Bone and vitamin D status in patients with anorexia nervosa

Stine Aistrup Eriksen[1], Hanne Prietzel[5], Jenna Rosenqvist Ibsen[3], Marlene Briciet Lauritsen[4, 5], Peter Vestergaard[1, 3] & Gry Kjaersdam Telléus[1, 2, 6]

ABSTRACT

INTRODUCTION: The aim of the present study was to investigate bone status and biological mechanisms involved in the negative impact of anorexia nervosa (AN) on osteogenesis.

MATERIAL AND METHODS: A total of 30 AN patients from Aalborg University Hospital who underwent bone scans were included in a cross sectional study. Biochemical data, bone scans (dual-energy X-ray absorptiometry (DXA)) as well as general health and medical information had been collected during the 2009-2011 period and stored via local and national clinical databases in Denmark, and from these databases we identified all patients with an AN diagnosis who underwent bone scans.

RESULTS: AN patients had a mean Z-score of –1.5 to –1.6 in lumbar spine and total hip, respectively. The hip Z-score decreased with duration of disease, and a positive correlation was seen between serum 25-hydroxy-vitamin D level and spine Z-score but not hip Z-score. Bone mineral density did not seem to change with time since diagnosis. Additionally, a negative correlation between serum 25-hydroxy-vitamin D levels and serum total alkaline phosphatase levels was found. A serum 25-hydroxy-vitamin D level below 50 nmol/l was associated with increased alkaline phosphatase levels.

CONCLUSION: In conclusion, rather than clinical measures including BMI and biochemical measures disease duration was the main predictor of bone status. This implies that long-term disease should be a main factor in selecting patients for referral to DXA. Moreover, results from this study indicate normal osteoblastic response to malnutrition.

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TRIAL REGISTRATION: The present study was not registered due to its register-based design. However, the study was approved by the Danish Data Protection Agency.

Anorexia nervosa (AN) is an eating disorder characterised by low body weight (a body mass index (BMI) ≤ 17.5 kg/m^2). Bone loss associated with AN may be of a more serious nature than postmenopausally induced bone loss. Already within the first year of disease, a decrease in the bone density, measured through bone scans typically of bone mineral density (BMD), has been observed in patients with AN, and this condition may persist throughout life [1]. Bone turnover seems affected in AN in a way that is not fully understood. The formation of new bone seems reduced in both teenagers and adults with AN, whereas the degradation (resorption) of bone seems decreased in teenagers, but increased in adults [2]. This pattern of decreased bone formation could possibly explain why BMD may not respond adequately to treatment with bone active drugs because no osteoblastic potential may be present. The low resorption in teenagers may mimic adynamic bone disease, which is especially critical at a point in life when bone needs to be accreted. In adults, the increased bone resorption but decreased formation may signal an uncoupling of bone turnover with a low osteoblastic potential but a pool of osteoclasts, which are not properly inhibited.

Previous studies have investigated various associations between BMD and different clinical and paraclinical measures [3-6]; however, no clear consensus has so far been reached regarding the specific mechanisms involved in the negative impact of AN on bone. Based on data from a Danish clinical database containing these above-mentioned factors, the aims of the present study were to investigate: i) BMD among AN patients in the database, and to ii) elucidate which factors from the physical examination and the biochemical measures influence BMD in this group of patients.

MATERIAL AND METHODS

Subjects

The study included all patients seen at the Section of Eating Disorders, Department of Psychiatry, Aalborg University Hospital, Denmark, between 1 January 2009 and 31 December 2011. A total of 327 patients were screened, and 138 met the Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV) criteria for AN. Among these 138 patients, 30 underwent dual-energy X-ray absorptiometry (DXA) scans based on the recommendations from the National Board of Health. This paper is a cross-sectional study presenting the results for the 30 patients of i) the psychiatric status by interview, ii) the bone status by DXA and iii) the biochemical status.

Psychiatric status

On January 2009, a database was established at the Unit

ORIGINAL ARTICLE

1) Department of Clinical Medicine, Aalborg University
2) Section of Eating Disorders, Department of Psychiatry, Aalborg University Hospital
3) Department of Endocrinology, Aalborg University Hospital
4) Research Unit for Child and Adolescent Psychiatry, Aalborg University Hospital
5) Clinic for Child and Adolescent Psychiatry, Aalborg University Hospital
6) Unit for Psychiatric Research, Aalborg University Hospital

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TABLE 1

Comparison of anorexia nervosa patients who underwent dual-energy X-ray absorptiometry and those who did not.

