of the psychiatrists and nutritionists, and standardized measures with the Mini International Neuropsychiatric Interview (MINI).[18] To define normative values, a control group (CON; age, 13.8-50.2 years) was recruited from advertisements in local newspapers or from the staff and medical students of the Departments of Nuclear Medicine, Endocrinology and Psychiatry of the Lapeyronie Hospital, CHRU Montpellier. This group comprised 130 healthy normal-weight female adolescents and premenopausal adult women with BMI ranging from 18 to 25 kg/m$^2$. None had a history of eating disorders or other

psychiatric illness determined by the SCOFF questionnaire[19] and the MINI.[18] All the controls presented normal menstrual cycles or minor alterations in duration (~28 days) and performed only leisure physical activities. No control subject or AN patient had impaired glucose regulation or diabetes mellitus, and none was taking a medication known to affect glucose or bone metabolism.

#### 2.1.1 | Methods

This case-control study has been described in detail elsewhere.[9] Briefly, standing height was measured with a stadiometer to the nearest 0.1 cm. Weight was determined using a weight scale with a precision of 0.1 kg. BMI was calculated as weight (kg) divided by the square of height (m). Height standard deviation score (height SDS) and weight SDS were calculated according to the French standard curves. Multidisciplinary clinical assessments were carried out by experienced psychiatrists and nutritionists. The diagnosis was established by consensus using the best-estimated procedure through medical records and information from relatives, the nonstandardized clinical assessments of the psychiatrists and nutritionists, and the standardized measures with the MINI. Moreover, weight history was self-reported by each patient.

#### 2.1.2 | Medical and menstrual histories

Each subject or her parents responded to a medical questionnaire designed to assess the general medical, menstrual (age of menarche, menstrual function) and disease histories (age of AN onset, duration of AN, weight variations).

#### 2.1.3 | Resting energy expenditure (REE) measurements

Resting energy expenditure was measured over a period of at least 30 min by indirect calorimetry (Quark RMR, Cosmed, Rome, Italy) after an overnight fast in the patients with AN.

#### 2.1.4 | Assays

Blood samples (25 mL) were collected in the morning (08 h30-09 h30) in sterile chilled tubes by standard venipuncture technique. The samples were allowed to clot at room temperature and were then centrifuged at 1050 g for 10 minutes at 4°C. Plasma samples were stored at −80°C until analysis. All samples were run in duplicate, and to reduce inter-assay variation, the plasma samples were analysed in a single session. The date of the last menses was not recorded for CON, and hormonal values were thus obtained at an unsynchronized menstrual stage. Serum osteocalcin (OC), procollagen type I N-terminal propeptide (PINP), type I-C telopeptide breakdown products (CTX) and leptin were evaluated.

OC, PINP and CTX were assayed using Cobas 6000 (Roche Diagnostic, Mannheim, Germany). The inter- and intra-assay coefficients of variation (CVs) for the latter three parameters were lower than 7%.

The intra- and inter-assay CVs for leptin were, respectively, <5% and <7.6% (Mediagnost GmbH, Reutlingen, Germany). The leptin/whole body fat mass ratio was calculated.

#### 2.1.5 | Areal bone mineral density, body fat and fat-free soft tissues

Dual-energy X-ray absorptiometry (DXA [Hologic QDR-4500A, Hologic, Inc., Waltham, MA]) measured the areal bone mineral density (aBMD; g/cm$^2$) of the whole body and at specific bone sites: the anteroposterior lumbar spine (L1-L4), the dominant arm radius, hip and femoral neck (FN). The soft tissue body composition (fat mass [FM, kg], percentage of body fat mass [% FM] and fat-free soft tissue [FFST, kg]) was derived from the whole body scan. All scanning and analyses were performed by the same operator to ensure consistency, after following standard quality control procedures. Quality control for DXA was checked daily by scanning a lumbar spine phantom consisting of calcium hydroxyapatite embedded in a cube of thermoplastic resin (DPA/QDR-1; Hologic x-calibre anthropometric spine phantom). The CVs given by the manufacturer were 0.8% for spine and radius, 1.1% at the hip, and <1% for FFST and FM.

