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Objective: The threefold aim was to (1) compare areal bone mineral density (aBMD), bone turnover markers, and periostin levels in young women with either anorexia nervosa (AN) or obesity (OB) and controls (CON); (2) model the profiles according to age; and (3) determine the parameters associated with aBMD.

Subjects and Methods: One hundred and fifty-two young women with ages ranging from 16.0 to 27.0 years were subdivided into 3 groups (AN, OB, CON). The CON group was age-matched by ±6 months. aBMD, bone turnover markers, and periostin levels were evaluated.

Results: aBMD modeling showed that hip aBMD was higher in OB than in the other 2 groups from 19 years, and AN presented lower values than CON from 21 years. aBMD at the lumbar spine was higher in older OB and CON women, starting from 20 to 22 years, but in AN the difference with the other 2 groups increased with age. Periostin levels were lower in OB than in AN or CON, but no variation with age was observed. Compared with controls, OB and AN presented similarly lower markers of bone formation, although markers of bone resorption were lower in OB and higher in AN. A modeling approach showed that markers of bone formation and resorption were lower in older than in younger CON, whereas the values of

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Abbreviations: aBMD, areal bone mineral density; AN, anorexia nervosa; BMI, body mass index; CON, controls; CTX, type I-C telopeptide breakdown products; CV, coefficient of variation; FM, fat mass; IGF, insulin-like growth factor; LBM, lean body mass; OB, obesity; OC, osteocalcin; PBM, peak bone mass; PINP, procollagen type I N-terminal propeptide.

these bone markers remained relatively constant in AN and OB. In all groups, lean body mass (LBM) was the parameter most positively correlated with aBMD.

Conclusion: This study demonstrated that weight extremes (AN or OB) influence aBMD, bone remodeling and periostin profiles. Moreover, factors related to aBMD were specific to each condition, but LBM was the parameter most consistently associated with aBMD.

Key Words: anorexia nervosa, obesity, bone mass acquisition, periostin, bone remodeling markers

Childhood and adolescence are crucial periods for bone mass acquisition within a relatively short period of time (1). Various factors influence the peak bone mass (PBM), which is defined as the optimal value reached around the end of the second decade (2,3). Since PBM is an important determinant of the risk of future osteoporosis (4), a better understanding of the factors underlying bone mass acquisition is crucial in helping adolescents and young adults to reach optimal bone mass.

Among the factors likely to influence PBM, weight appears to have a crucial role. This has been particularly observed in subjects with anorexia nervosa, who are known to be at risk of inadequate bone accrual and its detrimental effects, mostly due to factors such as low body weight, lean body mass and fat mass, low levels of bone trophic hormones (ie, insulin-like growth factor-I [IGF-I] and estrogen) and higher stress hormone levels (ie, cortisol) (5,6). Although weight gain and the return of menses are the most efficient ways to increase bone mass (7), their normalization still results in suboptimal bone accrual without full catch-up (7,8). Conversely, adolescents with obesity, who present high body weight and fat mass, are known to have higher areal bone mineral density (aBMD) than normal-weight controls (9,10). However, it was recently reported that, after controlling for body weight, strength estimates are lower in adolescent girls with obesity than in controls and those with anorexia nervosa (10). Also, bone strength and bone microarchitecture were found to be deleteriously altered in premenopausal women with obesity compared with controls, which may increase their fracture risk (11). These data suggested that the higher aBMD in obesity may not itself be an indicator of stronger bone (11).

In addition to the effects of variations in hormones and metabolic factors, the difference in bone mass acquisition between subjects with anorexia nervosa and obesity may be partly due to 2 extreme body weights that generate specific mechanical constraints on the skeleton. The response of bone tissue to weight loss or gain may affect the levels of periostin, a matricellular protein of 90 kD secreted by osteocytes and osteoblasts (12,13) that plays a crucial role in bone formation partly by promoting osteoblast differentiation and proliferation (14). Experimental preclinical studies have demonstrated that an increase in mechanical constraints using, for example, an axial compression load on mouse tibia (13) or intensive training (12) results in the overexpression of periostin and the downregulation of sclerostin (13). In humans, circulating periostin levels have been reported to be either weakly or not correlated with aBMD (15–17), while higher serum periostin levels have been associated with a higher fracture risk in postmenopausal women (16,17). However, the implication of periostin in PBM during normal development and in girls with extreme body weight (ie, anorexia nervosa and obesity) has not been investigated.

The 3-fold aim of this study was to (1) compare the effects of 2 diseases in adolescents and young adults: anorexia nervosa and obesity, on aBMD, bone turnover and periostin levels; (2) model the profiles of aBMD, bone turnover markers, and periostin levels for each condition with age; and (3) determine the anthropometric, gynecological (age of menarche), and biological parameters most associated with aBMD at each skeletal site.

Subjects and Methods

Study approval was obtained from the Regional Research Ethics Committee (Comité de Protection des Personnes Sud-Mediterranee IV, Montpellier, France; reference: 11 02 03) and permission for the clinical trials was granted by the French Agency for the Safety of Health Products (Agence Française de Securite Sanitaire des Produits de Santé; AFSSAPS; reference: 2011-A00108-33). Informed consent was obtained from all subjects, as well as from the parents of subjects <18 years old. As noted, all subjects <18 years old provided consent.

Subjects

One hundred and fourteen adolescents and young women with ages ranging from 16.0 to 27.0 years were enrolled in this study. All were Caucasian. Thirty-eight

were diagnosed with anorexia nervosa and fulfilled the criteria for the diagnosis of the restrictive form as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV: amenorrhea, body mass index (BMI) <17.5 kg/m^2, fear of gaining weight, and altered body size perception (18). A full description of the diagnostic procedure can be found elsewhere (19). Thirty-eight were women with obesity as defined by a BMI >95th percentile for age in subjects <18 years and by a BMI >30 kg/m^2 in subjects ≥18 years. All were recruited from the Endocrinology Department of Montpellier University Hospital, France.

