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Vertebral Fracture Assessment in Adolescents and Young Women with Anorexia Nervosa: A Case Series

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Abstract

Rates of vertebral fracture (VF) for young women with anorexia nervosa (AN) are not well understood. We sought to determine the rates of asymptomatic VF in patients suffering from AN, hypothesizing that VF rates would be higher in subjects with low BMD Z-scores. We recruited young women with AN (n=80) for participation in a longitudinal trial. Dual-energy X-ray absorptiometry images of the lateral thoracic and lumbar spine were obtained for vertebral fracture assessment at 0, 6, 12, and 18 months. Thirteen subjects (16%) had a low spinal BMD at baseline (BMD Z-score ≤ –2 SD). Using the Genant semiquantitative technique, 2/80 subjects at baseline (2.5%) had evidence of a single, Genant grade 1 deformity. One subject had a Genant Grade 2 deformity. Over the 18-month trial, 10 incident vertebral fractures occurred in 9 subjects (12.5%). Using quantitative techniques, only two subjects had a >15% loss in vertebral height. Neither anthropometric data nor markers of disease severity were associated with fracture. In conclusion, ill young women with AN were at low risk for asymptomatic VF in our cohort. Vertebral fractures were not predicted by duration of illness, severity of malnutrition, or traditional measures of aBMD at the lumbar spine.

Keywords

anorexia nervosa; adolescents; vertebral fracture; vertebral fracture assessment

Introduction

In adults, a vertebral fracture (VF) is almost synonymous with osteoporosis(1). Vertebral fractures are the most common type of fragility fracture, and frequently occur with no identifiable trauma. Although most are mild deformities without symptoms(2), VFs may still have clinical consequences, as they are associated with a five-fold increased risk of future

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symptomatic fracture(3, 4) independent of bone mineral density (BMD)(5). Additionally, in adults, there is a much higher rate of morbidity and mortality following VFs(5).

Within the realm of pediatrics, few studies have explored the impact of diseases that affect skeletal health on fracture rates of the spine(6-9). While low BMD in adults is associated with high rates of low-impact fracture, few data exist for younger patients. This deficit of knowledge has, in part, been related to a lack of safe and effective clinical tools to help clinicians detect unrecognized VFs. Traditional spinal x-rays and/or computed tomography (CT) scans are associated with significant radiation exposure. Costs of MRI are high, and availability may be limited. With the advent of technologies such as dual-energy X-ray absorptiometry (DXA), vertebral fracture assessment (VFA) can be performed at the same time as overall skeletal health is assessed, and with far less radiation than standard radiography (3 μSv vs. 600 μSv)(1).

Adolescents and young women with anorexia nervosa (AN) have numerous risk factors for low BMD, including nutritional deficits, alterations in the hormonal milieu, and low body mass. These negative influences on the skeleton lead to higher rates of peripheral fractures(10). However, rates of VF for these patients are not well understood. Thus, we sought to determine the rates of asymptomatic VF in adolescents and young women suffering from AN. We hypothesized that rates of VF would be higher in subjects with low BMD Z-scores.

Materials and Methods

Study design

Between 2003 and 2008, 94 young women were enrolled into a randomized, double-blind clinical trial exploring the effects of adrenal and gonadal hormone replacement . Full details of the trial have been previously published(11). Eligible patients were female, age 13-26 years, skeletally mature, and met criteria for AN as evidenced by amenorrhea, fear of weight gain, and malnutrition. All patients were otherwise healthy and taking no medications known to affect BMD. The study protocol was approved by the local institutional review board. Informed consent was obtained from study participants or their parent/guardian.

The treatment arm received 18 months of oral micronized DHEA (50 mg daily; Belmar Pharmacy, Colorado; IND 52,192). DHEA was initially given with conjugated equine estrogens (0.3mg daily; Premarin®, Wyeth) for the first 3 months to minimize estrogen-associated side effects, followed by 15 months of DHEA+COC (20μg ethinyl estradiol + 0.1mg levonorgestrel; Alesse®, Wyeth Pharmaceuticals). The other group received placebo for the entire study. After randomization, participants returned for assessments at 3, 6, 12, and 18 months. All subjects were advised to consume the recommended daily intake of both calcium and vitamin D(12).