### 2.2 | Statistical analysis

The study population is described with means and standard deviations (SD) for quantitative variables and frequencies for qualitative variables. The continuous variable distributions were tested with the Shapiro-Wilk statistic. Quantitative variables were compared with the parametric Student's t test when the distribution was Gaussian, and with the Mann-Whitney test otherwise. For qualitative variables, groups were compared using the Chi-square test or Fisher test.

To take into account age, weight and hormonal contraceptive use as potential confounding factors on bone metabolism, aBMD and biological factors, linear regression adjusted for these three factors was performed for some of the comparisons between the AN-R and AN-BP groups.

Separately within the AN-R and AN-BP groups, Pearson or Spearman correlation coefficients were calculated to measure the strength and direction of the relationships between the aBMD, anthropometric, gynaecological, biological and metabolic characteristics. Partial correlation coefficients adjusted on hormonal contraceptive use were also calculated.

Statistical significance was set at 0.05 and analyses were performed using SAS version 9 (SAS Institute, Cary, NC).

## 3 | RESULTS

### 3.1 | Comparison between patients with AN and controls

#### 3.1.1 | Anthropometric and gynaecological characteristics

Subject characteristics are shown in Table 1. Ages ranged from 13.8 to 50.2 years, with a mean age of 21.8 ± 6.5 years for

CON and 22.6 ± 6.8 years for patients with AN. As expected, body weight, BMI, % FM, total FM (kg) and FFST were markedly lower in AN patients than in CON due to undernutrition ($P < .001$). When weight SDS and height SDS were calculated according to the French standard curves, AN patients also presented low values for weight (−1.7 ± 1.0) and normal values for height (+0.3 ± 1.1). The mean age of AN onset was 17.5 ± 4.2 (range: 10.0-38.2) years and the mean AN duration was 5.1 ± 6.0 (range: 0.2-30.2) years.

Concerning the gynaecological profile (Table 2), the age of menarche was not different between groups (12.6 ± 1.4 years for CON vs 12.8 ± 1.5 for AN). The mean duration of amenorrhoea for those not taking hormonal contraceptives was 26.3 ± 47.2 months, and only seven patients presented with primary amenorrhoea. Hormonal contraceptive use was significantly lower in patients than in controls (27.8% vs 51.2%, respectively, $P < .001$). Menstrual disorders were more frequent in patients than in CON (87.3% vs 24.2%, $P < .001$), and controls with menstrual disorders had only minor variations in cycle duration (~28 days).

### 3.1.2 | Areal bone mineral density, hormonal and biochemical parameters

aBMD values at all bone sites were significantly lower in patients with AN than in CON ($P < .001$). The mean difference was −3.2% at whole body, −11.1% at lumbar spine, −12.3% at FN, −14.9% at hip and −3.7% at radius (Table 3).

Regarding bone remodelling, patients with AN presented lower mean values for markers of bone formation (OC: −34.1% $P < .001$ and PINP: −39.7%, $P < .001$) and a higher mean value for the bone resorption marker (CTX: +42.3%, $P < .001$). Leptin levels were significantly lower in patients.