The control group was recruited from the community by advertisement. It consisted of 38 healthy normal-weight adolescents and young women with 18 < BMI < 25 kg/m^2. None had a history of eating disorders or other psychiatric illness as determined by the Sick, Control, One, Fat, and Food (SCOFF) questionnaire (20) and the Mini International Neuropsychiatric Interview (21). All presented with normal menstrual cycles, had no lifetime history of eating disorders, and performed only leisure physical activities for less than 3 hours/week. Controls and subjects with anorexia nervosa and obesity were age matched (±6 months).

No subject was taking medication known to affect bone metabolism, presented with primary amenorrhea, used hormonal contraceptives (previous 1 year), or had ever been pregnant.

Methods

This study followed a case–control design. 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).

Medical and menstrual histories

Each subject or her parents responded to a medical questionnaire designed to assess the general medical and menstrual history, with questions on the age of menarche and the presence of menstrual disorders. Age of menarche, duration of the eating disorder, and menstrual function were determined for each one.

Assays

Blood samples (25 mL) were collected in fasting conditions in the morning (8.30–10.00 AM) in sterile chilled tubes by a standard venipuncture technique. The samples were allowed to clot at room temperature and were then centrifuged at 2500 rpm for 10 minutes at 4°C. Serum samples were stored at –80°C until analysis. All samples were run in duplicate and analyzed in a single session to reduce interassay variation. The dates of the subjects' last menses were not recorded and hormonal values were thus obtained at an unsynchronized menstrual stage.

For the markers of bone remodeling, serum samples were assayed using a Cobas 6000 (Roche Diagnostic, Mannheim, Germany) analyzer for osteocalcin (OC), procollagen type I N-terminal propeptide (PINP), and type I-C telopeptide breakdown products (CTX). The inter- and intra-assay coefficients of variation (CVs) for the last 3 parameters were lower than 7%.

Serum periostin levels were measured with a quantitative sandwich enzyme-linked immunosorbent assay from Biomedica (BI 20433; Vienna, Austria). The intra-assay and interassay CVs were ≤3% and ≤6%, respectively. The periostin enzyme-linked immunosorbent assay uses a mouse monoclonal antibody directed against the mid-region and a goat polyclonal antibody directed against epitopes that spread across the whole periostin molecule and are mostly conserved between the isoforms. The measuring range for the assay is 125 to 4000 pmol/L.

Bone mineral density, body fat, and lean body mass

Dual-energy X-ray absorptiometry (Hologic QDR-4500A, Hologic, Inc., Waltham, MA) measured aBMD (g/cm^2) of the whole body and at specific bone sites: the anteroposterior lumbar spine (L1–L4), the dominant arm radius, and hip. The soft tissue body composition (fat mass [FM] kg, percentage of body fat mass [% FM] and lean body mass [LBM] kg) were 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 dual-energy X-ray absorptiometry was checked daily by scanning a lumbar spine phantom consisting of calcium hydroxyapatite embedded in a cube of thermoplastic resin (Hologic X-CALIBER Model DPA/QDR-1 anthropometric spine phantom). The CVs were 0.8% for spine and radius, 1.1% at the hip, and <1% for LBM and FM.

Statistical Analysis

The characteristics of the adolescents and young women enrolled in this study are described with proportions for categorical variables and means and standard deviation (SD) values for continuous variables (age, weight, aBMD, etc.). These characteristics were compared between groups 2 by 2 using the Student t-test for quantitative variables when the data distribution was normal and the Mann–Whitney U test when the variables were

skewed. *P*-values were adjusted for multiple comparisons using Hommel's method.

We first modeled the yearly aBMD variation in the 3 groups using a thin plate regression spline model (Proc TPSPLINE in SAS) (22). This kind of nonparametric model allows great flexibility in the possible form of the regression when no prior knowledge about the model is available. The results are expressed graphically with their 95% Bayesian confidence interval (23).

We assessed the association of bone markers, body composition measurements (FM and LBM), and anthropometric or gynecological parameters with aBMD according to the body weight group using multivariable linear regression models. The dependent variable was aBMD (whole body, hip, lumbar spine, or radius), and the independent variables were the interest marker (each marker in a different model), the body weight group, age, the interaction between the interest marker and the body weight group, and the interaction between age and the body weight group. The effects of the marker on aBMD in each body weight group were estimated and analyzed by adding the overall effect of the markers and the specific interaction of each one with the group (using the "estimate" function in PROC GLM). The results are expressed as beta coefficients (and standard errors of measurement, SEM), which can be interpreted as the increase in aBMD when the markers increase by 1 point.

The links between the duration of the disease, the age at disease onset, and the duration of amenorrhea were specifically evaluated in subjects with anorexia nervosa using multivariable linear regression models adjusted for age.

Statistical analyses were performed at the conventional 2-tailed α level of .05 using SAS version 9.1 (SAS Institute, Cary, NC).

Results

The anthropometric and gynecological characteristics of the subjects are summarized in Table 1. The ages ranged from 16.0 to 27.0 years, with a comparable mean age across groups. As expected, subjects with obesity had higher weight, BMI, whole-body FM (kg and %), and LBM than the other 2 groups (all $P < .001$), whereas subjects with anorexia nervosa presented lower values than the other 2 groups (all $P < .001$). Menarche had occurred significantly earlier in subjects with obesity (11.7 ± 2.0 years) than controls (13.0 ± 1.3 years, $P = .006$) and subjects with anorexia nervosa (12.9 ± 1.3 years, $P = .008$). Subjects with anorexia nervosa presented a longer duration since the last menstruation than subjects with obesity ($P < .001$) and controls ($P < .001$). The mean duration of anorexia nervosa was 3.9 ± 2.9 years and the mean age at disease onset was 17.0 ± 2.1 years (data not shown). It was more difficult to precisely identify the onset of obesity, but overweight was already present for the majority of these subjects in the peripubertal period.