	DXA (N = 30)				No DXA (N = 108)				p-value
	n	%	mean	SD	n	%	mean	SD	
Sex									
Females	27	90.0	–	–	103	95.4	–	–	–
Males	3	10.0	–	–	5	4.6	–	–	0.371
Age at BAB, yrs	–	–	20.2	6.1	–	–	16.6	3.0	0.001
Height, cm	–	–	169.0	7.3	–	–	166.4	7.6	0.098
Weight, kg	–	–	45.8	8.6	–	–	44.0	5.8	0.286
BMI, kg/m^2	–	–	16.0	2.3	–	–	15.8	1.3	0.758

BAB = evaluation of anorexia and bulimia; BMI = body mass index; DXA = dual-energy X-ray absorptiometry; SD = standard deviation.

TABLE 2

Baseline characteristics of the 30 anorexia nervosa patients who underwent dual-energy X-ray absorptiometry. Records were incomplete for some patients and the numbers may thus not sum up to 30.

Age at DXA, mean ± SD, yrs	20.9 ± 5.8
BMI at DXA, mean ± SD, kg/m^2	17.4 ± 2.4
Weight at DXA, mean ± SD, kg	50.1 ± 9.4
Height at DXA, mean ± SD, cm	169.0 ± 7.3
Z-score in lumbar spine L1-L4, mean ± SD	–1.5 ± 1.1
Total bone mineral density in lumbar spine L1-L4, mean ± SD, g/cm^2	0.86 ± 0.11
Total bone mineral content in lumbar spine L1-L4, mean ± SD, g	50.6 ± 9.7
Total area in lumbar spine L1-L4, mean ± SD, cm^2	59.2 ± 7.9
Z-score in hip mean ± SD	–1.6 ± 1.3
Total bone mineral density in hip, mean ± SD, g/cm^2	0.83 ± 0.14
Total bone mineral content in hip, mean ± SD, g	28.4 ± 5.8
Total area in hip, mean ± SD, cm^2	34.4 ± 4.0
Duration from 1. symptom to baseline, mean ± SD, yrs	3.2 ± 3.7
Presence of menstruations at baseline, n/N (%)	25/27 (93)
Current use of oral contraceptives at baseline, n/N (%)	5/27 (19)
Prior use of oral contraceptives at baseline, n/N (%)	11/27 (41)
Self-perceived reduction in muscle strength at baseline, n/N (%)	15/29 (50)
Objective presence of muscle atrophy at baseline, n/N (%)	16/29 (53)
Presence of lanugo hairs at baseline, n/N (%)	13/29 (43)
Peripheral cyanosis at baseline, n/N (%)	10/29 (33)
Poor status of gingivae, n/N (%)	1/29 (3)
Serum albumin concentration, mean ± SD (normal range), g/l	45 ± 4 (36-48)
Serum cobalamin concentration, mean ± SD (normal range), pmol/l	500 ± 245 (200-600)
Serum total alkaline phosphatase concentration, mean ± SD (normal range), IU/l	73 ± 37 (35-105)
Plasma ionised calcium concentration, mean ± SD (normal range), mmol/l	1.22 ± 0.03 (1.18-1.32)
Serum creatinine concentration, mean ± SD (normal range), µmol/l	70 ± 16 (45-90)
Serum 25-hydroxy-vitamin D concentration, mean ± SD (normal range), nmol/l	75 ± 32 (50-150)
Serum thyroid-stimulating hormone concentration, mean ± SD (normal range), IU/l	1.84 ± 1.22 (0.1-4.0)

DXA = dual-energy X-ray absorptiometry; SD = standard deviation.