**TABLE 1** Clinical profiles of participants

| | Controls | AN | AN-R | AN-BP |
|---|---|---|---|---|
| Number of subjects | 130 | 286 | 204 | 82 |
| Age, y | 21.8 ± 6.5 | 22.6 ± 6.8 | 22.0 ± 6.8 | 24.0 ± 6.8[c] |
| Anthropometric data | | | | |
| Weight, kg | 59.0 ± 7.6 | 43.1 ± 5.7*** | 42.4 ± 5.9 | 44.7 ± 4.8[b] |
| Weight, SDS | 0.9 ± 1.2 | −1.7 ± 1.0*** | −1.8 ± 1.0 | −1.4 ± 0.8[a] |
| Height, cm | 165.1 ± 6.0 | 164.1 ± 6.3 | 164.1 ± 6.1 | 164.1 ± 6.7 |
| Height, SDS | 0.5 ± 1.1 | 0.3 ± 1.1 | 0.3 ± 1.1 | 0.2 ± 1.2 |
| BMI, kg/m$^2$ | 21.6 ± 2.3 | 16.0 ± 1.6*** | 15.7 ± 1.7 | 16.6 ± 1.2[c] |
| Lowest BMI | – | 14.5 ± 1.8 | 14.4 ± 1.9 | 14.9 ± 1.6 |
| Age lowest BMI | – | 20.7 ± 6.0 | 20.2 ± 5.9 | 22.0 ± 6.2[b] |
| Highest BMI | – | 20.6 ± 3.2 | 20.3 ± 3.1 | 21.2 ± 3.4[a] |
| Age highest BMI, y | – | 17.7 ± 4.1 | 17.4 ± 4.0 | 18.4 ± 4.3[a] |
| 6-month weight, kg | – | 45.7 ± 7.3 | 45.6 ± 7.5 | 46.0 ± 7.0 |
| 6-month weight variation, kg | – | 2.4 ± 6.0 | 2.9 ± 6.1 | 1.3 ± 5.9 |
| Waist circumference, cm | – | 64.5 ± 6.7 | 63.9 ± 6.4 | 66.0 ± 7.3[a] |
| Hip circumference, cm | – | 79.4 ± 5.5 | 78.9 ± 5.6 | 80.4 ± 5.2[a] |
| WB fat mass, % | 27.8 ± 4.8 | 16.0 ± 5.3*** | 15.6 ± 5.4 | 16.9 ± 5.0[a] |
| WB fat mass, kg | 16.5 ± 4.6 | 7.1 ± 2.8*** | 6.8 ± 2.9 | 7.8 ± 2.7[a] |
| WB fat-free soft tissue, kg | 40.4 ± 4.4 | 34.5 ± 4.7*** | 34.1 ± 4.9 | 35.7 ± 3.8[b] |
| Characteristics of AN | | | | |
| Age of AN onset, y | – | 17.5 ± 4.2 | 17.6 ± 4.6 | 17.2 ± 3.3 |
| Duration of AN, y | – | 5.1 ± 6.0 | 4.4 ± 5.6 | 6.8 ± 6.6[c] |
| Switch, n (%) | – | 47 (16.4) | 13 (6.4) | 34 (41.5)[c] |
| Switch duration, y | – | 2.6 ± 2.6 | 1.5 ± 1.4 | 3.0 ± 2.8 |
| Hyperactivities, n (%) | – | 78 (27.5) | 62 (30.5) | 16 (19.8) |

Data are presented as mean ± standard deviation.
AN, patients with anorexia nervosa; AN-BP, anorexia nervosa-binge eating/purging; AN-R, anorexia nervosa-restrictive; BMI, body mass index; WB, whole body.
Significant difference between binge eating and restrictive types for [a]p<0.05, [b]p<0.01, [c]p<0.001.
Significant difference between controls and patients with AN, ***$P < .001$.

**TABLE 2** Gynaecological data of participants

| | Controls n = 130 | AN n = 286 | AN-R n = 204 | AN-BP n = 82 |
|---|---|---|---|---|
| Age of menarche, y | 12.6 ± 1.4 | 12.8 ± 1.5 | 12.7 ± 1.4 | 13 .0 ± 1.6 |
| Menstrual disorders[a], n (%) | 15 (24.2)[b] | 178 (87.3)*** | 131 (87.3) | 47 (87.0) |
| Duration of amenorrhoea[a], mo | - | 26.3 ± 47.2 | 25.8 ± 44.6 | 28.0 ± 54.5 |
| Primary amenorrhoea, n (%) | 0 (0) | 7 (2.4) | 6 (2.9) | 1 (1.2) |
| Hormonal contraceptive, n (%) | 66 (51.2) | 79 (27.8)*** | 51 (25.3) | 28 (34.2) |

Data are presented as mean ± standard deviation.
AN, patients with anorexia nervosa; AN-BP, anorexia nervosa-binge eating/purging; AN-R, anorexia nervosa-restrictive.
[a]Menstrual disorders and duration of amenorrhoea were reported only in patients not taking hormonal contraceptive.
[b]Controls presented only minor alterations in the duration of menstrual cycles (~28 d).
***Indicates a significant difference between patients with AN and controls, $P < .001$. No significant difference was observed between binge eating and restrictive types.

### 3.2 | Comparison according to the anorexia nervosa type

Patients with AN-BP were older than those with AN-R and presented higher weight, BMI, waist and hip circumferences, whole body FM (kg and %), and whole body FFST. They were also older at their lowest BMI and highest BMI (Table 1).