Bone characteristics

Areal bone mineral density. Table 1 and Fig. 1 present the aBMD for the 3 groups at various bone sites. Compared with controls, subjects with obesity presented higher aBMD at the hip and radius, while subjects with anorexia nervosa presented lower values at the hip and lumbar spine. The differences between controls and subjects with obesity ranged between +4.3% for the whole body and +11.3% for the hip. The differences between controls and subjects with anorexia nervosa ranged from –2.1% for the whole body and –14.4% for the hip.

When aBMD was modeled for each group from individual values (Fig. 2), we observed that it reached its maximal values starting from 20 to 22 years in subjects with obesity and controls, whereas aBMD in subjects with anorexia nervosa appeared to be lost as the disease progressed. More specifically, aBMD at the hip was significantly higher in subjects with obesity than in the other 2 groups from 19 years, and subjects with anorexia nervosa presented significantly lower values than controls after 20 years. At the lumbar spine, aBMD was higher in subjects with obesity and controls at 20 to 22 years, while in subjects with anorexia nervosa the difference with the other 2 groups increased with age and became significant from 19 years onward. Whole-body aBMD and aBMD at the radius were higher in subjects with obesity than in subjects with anorexia nervosa from 21 years and 18.5 years, respectively.

Bone biochemical markers and periostin

Markers of bone turnover and periostin levels are described in Table 1. Markers of bone formation (OC and PINP) were significantly or tended (CON vs AN for PINP; $P = .07$) to be lower in both groups of patients, whereas the marker of bone resorption (CTX) was only higher in subjects with anorexia nervosa than in controls. When the 2 groups of patients were compared, only CTX was higher in subjects with anorexia nervosa than in subjects with obesity. Periostin levels were significantly lower in subjects with obesity than in the other 2 groups. Moreover, periostin levels were correlated positively with markers of bone formation (OC and PINP) in the entire population and in subjects with obesity and anorexia nervosa. In the entire population

Table 1. Clinical profiles of the subjects.

Variables	Controls	Patients with anorexia nervosa	Patients with obesity	CON vs AN	CON vs OB	AN vs OB
Number	38	38	38			
Age, years	21.0 ± 3.2	21.0 ± 3.2	21.3 ± 2.9	ns	ns	ns
Weight, kg	59.4 ± 9.5	41.7 ± 6.2	112.6 ± 12.1	<.001	<.001	<.001
Height, cm	165.6 ± 6.4	165.3 ± 6.4	163.6 ± 5.3	ns	ns	ns
BMI, kg/m^2	21.6 ± 2.7	15.2 ± 1.5	42.2 ± 5.0	<.001	<.001	<.001
Body composition						
Fat mass, kg	16.8 ± 5.8	6.8 ± 5.0	53.8 ± 9.2	<.001	<.001	<.001
Fat mass, %	27.6 ± 6.4	14.2 ± 4.5	46.9 ± 4.0	<.001	<.001	<.001
Lean body mass, kg	40.6 ± 4.9	34.5 ± 4.7	58.2 ± 5.0	<.001	<.001	<.001
Areal bone mineral density						
Whole body (g/cm^2)	1.069 ± 0.097	1.047 ± 0.077	1.117 ± 0.087	ns	ns	<.001
Z-score (SD)	0.05 ± 1.32	–0.14 ± 1.01	0.24 ± 1.11	ns	ns	ns
Hip (g/cm^2)	0.934 ± 0.111	0.800 ± 0.161	1.052 ± 0.144	<.001	<.001	<.001
Z-score (SD)	–0.02 ± 0.88	–1.14 ± 1.15	0.81 ± 1.12	<.001	.003	<.001
Lumbar spine (g/cm^2)	0.993 ± 0.128	0.877 ± 0.138	1.056 ± 0.107	<.001	.006	<.001
Z-score (SD)	-0.29 ± 1.15	-1.22 ± 1.29	0.47 ± 0.97	<.001	.002	<.001
Radius (g/cm^2)	0.549 ± 0.047	0.525 ± 0.046	0.588 ± 0.046	.003	<.001	<.001
Z-score (SD)[a]	0.26 ± 1.15	-0.61 ± 0.91	1.76 ± 1.20	<.001	<.001	<.001
Bone markers						
Osteocalcin, ng/mL	35.7 ± 20.9	25.1 ± 10.8	23.1 ± 4.9	.003	<.001	ns
PINP, ng/mL	87.4 ± 56.1	64.2 ± 36.8	74.7 ± 25.2	**.07**	.817	**.088**
CTX, ng/mL	0.603 ± 0.252	1.065 ± 0.507	0.464 ± 0.134	<.001	.007	<.001
Periostin, pmol/L	894.8 ± 220.4	862.8 ± 180.8	752.2 ± 203.1	ns	.008	.009
Gynecological profile						
Age of menarche, years	13.0 ± 1.3	12.9 ± 1.3	11.7 ± 2.0	ns	.006	.008
Amenorrhea, number (%)	0 (%)	35 (92.1%)	2 (5.2%)	**<.001**	**ns**	**<.001**
Duration since last menstruation, months	0.6 ± 0.6	24.6 ± 31.4	2.5 ± 6.0	<.001	ns	<.001

Data are presented by the mean ± standard deviation.

Abbreviations: BMI, body mass index; PINP, procollagen type I N-terminal propeptide; CTX, serum type I-C telopeptide breakdown products; ns, nonsignificant. Two by two comparisons were made using the Student t-test or the Mann–Whitney U test. *P* values in bold were adjusted for multiple comparisons using the Hommel's method.