for Psychiatric Research at the Section of Eating Disorders, Department of Psychiatry, Aalborg University Hospital, Denmark. The database contains information on all individuals in the Region of Northern Denmark referred to and assessed for an Eating Disorder. All referred patients were assessed for eating disorder according to a standardised diagnostic assessment battery, consisting of the following elements: i) assessment of the AN symptomatology (Eating Disorder Examination (EDE), Version 16 [7], ii) interview with patients to obtain background information, iii) interview with parents (for patients under the age of 18 or living at home) regarding onset and development, iv) assessment of somatic condition, v) electrocardiogram, and vi) physical examination and blood tests. Included in the physical examination were a clinical evaluation of the oral cavity and dental status and the presence of lanugo hairs, among other measures. In addition to this, the patients were screened for additional psychopathies and were examined for neurological conditions. The diagnosis was based on EDE, Version 16, which holds a good internal consistency, discriminant and concurrent validity, and inter-rater reliability for assessment of eating disorders [7]. All assessments were carried out during the first hospital contact.

Biochemical measures

At the first visit, routine biochemistry including a full haematological screen, electrolytes in serum, vitamin D status (total 25-hydroxy-vitamin D in serum), and tests of liver functioning were performed by an ISO 9000-certified laboratory.

Bone mineral density assessment

Bone mineral density, (BMD, g/cm^2), bone mineral content (BMC, g) and total area (cm^2) in lumbar spine (L2-L4) and total hip were measured for 30 of the 138 included subjects, and were measured by the same Hologic DXA scanner, Discovery-A (Hologic, Bedford, MA, USA). Age, weight, height, sex and ethnicity were registered when the DXA scan was performed. Z-score

and T-score for each subject were calculated by the Hologic machine's programme using Danish reference standards [8]. Based on the age of the included AN patient group (all below 50 years), only Z-scores were applied in the following according to the 2005 ISCD Official Positions. A Z-score of –2.0 or lower was defined as below the expected range for the age group, and a Z-score above –2.0 is within the expected range for the age group [9].

Statistics

Mean and standard deviation were used as descriptive statistics. Continuous variables such as age, height, BMI, etc. were compared using Student's t-test for two samples. Levene's test for equality of variances was performed. Bivariate correlations were explored using Pearson's correlation coefficient, and multivariate correlations were explored using multiple linear regression. Based on all available measures among the 30 AN patients, a locally weighted scatterplot smoothing (LOESS) plot was used to assess the association between BMD and vitamin D levels. Analyses were performed using IBM SPSS 20.0.

Trial registration: The present study was not registered owing to its register-based design; however, the study was approved by the Danish Data Protection Agency.

RESULTS

A total of n = 327 patients diagnosed with an eating disorder were registered in the local database at the Unit for Psychiatric Research, Aalborg University Hospital, Denmark, between 2009 and 2011. These patients were screened in the cross-sectional study and n = 138 met the DSM-IV criteria for AN, and a subgroup (n = 30) of these patients underwent DXA scans. Baseline characteristics of the AN patients who underwent DXA scans and those who did not are provided in **Table 1**. Among those who were DXA scanned, the age was higher (20.2 versus 16.6 years, respectively), and the patients tended to be taller (probably due to older age), while body weight and body mass index were similar.

Table 2 shows the characteristics at the time of DXA scanning and selected baseline characteristics and biochemical characteristics. The age at the time of scan was slightly higher than at baseline (20.9 versus 20.2 years, i.e. the mean time from diagnosis to DXA scanning was around eight months). The BMI was considerably higher at the time of the scan (17.4 versus 16.0 kg/m^2) owing to an increase in mean body weight from 45.8 kg at baseline to 50.1 kg at the scan (around 10% increase in absolute terms), while the height was unchanged. Numerous patients had signs and symptoms of muscle wasting (Table 2). The biochemical parameters were mostly within the normal range. A longer duration of symptoms before baseline was associated with a lower spine and hip Z-score (**Table 3**). Four years from onset of symptoms until first interview was associated with a much higher prevalence of a low Z-score (50-60% had Z-scores < –2) than in patients who had presented with symptoms for less than one year before their first interview (12.5% had a low Z-score). Moreover, the table shows a steep decline in serum vitamin D (25-hydroxy-vitamin D) levels with time from onset of symptoms.