Concerning disease-related factors, the age of AN onset did not differ between the two groups, but the AN duration was longer in AN-BP than in AN-R (6.8 ± 6.6 vs 4.4 ± 5.6 years, $P < .001$). Forty-seven (16.4%) patients switched between the two types, but there was a tendency ($P = .06$) towards switching more from AN-R to AN-BP (n = 34; 41.5%) than from AN-BP to AN-R (n = 13; 6.4%). Patients with AN-R seemed to show more hyperactivity (ie, increase in physical activities related to weight/shape concerns) than those with AN-BP ($P = .065$).

No difference between the two types was observed for the gynaecological profile, including age of menarche, prevalence of menstrual disorders, duration of amenorrhoea, and use of hormonal contraceptives (Table 2).

AN-BP patients presented moderate but significantly higher aBMD than AN-R at the radius (+2.5%, $P < .05$) and lumbar spine (+3.7%, $P < .05$) and a tendency for whole body (+ 2.1%, $P = .06$; Table 3). Concerning bone remodelling markers and blood parameters, only CTx levels were higher in AN-R than in AN-BP (+22.1%, $P < .01$). Conversely, REE values were significantly higher (+ 6.3%, $P < .01$) in AN-BP than in AN-R patients.

After adjustment on age, weight and hormonal contraceptive use, all these differences between AN-R and AN-BP patients became nonsignificant.

Crossover between the AN types over the course of the disease is not uncommon, especially in the first 5 years.[20] Thus, to compare between patients with a specific type (AN-BP or AN-R) and a low risk of switching, we took into account only those patients with AN of duration exceeding 5 years. Table 4 presents the main characteristics of two groups: 48 AN-R and 38 AN-BP with a mean disease duration of about 12 years. The two groups did not differ in terms of age, BMI, body composition (FM and FFST), history of the disease (age of AN onset and AN duration), gynaecological profile, bone turnover markers or energy metabolism. The only differences between the two groups were the higher weight and BMI in the AN-BP patients over the course of the disease and a higher frequency of hyperactivity in the AN-R patients. aBMD tended to be higher in the AN-BP group at whole body ($P = .08$), lumbar spine ($P = .09$) and radius ($P = .10$) compared with that in the AN-R group. However, these tendencies disappeared after weight and age adjustment.

### 3.3 | Correlations between clinical or biological data and aBMD according to anorexia nervosa type

Correlations between aBMD and clinical and biological data are displayed in Table 5 for patients with AN-BP and AN-R. Briefly, in the two groups of patients, aBMD was positively correlated with weight, height, BMI, lowest BMI, weight at 6 months, and whole body FM and FFST. Conversely, aBMD was negatively correlated with duration of AN or amenorrhoea, PINP and leptin/FM. These correlations were mainly found at the lumbar spine, femoral neck, and hip, and to a lesser extent at the radius.

Some differences were nevertheless found between AN-BP and AN-R groups, with the highest BMI and the 6-month weight variation positively correlated with aBMD in AN-R patients only, whereas iPTH and OC levels were negatively correlated with aBMD in AN-BP patients only.

The same correlation results were found after adjustment for hormonal contraceptive use.

## 4 | DISCUSSION

Our results in a large group of patients show that the anorexia nervosa type is associated with specificities in terms of disease history