[a]Z-score for the radius was only available in subjects >18 years.

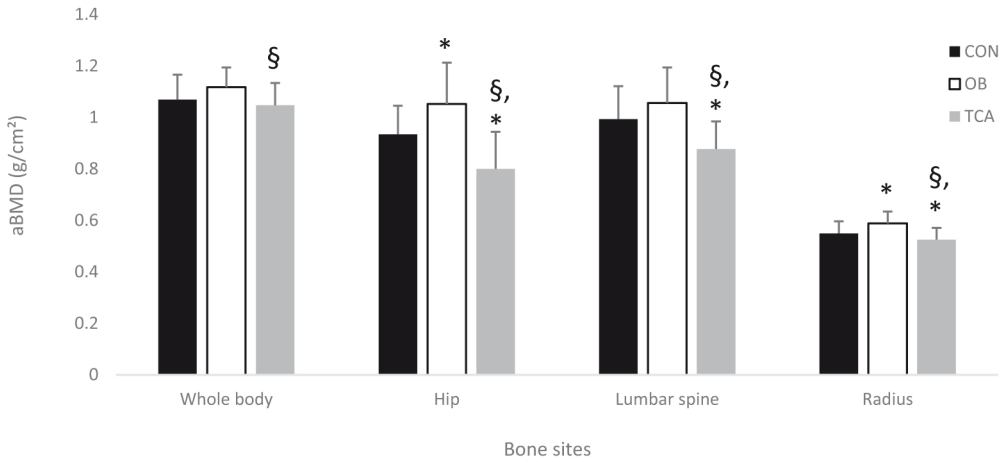

Figure 1. Areal bone mineral density is expressed by mean and SD. Abbreviations: AN, subjects with anorexia nervosa; CON, control group; OB, subjects with obesity. * indicates a significant difference with the control group ($P < .001$). § indicates a significant difference with patients with obesity ($P < .001$).

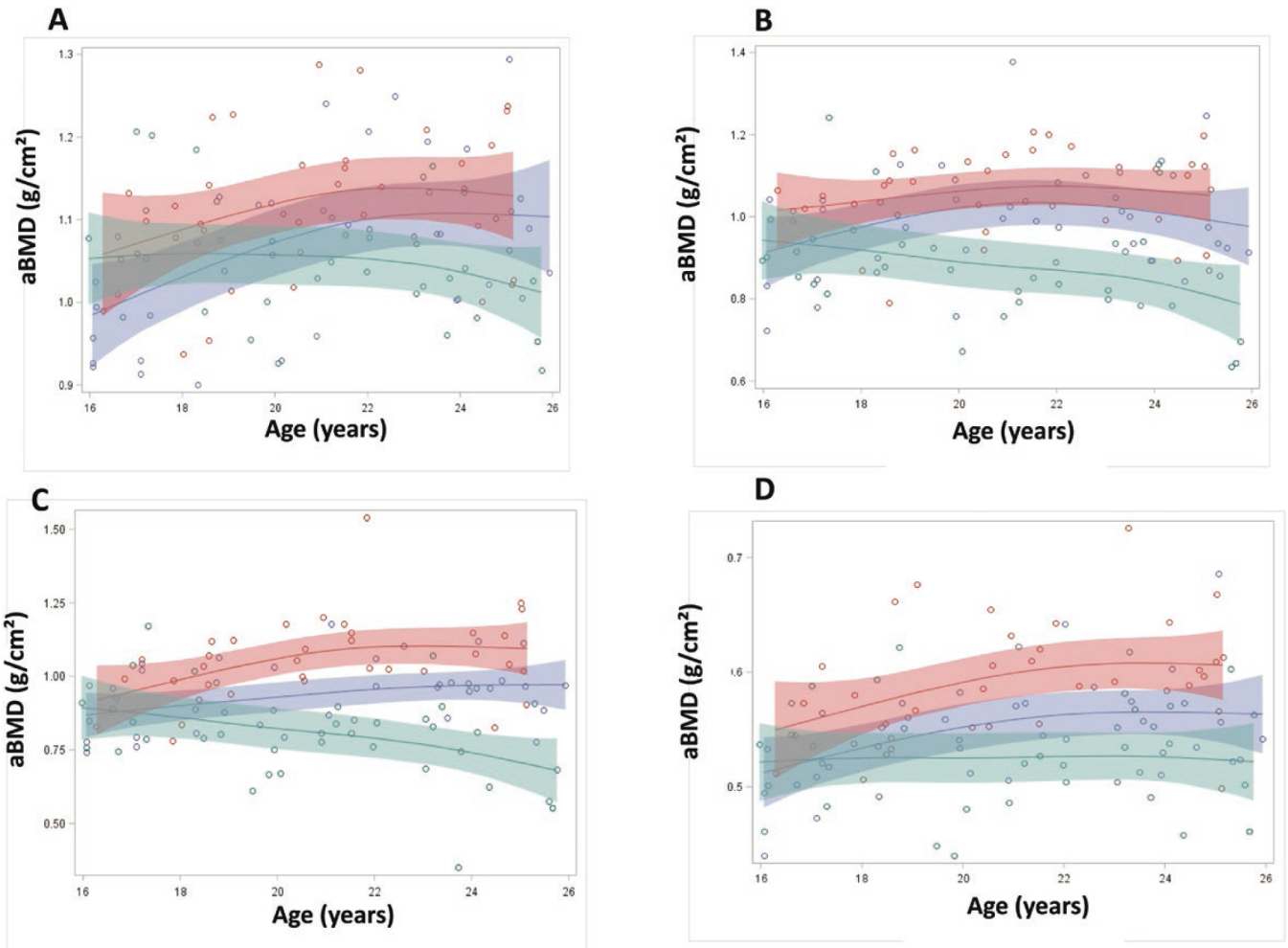

Figure 2. Modeling of areal bone mineral density (aBMD) at various bone sites (A: whole body; B: lumbar spine; C: Hip and D: radius) in patients with anorexia nervosa (AN, green), with obesity (OB, red) and in controls (CON, blue). The dashed curves with the same color represent the 95% confidence intervals.

only periostin levels were also negatively correlated with whole-body FM and LBM.