A higher serum 25-hydroxy-vitamin D level was associated with a higher spine Z-score, but not total hip Z-score (data not shown but available from the authors upon request). Based on all available measures among the 30 AN patients, low serum 25-hydroxy-vitamin D levels were associated with increasing serum total alkaline phosphatase levels, especially below 50 nmol/l (**Figure 1**). In a stepwise linear regression analysis, only duration of disease prior to baseline correlated with spine and hip Z-score, whereas serum vitamin D, serum alkaline phosphatase, serum creatinine, serum calcium, BMI, oral contraceptive use, muscle weakness, muscle atrophy, peripheral cyanosis, and poor gingival status did not. In the stepwise multiple linear regression analysis, the regression coefficient was –0.17 ± 0.05 per year with a squared correlation coefficient (r^2) of 0.42 for the spine and –0.17 ± 0.05 with a squared correlation

TABLE 3

Correlation between duration of anorexia nervosa and prevalence of Z-score ≤ –2.

Duration of AN at baseline, yrs	n	Serum 25(OH)D, nmol/l	Z-score ≤ –2/> –2 (% ≤ –2 of total)	
			spine	hip
≤ 1	8	101 ± 32	1/7 (12.5)	1/7 (12.5)
1.1-4	9	75 ± 29	2/7 (22.2)	1/8 (11.1)
> 4	8	46 ± 16	5/3 (62.5)	4/4 (50)

AN = anorexia nervosa; 25(OH)D = 25-hydroxy-vitamin D concentration.

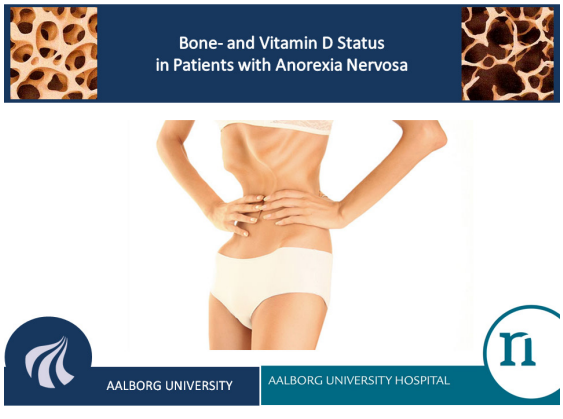

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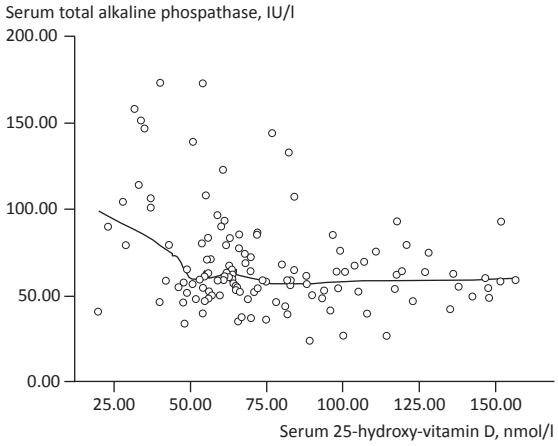
FIGURE 1

Correlation (LOESS plot: a locally weighted scatterplot smoothing) between the concentrations of serum total alkaline phosphatase and serum 25-hydroxy-vitamin D. This plot is based on multiple simultaneous measures of alkaline phosphatase and vitamin D among the 30 anorexia nervosa patients who underwent dual-energy X-ray absorptiometry.



coefficient of 0.46 for the hip. Including the duration from diagnosis to time of scan did not change the results. There was no collinearity between duration from onset of symptoms and BMI.

To adjust results for use of different drugs, all medication ever prescribed for the AN patients was reviewed. The most prevalent potentially bone-active drug was selective serotonin reuptake inhibitors, which were used by eight of 30 patients. Multivitamin supplements were used by 4/30, and levothyroxine, calcium supplements, and neuroleptics by one of 30 for each of these drugs. None of these drugs affected the Z-scores of the AN patients and neither changed the results.

DISCUSSION

Bone mineral density in anorexia nervosa patients

In the present study, we confirmed findings from previous studies demonstrating that a low BMD is highly prevalent in adolescents with AN [10], as a BMD below the expected for the age was observed in approximately one third of the AN patients included.