**TABLE 3** Areal bone mineral density, biochemical and energy parameters of participants

| | Controls n = 130 | AN n = 286 | AN-R n = 204 | AN-BP n = 82 |
|---|---|---|---|---|
| Areal bone mineral density | | | | |
| Whole body aBMD, g/cm$^2$ | 1.069 ± 0.074 | 1.035 ± 0.087*** | 1.029 ± 0.083 | 1.051 ± 0.096 |
| Whole body Z-score, SD | 0.0 ± 0.8 | −0.3 ± 1.1*** | −0.3 ± 1.2 | −0.3 ± 1.1 |
| Lumbar spine aBMD, g/cm$^2$ | 0.981 ± 0.106 | 0.872 ± 0.119*** | 0.863 ± 0.117 | 0.895 ± 0.121[a] |
| Lumbar spine Z-score, SD | −0.3 ± 0.9 | −1.3 ± 1.1*** | −1.2 ± 1.1 | −1.4 ± 1.1[a] |
| Femoral neck aBMD, g/cm$^2$ | 0.840 ± 0.111 | 0.737 ± 0.125*** | 0.739 ± 0.126 | 0.731 ± 0.123 |
| Hip aBMD, g/cm$^2$ | 0.941 ± 0.139 | 0.801 ± 0.130*** | 0.800 ± 0.132 | 0.805 ± 0.128 |
| Hip Z-score, SD | −0.2 ± 0.8 | −1.5 ± 1.1*** | −1.4 ± 1.0 | −1.5 ± 1.0 |
| Radius aBMD, g/cm | 0.545 ± 0.037 | 0.525 ± 0.046*** | 0.522 ± 0.045 | 0.535 ± 0.050[a] |
| Radius Z-score spine, SD | 0.0 ± 0.8 | −0.5 ± 1.1*** | −0.3 ± 1.2 | −0.5 ± 1.0[a] |
| Biological parameters | | | | |
| iPTH, ng/mL | 29.9 ± 11.3 | 31.5 ± 19.0 | 31.5 ± 20.2 | 31.6 ± 15.3 |
| Vitamin D, ng/mL | 29.5 ± 14.4 | 34.4 ± 13.8* | 35.2 ± 14.0 | 32.4 ± 13.2 |
| CTX, ng/mL | 0.548 ± 0.269 | 0.780 ± 0.492*** | 0.831 ± 0.543 | 0.647 ± 0.290[b] |
| PINP, ng/mL | 99.2 ± 111.5 | 59.8 ± 42.0*** | 61.1 ± 44.4 | 56.6 ± 35.3 |
| OC, ng/mL | 35.8 ± 21.3 | 23.6 ± 12.9*** | 23.7 ± 14.0 | 23.6 ± 9.6 |
| Leptin, ng/mL | 10.1 ± 6.0 | 1.5 ± 1.9*** | 1.5 ± 1.9 | 1.5 ± 1.9 |
| Leptin/whole body fat mass ratio | 0.66 ± 0.94 | 0.20 ± 0.19*** | 0.20 ± 0.19 | 0.21 ± 0.20 |
| Energy metabolism | | | | |
| REE kcal/d | - | 1055.3 ± 173.7 | 1036.5 ± 173.4 | 1101.7 ± 166.4[b] |
| Predicted REE values, % | - | −17.4 ± 11.6 | −18.9 ± 11.5 | −13.7 ± 11.2[b] |

Data are presented as mean ± standard deviation.

AN, patients with anorexia nervosa; AN-BP, anorexia nervosa-binge eating/purging; AN-R, anorexia nervosa-restrictive; BMD, bone mineral density; CTX, type I-C telopeptide breakdown products; iPTH, intact parathyroid hormone; OC, osteocalcin; PINP, procollagen type I N-terminal propeptide; REE, resting energy expenditure.

Significant difference between binge eating and restrictive types for [a]$p<0.05$ and [b]$p<0.01$.

Significant difference between patients with AN and controls for *$P < .05$ and ***$P < .001$.

and clinical and metabolic data. However, the AN type does not seem associated with specific aBMD or bone turnover.

In this study based on 286 AN patients, we report for the first time the clinical and biological profiles of both types of AN. We demonstrate that patients with AN-BP present a less severe undernutrition profile than those with AN-R. This profile is characterized by better preserved weight, BMI, and whole body FM and FFST, as well as by higher REE. Our results are in agreement with most of the previously reported data,[11,21] but differ from those of Urano's group,[22] who observed no statistical difference in body weight, BMI and percentage of ideal body weight between the two types of AN in Japanese patients. Less severe disease status and insufficient statistical power due to a smaller sample size may partially explain the divergent data of Urano's group.

Interestingly, we found that the differences between the two AN types concerned not only current anthropometric characteristics, but also specific body weight variations during the history of the disease. Moreover, the AN duration, percentage of switching between types, and degree of hyperactivity varied according to the type.

The differences in past and current anthropometric data and disease-related factors observed in this study were theoretically expected to affect bone mass differently. Indeed, such clinical factors as weight, BMI, and lean mass are positively correlated with aBMD in AN patients.[9,13,17,23] Conversely, factors considered to have deleterious effects on bone mass include the duration of the disease or amenorrhoea, the degree of underweight reached as well as the minimum weight, BMI under 15-17 kg/m$^2$, and the minimum lifetime BMI duration, which may represent the severity of underweight since AN onset.[9-11,17,21,23,24] Whatever the AN type in our cohort, body weight and FFST—more than FM—and the lowest BMI were positively correlated with aBMD, whereas the duration of the disease or amenorrhoea was negatively correlated. Taking into account the past and current anthropometric and biological characteristics of these patients suffering from each type of AN, we expected the AN-R patients to present greater demineralization. In line with our hypothesis, we found that the patients with AN-BP presented moderate (2.5% to 3.7%) but significantly lower localized reduction in aBMD than those with AN-R for lumbar spine and radius, as well as a tendency for whole body (2.1%). Our results thus suggest that better