We modeled the bone marker values for each group from individual values (Fig. 3A-C) and found that PINP, OC, and CTX became lower with age in controls. In contrast, the marker values for the 2 patient groups remained relatively constant with age. Compared with control values, the markers of bone formation were

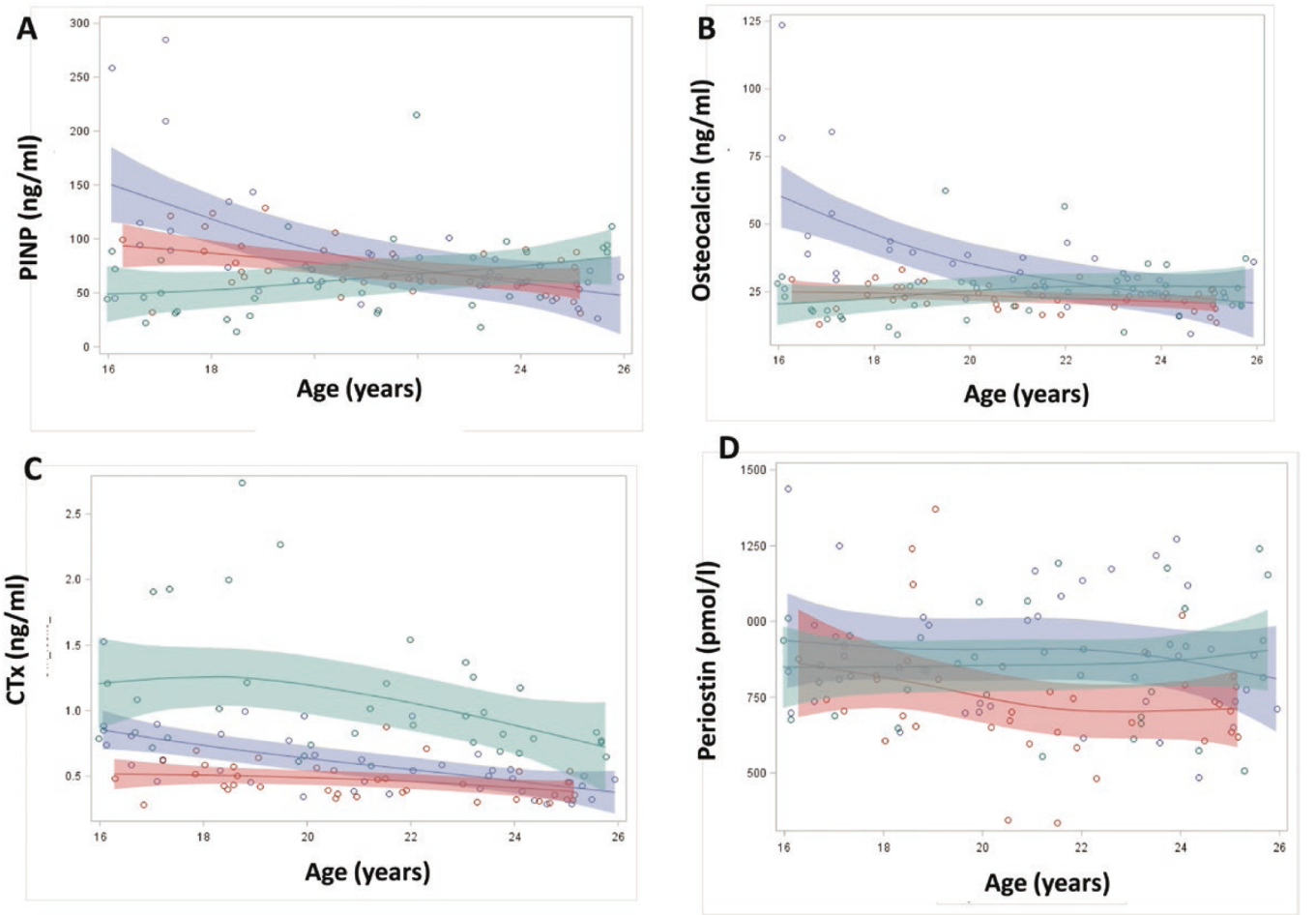

Figure 3. Modeling of bone biochemical markers (A: PINP [procollagen type I N-terminal propeptide], B: osteocalcin, C: CTX [type I-C telopeptide breakdown products] and D: periostin) in patients with anorexia nervosa (AN, green), with obesity (OB, red) and in controls (CON, blue). The dashed curves with the same color represent the 95% confidence intervals.

lower up to 19 years, while CTX was higher in subjects with anorexia nervosa than in the other 2 groups at each age.

Periostin levels were relatively stable at each age and no clearly significant difference emerged between groups (Fig. 3D).

Tables 2 to 4 present the links between the parameters and aBMD measured at the skeletal sites for each group. Briefly, OC and PINP were inversely related to aBMD at the lumbar spine and radius in controls, whereas PINP was inversely related to aBMD at the hip in subjects with anorexia nervosa. Periostin was inversely related to aBMD only at the total hip in subjects with anorexia nervosa. However, the association between aBMD and the bone markers did not differ between groups (no significant interaction). Concerning the anthropometric characteristics, BMI was significantly associated with aBMD at each bone site only in controls, and this association differed between groups only at the lumbar spine. Whole-body FM was related to aBMD at the lumbar spine and radius in controls only, but the link did not differ between groups. LBM was highly correlated with whole-body aBMD in each group, although this association was also noted at the total hip, lumbar spine, and radius for controls and subjects with anorexia nervosa only. The groups showed a tendency toward difference at the lumbar spine (P interaction = .059) and radius (P = .085). Age at menarche was inversely related to aBMD at all skeletal sites only in controls, total hip excepted. The effect of the age at menarche was significantly different between groups for the whole body and lumbar spine and tended to differ at the radius (P = .057).