In this cross-sectional study, we show that the main determinant for bone loss, assessed by BMD, was time from onset of symptoms to time of diagnosis. Moreover, BMD did not seem to change with time from diagnosis. Even with a few years of disease duration, a pronounced bone deficit was seen (50-60% with Z-scores below –2.0). The lack of an increase in BMD with time after diagnosis could indicate an irreversible bone loss. Such irreversible bone loss may occur through e.g. resorption and lack of formation causing breaks in trabeculi. Other studies have confirmed this finding, showing that BMD may not retain normal levels after rehabilitation of AN, and that this could be due to a persistent increase in bone resorption [11].

In concordance with the results of the present study, a negative correlation between disease duration and BMD was found in previous studies of AN patients, together with evidence showing that this negative influence on bone can be initiated after only short disease duration [12]. Some studies of AN patients have shown that BMD at the spine or hip increases after weight normalisation (BMI > 17.5 kg/m2) in the short term (months to few years) [13, 14], whereas others have been unable to show any significant increase in BMD within this time frame [4, 15]. Some of these studies, however, have shown some degree of normalisation of bone turnover markers in relation to nutritional recovery [4, 15], which could indicate an improvement in bone turnover that may only be detectable at the BMD level after several years of weight normalisation. This hypothesis can be supported by longitudinal studies of previous AN patients that have maintained a normal weight for more than 10 years and showed an increase in BMD. The observed increase in BMD was not, however, sufficient for restoration of BMD to a level comparable to that of normal healthy and age-matched individuals [16].

Weight and BMI were similar among DXA scanned patients and non-scanned patients. When accounting for the higher age among the non-scanned patients compared with the age among the scanned patients, these patients are approaching their expected weight for their age compared with those of the scanned patients. This difference may account for the fact that only 30 patients were DXA scanned.

Vitamin D levels in anorexia nervosa patients

The main determinant of Z-score was duration of illness and not BMI, i.e. the duration may be an indicator of a more severe affection of bone not related to BMI. Vitamin D levels also declined with time from onset of the disorder, but as such did not determine BMD. However, despite lack of a direct correlation between vitamin D levels and BMD, the osteoblasts still seemed to be able to respond to low vitamin D levels in the same way as is seen in subjects not suffering from AN. This may indicate an osteoblastic reserve and not adynamic bone disease.

Several studies have observed serum vitamin D levels within the normal range among AN patients or even higher levels compared with controls [6, 17]. The reason for this is not fully known; however, it is believed to be a result of higher supplemental intake among patients with AN and/or changes in metabolic clearance and storage in adipose tissue [18]. This is consistent with our results where the average serum vitamin D levels

were within the normal range, whereas six (20%) AN patients had a serum vitamin D level < 50 nmol/l.

Limitations

In the present study, BMD was used as the major determinant of bone status among AN patients; however, recent studies have shown that bone microarchitecture, as measured through Flat-panel volume computed tomography, may represent a better measure for the negative bone changes associated with AN than DXA scans [19].

Moreover, the register-based design limits the analysis to results included in the routine blood sample. Interesting biochemical measures relevant to the effect of AN on bone, such as cortisol levels [20], could thus not be included in the present study. Serum 25-hydroxy-vitamin D was measured among AN patients at the time of diagnosis, whereas DXA scans were performed an average eight months later. Thus, the association between Z-scores and vitamin D should be interpreted with caution, given that vitamin D levels show seasonal changes and that AN patients were given between 5-25 micrograms of vitamin D supplements as part of the treatment regime.

CONCLUSION

Bone density is decreased in AN, and the main determinant for hip and spine BMD is duration of disease. Long duration could thus be a factor referral for DXA. The lack of change in BMD with time since diagnosis may indicate an irreversible bone loss. Patients with AN display biochemical signs of increased bone turnover, which is a normal response among healthy people, expressed as higher levels of total alkaline phosphatase at serum 25-hydroxy-vitamin D below 50 nmol/l. This indicates normal response of the osteoblasts to malnutrition.

CORRESPONDENCE: *Stine Aistrup Eriksen,* Department of Clinical Medicine, Aalborg University, Room 320, Sdr. Skovvej 15, 9000 Aalborg, Denmark. E-mail: stine.eriksen@rn.dk

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