**TABLE 4** Main characteristics of patients with anorexia nervosa exceeding 5 y

| | AN-R N = 48 | AN-BP n = 38 |
|---|---|---|
| Age, y | 29.3 ± 6.9 | 28.5 ± 6.9 |
| Weight, kg | 42.3 ± 6.9 | 44.0 ± 5.11 |
| BMI, kg/m$^2$ | 15.6 ± 2.1 | 16.4 ± 1.4 |
| WB fat mass, % | 15.8 ± 6.1 | 16.2 ± 5.5 |
| WB fat mass, kg | 6.9 ± 3.1 | 7.3 ± 2.9 |
| WB fat-free soft tissue, kg | 33.9 ± 5.3 | 35.3 ± 4.0 |
| Highest weight, kg | 52.5 ± 8.2 | 56.6 ± 11.3[a] |
| Highest BMI, kg/m² | 19.4 ± 2.6 | 21.1 ± 4.0[b] |
| Age of AN onset, y | 16.8 ± 4.5 | 16.3 ± 3.1 |
| Duration of AN, y | 12.5 ± 6.4 | 12.2 ± 6.1 |
| Hyperactivities, n (%) | 17 (35.4%) | 5 (13.5%)[a] |
| Duration of amenorrhoea, mo | 68.0 ± 72.9 | 54.5 ± 77.1 |
| Whole body aBMD (g/cm$^2$) | 0.999 ± 0.090 | 1.038 ± 0.110 |
| Whole body Z-score (SD) | −0.9 ± 1.0 | −0.5 ± 1.3 |
| Lumbar spine aBMD, (g/cm$^2$) | 0.830 ± 0.138 | 0.880 ± 0.131 |
| Lumbar spine Z-score (SD) | −1.9 ± 1.3 | −1.4 ± 1.2 |
| Femoral neck aBMD, (g/cm$^2$) | 0.666 ± 0.136 | 0.689 ± 0.131 |
| Hip aBMD (g/cm$^2$) | 0.723 ± 0.138 | 0.752 ± 0.124 |
| Hip Z-score (SD) | −2.0 ± 1.1 | −1.8 ± 1.0 |
| Radius aBMD (g/cm$^2$) | 0.510 ± 0.050 | 0.530 ± 0.057 |
| Radius Z-score spine (SD) | −0.9 ± 1.1 | −0.5 ± 1.2 |
| CTX, ng/ml | 0.640 ± 0.330 | 0.580 ± 0.300 |
| PINP, ng/mL | 66.7 ± 39.6 | 58.3 ± 39.1 |
| OC, ng/mL | 25.6 ± 14.6 | 24.1 ± 10.2 |
| Leptin, ng/mL | 1.8 ± 1.6 | 1.6 ± 1.8 |
| Leptin/whole body fat mass ratio | 0.24 ± 0.15 | 0.23 ± 0.20 |
| REE, kcal/d | 1105.9 ± 185.9 | 1129.0 ± 167.3 |
| Predicted REE values, % | −11.1 ± 11.0 | −9.9 ± 11.0 |

Data are presented as mean ± standard deviation.

AN-BP, anorexia nervosa-binge eating/purging; AN-R, anorexia nervosa-restrictive; BMD, bone mineral density; BMI, body mass index; CTX, type I-C telopeptide breakdown products; OC, osteocalcin; PINP, procollagen type I N-terminal propeptide; REE, resting energy expenditure; WB, whole body.