The links between the duration of anorexia, the age at onset, and the duration of amenorrhea were specifically evaluated in these subjects. The durations of anorexia nervosa and amenorrhea were mostly negatively associated, whereas the age at onset was positively associated, with whole-body and site-specific aBMD.

Discussion

In this study, we investigated the effects of both anorexia nervosa and obesity on bone metabolism during

Table 2. Association between bone markers and aBMD according to groups.

		Effect of osteocalcin[a]			Effect of PINP[a]			Effect of CT [a]			Effect of periostin [a]		
Effect on aBMD	**Groups**	**Beta (SEM)[b]**	***P* values for beta = 0**	***P* values for comparison between groups**	**Beta (SEM)[b]**	***P* values for beta = 0**	***P* values for comparison between groups**	**Beta (SEM)[b]**	***P* values for beta = 0**	***P* values for comparison between groups**	**Beta (SEM)[b]**	***P* values for beta = 0**	***P* values for comparison between groups**
Whole body													
	CON	–0.0012 ± 0.0008	.131	.580	–0.0004 ± 0.0002	.1459	0.585	–0.0172 ± 0.0693	.804	.881	0.0239 ± 0.0633	.706	.376
	OB	–0.0045 ± 0.0030	.135		–0.0010 ± 0.0005	.0568		–0.0409 ± 0.1112	.713		–0.0874 ± 0.0700	.214	
	AN	–0.0015 ± 0.0013	.249		–0.0005 ± 0.0003	.1875		0.0070 ± 0.0294	.812		–0.0948 ± 0.0767	.219	
Total hip													
	CON	–0.0020 ± 0.0013	.118	.820	–0.0005 ± 0.0004	.2720	0.546	0.0177 ± 0.1087	.871	.963	–0.009 ± 0.0981	.925	.176
	OB	–0.0047 ± 0.0048	.334		–0.0012 ± 0.0009	.1841		–0.0237 ± 0.1771	.894		–0.0421 ± 0.1100	.702	
	AN	–0.0030 ± 0.0020	.143		–0.0012 ± 0.0006	.0354		0.0258 ± 0.0461	.577		**–0.2845 ± 0.1189**	**.019**	
Lumbar spine													
	CON	**–0.0032 ± 0.0012**	**.008**	.173	–0.0008 ± 0.0004	.0519	0.792	–0.0273 ± 0.0989	.783	.630	–0.0841 ± 0.0912	.359	.686
	OB	–0.0023 ± 0.0043	.595		–0.0002 ± 0.0008	.7385		0.1041 ± 0.1586	.513		–0.0794 ± 0.1008	.432	
	AN	0.0010 ± 0.0018	.599		–0.0005 ± 0.0005	.3531		0.0714 ± 0.0419	.092		–0.1946 ± 0.1105	.081	
Radius													
	CON	**–0.0009 ± 0.0004**	**.055**	.744	–0.0002 ± 0.0001	.2157	0.649	0.0229 ± 0.0380	.548	.739	–0.0326 ± 0.0349	.353	.916
	OB	–0.0021 ± 0.0017	.209		–0.0000 ± 0.0003	.9278		–0.0330 ± 0.0611	.591		–0.0287 ± 0.0389	.463	
	AN	–0.0007 ± 0.0007	.313		–0.0003 ± 0.0002	.0836		0.0098 ± 0.0161	.543		–0.0513 ± 0.0389	.228	

Data are presented by the beta ± SEM. Bold values represent statistically significant results.

Abbreviations: aBMD, areal bone mineral density; PINP, procollagen type I N-terminal propeptide; CTX, serum type I-C telopeptide breakdown products; CON, control subjects; OB, patients with obesity; AN, patients with anorexia nervosa; SEM, standard error of the mean.

[a]Effects of each marker and each aBMD site were analyzed separately using multivariable linear regression models adjusted for age and interaction between age and body weight groups.

[b]The beta coefficient is interpreted as the increase in aBMD when the bone markers increase by 1 point. "*P*-values for beta = 0" indicates whether this increase is significantly different from 0 in each group; "*P*-values for comparison between groups" indicates whether this increase is significantly different between the OB, CON, and AN groups.

Table 3. Association between anthropometric or gynecological parameters and aBMD according to groups.