Significant difference between binging and restrictive types for [a]$p<0.05$, [b]$p<0.01$.

weight preservation and less severe weight loss during the history of the disease may partially protect bone health. Interestingly, this "more preserved" bone mass is probably due to a limited increase in bone resorption as demonstrated by the lower levels of CTX in the AN-BP patients without concomitant variation in bone formation. This difference in aBMD may also be attributed to better preservation of energy in patients with AN-BP. In this context, we recently demonstrated in a limited number (n = 50) of AN patients that REE correlated positively with markers of bone formation (OC and PINP) and negatively with the marker of bone resorption (CTX).[10] In the present study, we also show that REE also positively correlated with aBMD at all sites, radius excepted, probably due to the higher number of patients. These findings were only observed in AN-R patients, however, and body weight, age and hormonal contraceptive use may be confounding factors for these aBMD differences, because the aBMD differences disappeared after multiple adjustments. This suggests that better preservation of body composition and weight is a key determinant of the bone mass in AN patients. Our results agree with those of Legroux et al,[11] who also reported that the difference between the two types at femoral neck and lumbar spine did not remain significant after weight adjustment.

Little information is available on aBMD changes in subgroups of AN. In previous studies, nutritional behaviours seemed to play a limited role in bone alteration,[17,21,25] although higher[11] or lower aBMD values were reported in AN-BP compared with AN-R.[22] In Urano's study,[22] it was nevertheless surprising to find lower aBMD in AN-BP patients despite their higher body weight and higher bone formation markers. The limited sample size in these previous studies may have contributed to the inconclusive results.[17,21,25] Moreover, the discrimination between the two AN types is based on behavioural symptoms that frequently change during the course of the disease. To test this hypothesis, we compared two groups of patients having a minimum of 5 years as AN-R or AN-BP, a period beyond which a switch is less probable.[20] The higher weight and BMI and the lower degree of hyperactivity in AN-BP were the only significant differences compared with those in AN-R. Although we cannot exclude a sample size effect, it is likely that the disease chronicity reduced the difference between groups.

Although the clinical recommendations include avoiding excessive physical activity to limit energy expenditure, patients with AN in most cases present a hyperactive state that contributes to maintaining low body weight.[24] In our study, the prevalence of hyperactivity was higher among the AN-R patients compared with the AN-BP patients, which may have modified aBMD. However, the expected protective effect of physical activity on bone mass in this population has shown conflicting results, ranging from nonsignificant[24,26,27] to significantly protective.[28,29] The divergent results may be attributed to the different tools used to evaluate the physical activity level (questionnaire vs interview), some of which were probably not adapted to patients who suffer from a disease classically associated with denial behaviour.[28] Moreover, mechanical constraint, which is the strongest predictor of bone mass gain,[30] is generally not evaluated and may explain why the femoral neck, which is a weight-bearing skeletal site, has shown relatively preserved aBMD in women who exercise more,[28,29] although again this was not a universal finding.[31] In our study, the higher degree of hyperactivity in the AN-R type may partially explain why aBMD was comparable in AN-R and AN-BP patients at neck and hip, whereas it was lower in other bone sites of the AN-R patients. Moreover, it is likely that physical activity has a threshold effect, as suggested by Joyce et al,[32] who reported that moderate exercise in their AN patients was protective, whereas strenuous exercise was detrimental to bone mass.

This study has some limitations, and in particular its cross-sectional design does not authorize the conclusion that AN type

**TABLE 5** Correlation analysis between areal bone mineral density and various parameters in patients with anorexia nervosa

| | AN-R | | | | | AN-BP | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | aBMD (g/cm²) | | | | | aBMD (g/cm²) | | | | |
| Parameters | Whole body | Lumbar spine | Femoral neck | Hip | Radius | Whole body | Lumbar spine | Femoral neck | Hip | Radius |
| Weight, kg | 0.40*** | 0.38*** | 0.41*** | 0.33*** | 0.12 | 0.38*** | 0.40*** | 0.46*** | 0.41*** | 0.11 |
| Height, cm | 0.38*** | 0.25*** | 0.33*** | 0.27*** | 0.08 | 0.34** | 0.30** | 0.31** | 0.30** | 0.1 |
| BMI, kg/m² | 0.20** | 0.32*** | 0.28*** | 0.25*** | 0.06 | 0.13 | 0.21 | 0.26* | 0.22* | 0.02 |
| Lowest BMI, kg/m² | 0.36*** | 0.48*** | 0.45*** | 0.45*** | 0.15* | 0.2 | 0.37*** | 0.36** | 0.42*** | 0.13 |
| Age lowest BMI, y | 0.14 | −0.07 | −0.18* | −0.19** | 0.32*** | 0.14 | 0.1 | −0.16 | −0.13 | 0.27* |
| Highest BMI, kg/m² | 0.31*** | 0.17* | 0.15* | 0.19** | 0.25*** | 0.11 | 0.11 | 0.02 | 0.02 | 0.14 |
| Age highest BMI, y | 0.16* | 0.05 | −0.01 | −0.02 | 0.34*** | 0.28* | 0.23* | 0.09 | 0.13 | 0.22 |
| 6-month weight, kg | 0.53*** | 0.47*** | 0.52*** | 0.50*** | 0.23** | 0.38** | 0.38** | 0.44*** | 0.47*** | 0.21 |
| 6-month weight variation, kg | 0.26*** | 0.21** | 0.23** | 0.30*** | 0.15 | 0.18 | 0.15 | 0.2 | 0.28* | 0.22 |
| Hip circumference, cm | 0.19* | 0.22** | 0.14 | 0.1 | 0.11 | 0.1 | 0.14 | 0.19 | 0.16 | −0.23 |
| Fat mass, % | 0.01 | 0.20** | 0.14* | 0.09 | −0.15* | −0.08 | 0.05 | 0.18 | 0.11 | −0.1 |
| Fat mass, kg | 0.12 | 0.27*** | 0.24*** | 0.18* | −0.1 | 0.06 | 0.17 | 0.29** | 0.22* | −0.05 |
| Fat-free soft tissue, kg | 0.42*** | 0.33*** | 0.38*** | 0.31*** | 0.18* | 0.39*** | 0.36** | 0.34** | 0.33** | 0.11 |
| Age of AN onset, y | 0.24*** | 0.07 | 0.01 | 0.01 | 0.40*** | 0.17 | 0.19 | 0.07 | 0.17 | 0.2 |
| Duration of amenorrhoea, mo | −0.19** | −0.37*** | −0.30*** | −0.38*** | −0.07 | −0.33** | −0.37** | −0.32** | −0.37** | −0.13 |
| Duration of AN, y | −0.24*** | −0.27*** | −0.36*** | −0.39*** | −0.1 | 0 | −0.01 | −0.25* | −0.29** | 0.03 |
| iPTH, ng/mL | 0.13 | 0.05 | 0.04 | 0.08 | 0.11 | −0.42** | −0.25 | −0.37** | −0.40** | −0.29* |
| PINP, ng/mL | −0.21** | −0.11 | −0.13 | −0.19* | −0.25*** | −0.25* | −0.21 | −0.06 | −0.15 | −0.29* |
| OC, ng/mL | −0.11 | 0.02 | −0.03 | −0.05 | −0.18* | −0.39*** | −0.40*** | −0.12 | −0.23 | −0.45*** |
| Leptin/whole body fat mass ratio | −0.26* | −0.24* | −0.30** | −0.34** | −0.14 | −0.21 | −0.19 | −0.55** | −0.54** | −0.28 |
| REE, kcal/d | 0.18* | 0.20** | 0.20** | 0.19** | 0.02 | 0.16 | 0.13 | 0.17 | 0.11 | −0.12 |

Data are presented as coefficients of correlation.

AN-R, anorexia nervosa-restrictive; AN-BP, anorexia nervosa-binge eating/purging; BMI, body mass index; BMD, bone mineral density; iPTH, intact parathyroid hormone; CTX, type I-C telopeptide breakdown products; PINP, procollagen type I N-terminal propeptide; OC, osteocalcin; REE, resting energy expenditure.

Significant correlation for*$P < .05$,**$P < .01$ and***for $P < .001$.

influences bone status. However, this limitation is mitigated by the large sample size and the wide distribution of such characteristics as age, disease duration and weight history.

In conclusion, the study strongly supports the hypothesis that each type of AN has a specific profile in terms of weight history, disease duration, hyperactivity, body composition and REE. Nevertheless, the impact of these specific characteristics on aBMD, although significant, remains minor and disappears after adjustment for weight, age and hormonal contraceptive use and in patients with long disease duration. Globally, aBMD in the two subgroups was influenced by such well-identified common factors as weight, lowest BMI, and duration of AN or amenorrhoea. Moreover, we report for the first time a positive correlation between REE and aBMD, which reinforces the concept that energy stores and bone metabolism are strongly interdependent.[33,34]

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## CONFLICT OF INTEREST

Nothing to declare.

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