		Effect of BMI [a]			Effect of WB FM[a]			Effect of WB LBM[a]			Effect of age at menarche[a]		
Effect on aBMD	**Groups**	**Beta (SEM)[b]**	***P* values for beta = 0**	***P* values for comparison between groups**	**Beta (SEM)[b]**	***P* values for beta = 0**	***P* values for comparison between groups**	**Beta (SEM) [b]**	***P* values for beta = 0**	***P* values for comparison between groups**	**Beta (SEM)[b]**	***P* values for beta = 0**	***P* values for comparison between groups**
Whole body													
	CON	0.0126 ± 0.0049	**.0126**	.2911	0.0044 ± 0.0024	.0679	.5034	**0.0116 ± 0.0025**	**<.0001**	.2241	**–0.0311 ± 0.0102**	**.0029**	**.0136**
	OB	0.0050 ± 0.0027	.0680		0.0012 ± 0.0015	.4493		**0.0055 ± 0.0024**	**.0245**		0.0059 ± 0.0071	.4108	
	AN	0.1447 ± 0.0090	.111		0.0012 ± 0.0028	.6572		**0.0091 ± 0.0026**	**.0006**		–0.0018 ± 0.0108	.8711	
Total hip													
	CON	0.1778 ± 0.0079	**.0261**	.1884	0.0060 ± 0.0037	.1123	.7646	0.0148 ± 0.0040	**.0004**	.3215	–0.0259 ± 0.017	.1264	.3266
	OB	0.0057 ± 0.0044	.1898		0.0028 ± 0.0024	.2461		0.0079 ± 0.0045	.1058		0.0001 ± 0.013	.9814	
	AN	0.0274 ± 0.0143	.0587		0.0046 ± 0.0043	.2962		0.0158 ± 0.0041	**.0002**		0.0081 ± 0.018	.6493	
Lumbar spine													
	CON	0.0208 ± 0.0072	**.0048**	**.0362**	**0.0071 ± 0.0034**	**.0405**	.3167	**0.0172 ± 0.0037**	**<.0001**	.0592	–0.0399 ± 0.0150	**.0091**	**.0408**
	OB	0.0019 ± 0.0039	.6372		0.0014 ± 0.0022	.5262		0.0048 ± 0.0036	.1879		0.0022 ± 0.0105	.8309	
	AN	0.0230 ± 0.0130	.0818		0.0057 ± 0.0040	.1534		0.0113 ± 0.0038	**.0038**		0.0091 ± 0.0159	.5702	
Radius													
	CON	0.0080 ± 0.0027	**.0032**	.2903	**0.0028 ± 0.0013**	**.0298**	.6617	**0.0063 ± 0.0015**	**<.0001**	.0851	–0.0162 ± 0.0056	**.0053**	.0576
	OB	0.0039 ± 0.0015	**.0131**		0.0015 ± 0.0009	.0838		0.0018 ± 0.0015	.2270		0.0006 ± 0.0040	.8826	
	AN	0.0090 ± 0.0048	.0638		0.0014 ± 0.0015	.3416		**0.0029 ± 0.0015**	**.0563**		–0.0072 ± 0.0060	.2358	

Data are presented by the beta ± SEM. Bold values represent statistically significant results.

Abbreviations: aBMD, areal bone mineral density; BMI, body mass index; WB FM, whole-body fat mass; WB LBM, Whole-body lean body mass; CON, CON, control subjects; OB, patients with obesity; AN, patients with anorexia nervosa; SEM, standard error of the mean.

[a]Effect of each anthropometrics or gynecological parameters on each aBMD site were analyzed separately using multivariable linear regression models adjusted for age and interaction between age and body weight groups.

[b]The beta coefficient is interpreted as the increase in aBMD when the anthropometric or gynecological parameters increase by 1 point. "*P*-values for beta = 0" indicates whether this increase is significantly different from 0 in each group; "*P*-values for comparison between groups" indicates whether this increase is significantly different between the OB, CON and AN groups.

Table 4. aBMD and disease-related parameters in patients with anorexia nervosa.

Effect on aBMD	Effect of duration of AN[a]		Effect of age of AN onset[a]		Effect of duration since last menstruation[a]	
	Beta (SEM) [b]	*P*-values for beta = 0	Beta (SEM)[b]	*P*-values for beta = 0	Beta (SEM) [b]	*P*-values for beta = 0
Whole body	–0.0166 ± 0.0064	**0.0140**	0.0166 ± 0.0064	**0.0140**	–0.0008 ± 0.0005	0.1266
Total hip	–0.0271 ± 0.0127	**0.0403**	0.0271 ± 0.0127	**0.0403**	–0.0017 ± 0.0008	**0.0284**
Lumbar spine	–0.0318 ± 0.0107	**0.0053**	0.0318 ± 0.0107	**0.0053**	–0.0016 ± 0.0006	**0.0118**
Radius	–0.0114 ± 0.0037	**0.0044**	0.0114 ± 0.0037	**0.0044**	–0.0008 ± 0.0003	**0.0044**

Results are presented as beta ± SEM. Bold values represent statistically significant results.
Abbreviations: aBMD, areal bone mineral density; AN, anorexia nervosa; SEM, standard error of the mean.
[a]Effect of each parameters related to the disease on each aBMD site were analyzed separately using multivariable linear regression models adjusted for age.
[b]The beta coefficient is interpreted as the increase in aBMD when the anthropometric or gynecological parameters increase by 1 point. "*P*-values for beta = 0" indicates whether this increase is significantly different from 0.

early adulthood in women. The main results were the specific profiles of aBMD, bone turnover and periostin levels in the subjects with these diseases compared with normal-weight subjects. Moreover, we identified several factors related to the gynecological profile, disease characteristics, and anthropometric parameters that influenced aBMD in each group.

To our knowledge, only 1 very recent study compared the potential effects of these 2 common diseases, anorexia nervosa and obesity, on aBMD in adolescents and young adults (10). These diseases are respectively characterized by a deficit and an excess of body weight, each generating specific mechanical strains and endocrinological alterations that may have consequences on bone health.

This cross-sectional study confirmed that subjects with anorexia nervosa present lower aBMD values and an alteration of bone remodeling than normal-weight young women (5,10,11,24–26). The alteration of these bone characteristics may explain the increased fracture risk observed in this population (27). Conversely, adolescents with obesity generally present higher aBMD, particularly at weight-bearing bone sites such as the hip (9,10). The increase in body mass is considered to be the major factor in the modification of bone characteristics to support localized mechanical loading applied to the skeleton (28). However, we also observed higher aBMD values at the radius, which undergoes less mechanical loading, and this cannot be explained only by the gravitational forces associated with increased body weight. Other studies have also reported aBMD (29–31) and microarchitecture adaptations at the radius in subjects with obesity (32,33), with no clear explanation given. The results suggest that systemic, biologically active molecules linked to obesity may interact with bone metabolism. In addition, increased leptin levels (34,35) and estrogen secretion (36,37) are known to have positive actions on bone mass and thus limit later fracture risk (38). The reduced bone remodeling observed in our subjects with obesity points to the role of estrogens.

Although our findings provide deeper insight into how 2 opposite disease situations influence aBMD, the originality of this study is the innovative modeling of aBMD and bone markers based on a wide age range (16–27 years), stringent age matching (±6 months) between groups, and the homogeneous clinical characteristics within each group. Our results in the control group showed an increase in "estimated" aBMD from 16 to 20–22 years, with some differences according to the skeletal site, and then relative stability. Prospective studies have reported optimal bone mass gain in the earlier adolescent period, while PBM is usually considered to be reached by the end of the second decade of life (39–43). Moreover, our results are in accordance with a recent longitudinal study that followed the same individuals over a period of more than 25 years and found that the peak attainment of whole-body aBMD occurred at 22.31 years (44). The comparability of our data and these previous findings support the validity of this methodological approach, which can be used to model aBMD in subjects with both anorexia nervosa and obesity. Our results clearly show that these 2 groups of patients presented distinct models of aBMD. The subjects with obesity were characterized by systematically higher values of aBMD at each skeletal site and with increasing age, although the difference with the other 2 groups became more marked at the hip and radius from about 18 years. For the subjects with anorexia nervosa, it was interesting to observe that, conversely to what is usually observed during the growth period, aBMD appeared to be lost as age and disease duration progressed. This resulted in an accentuated aBMD difference over time compared with controls.

This study was designed to gain a deeper understanding of the biological modifications that act on aBMD, and especially sought to determine whether the differences in mechanical loading on the skeleton induced by extremes in body weight influence periostin secretion. Our results showed that subjects with anorexia nervosa had periostin values comparable to those of controls, while subjects with obesity presented lower values. These results may be somewhat surprising because the increase in mechanical loading on the skeleton, as observed in subjects with obesity with excess body weight, was associated with increased periostin levels (15). Interestingly, lower periostin levels were similarly reported in subjects with higher BMIs (45). It is likely that the increase in aBMD in subjects with obesity is a skeletal adaptation that reduces the perception of external mechanical strain. Moreover, obesity in adolescents is known to be associated with systemic inflammation (46), and increased proinflammatory molecules during the early phase of bone healing following fracture may be responsible for the initial fall in serum periostin levels (47). Conversely, the normal periostin levels in subjects with anorexia nervosa may be an accentuated response to increased strain on weaker bone. Kim et al. (17) reported higher periostin levels in postmenopausal women with lower aBMD and osteoporotic fracture and suggested that this might reflect a compensatory mechanism in which periostin expression is increased to overcome poor bone health. Rousseau et al. (16) also observed that high periostin levels are independently associated with increased fracture risk in postmenopausal women and suggested that women with lower bone mass and strength have higher mechanical strain on the remaining bone, which increases the periostin expression. Whatever the group, the levels of periostin did not seem to significantly vary across the adolescent and young adult periods. Caswell-Smith et al. also reported no differences in periostin levels in subjects between 18 and 75 years (45), and Fujimati et al. showed that children reached the cut-off value for adults by age 15 (48). Only Walsh et al. (49) reported higher values in 16- to 18-year-olds than in 30- to 32-year-olds.

A reduction in bone modeling/remodeling with age until a new steady state at about 20 years was observed in controls, coinciding with the stabilization of aBMD and confirming previous results (40). Conversely, in the 2 patient groups, the markers of bone formation were relatively stable over time and the difference with controls appeared to be clearly due to suppressed formation at an early age corresponding to the onset of disease. Concerning bone resorption, the CTX values were higher in subjects with anorexia nervosa, whatever the age, while these values tended to be lower in subjects with obesity than in controls.

The concomitant evaluation of 2 groups of patients with a wide range of BMIs helped us to better identify the factors that influence aBMD and to grade their effects according to the degree of deficient or excessive body weight. Interestingly, we confirmed in the control group that the later the age of menarche was, the lower the aBMD was in early adulthood. These data confirm that the onset and length of puberty have strong effects on bone mass acquisition (50–52). However, in subjects with obesity, the expected favorable effect of an early age of menarche on aBMD was not observed, probably because other factors related to obesity modulate this relationship. Among them, LBM seemed to have the strongest positive effect on aBMD and this observation was similar in the 3 groups for the whole body (no group interaction). In subjects with anorexia nervosa, it was previously reported, for example, that a decrease in LBM is a more important predictor of bone loss than a decrease in BMI or FM (53), while in adult subjects with obesity, LBM, but not FM, was independently associated with aBMD. More specifically, we found that the durations of both the disease and amenorrhea negatively affected aBMD in subjects with anorexia nervosa, although the later disease onset occurred, the lower the negative impact on aBMD was, confirming previous results (5). None of the bone remodeling markers or periostin seemed to be strongly associated with aBMD, whatever the group.

This study had limitations, particularly its cross-sectional design and the single measurements of aBMD and the biological parameters. However, these limitations are mitigated by the wide age range for the 3 groups around the time of peak bone mass, the high degree of age-matching, and the similar clinical profiles within groups. Moreover, the raw data associated with the data derived from modeling provide clear bone profiles for the 3 groups during the bone mass acquisition period. Longitudinal studies during weight recovery in subjects with anorexia nervosa or weight loss in subjects with obesity may help to further clarify the concomitant effects of weight on aBMD and periostin.

In conclusion, our study demonstrated that weight conditions influence aBMD, the profile of bone remodeling, and the periostin levels. Moreover, the factors related to aBMD appear to be specific for each condition, but lean body mass was the parameter most consistently associated with aBMD.

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