Study Evaluation

Dual-energy X-ray absorptiometry (DXA; QDR 4500, Hologic, Inc., Bedford, MA) images of the lateral thoracic and lumbar spine were obtained for vertebral fracture assessment at 0, 6, 12, and 18 months. At the same time points, aBMD of the total body, total hip, and lumbar spine (L1-L4) was measured. Measurements of aBMD were compared with age- and gender-matched controls(13, 14),(15) using pediatric, ethnic-specific software. With this instrument, the average *in vivo* precision for aBMD (expressed as percent coefficient of variation) was 0.62% at the spine and 0.72% at the total hip.

Height (cm) was measured using standardized procedure with a wall-mounted stadiometer. Weight (kg) was measured at each visit, post-voiding and in the fasting state, with subjects

wearing a hospital gown. All participants responded to a semi-structured interview to obtain demographic information and health history.

Vertebral Fracture Assessment

First, the Genant semiquantitative visual grading system of vertebral fractures (16) was performed by two observers (ADD and CMG)(7-9). Vertebrae T7 to L4 were graded on visual inspection as normal (grade 0), mildly deformed (grade 1, approximately 20-25% reduction in anterior, middle, and/or posterior height and a reduction of area 10-20%); moderately deformed (grade 2, approximately 25-40% reduction in any height and a reduction in area 20-40%); and severely deformed (grade 3, approximately 40% reduction in any height and area. A vertebral body was considered to be fractured if it was designated grade 1 or higher. This method has previously been shown to provide reasonable reproducibility, sensitivity, and specificity(17).

A quantitative assessment was also utilized to identify vertebral fractures based on the measurement of vertebral heights. An independent, blinded, experienced DXA technologist manually marked six points per vertebra at the anterior, middle, and posterior margins of the vertebral endplates. With these markers, we measured the anterior height (h_a), middle height (h_m), and posterior height (h_p). Using these heights, a incident fracture (a fracture developing over the course of the trial that was not present at baseline) was defined as a decrease in height of more than 15% on follow-up VFA images, as compared with baseline(16, 18).

Statistical Analyses

All statistical analyses were conducted using SAS. Student's t-test and Fisher's exact test, as appropriate, were utilized to compare baseline characteristics between the two treatment groups, to compare baseline characteristics between subjects who sustained fractures and those who did not, and to compare bone density changes at the time of fracture with concurrent measured changes in subjects without fracture. $P<0.05$ was taken as a statistically significant result.

Results

Patient Characteristics

Among the 94 randomized subjects, 14 (4 DHEA+COC, 10 placebo) became ineligible or withdrew before completing baseline measurements, resulting in a final sample of 80 (43 DHEA+COC, 37 placebo), aged 18.1 ± 2.7 yr (mean ± SD). The groups did not differ in baseline demographic characteristics (Table 1). Subjects had low BMI (18.0 ± 1.5 kg/m^2, range 14.8-22.9 kg/m^2) and amenorrhea of median duration 11 months, range 1-144 months. Subjects with amenorrhea for one month were six participants receiving COCs at recruitment who discontinued COCs ≥1 month prior to participation. Vitamin D concentrations were measured at baseline; if deficient (25OHD < 20 ng/mL), subjects were supplemented to achieve normal levels. At baseline, moderate skeletal deficits were noted at the spine, with 13 subjects (16%) showing low aBMD (aBMD-Z ≤ –2 SD; Table 1).

Baseline Skeletal Assessments: VF and aBMD

Using the Genant semiquantitative technique, 2 of the 80 subjects at baseline (2.5%) had evidence of a single, Genant grade 1 deformity located at T11 or L1. One additional subject (1.3%) had a Genant Grade 2 deformity at T9. Clinical characteristics of the three subjects exhibiting vertebral fractures at baseline are presented in Table 2. Two of the subjects with a prevalent fracture had been malnourished for quite some time (2 ½ to 3 years), and/or

amenorrheic for ~1 year or more. Despite this, none of these young women had a significantly low BMD for age at either the hip or spine.

Longitudinal Changes in VF

Over the 18-month trial, 10 incident vertebral fractures occurred in 9 subjects (12.5% subjects). Of these 10 VF, 8 were diagnosed based on the semiquantitative method (Table 3). Using quantitative techniques, only two subjects had a significant loss in vertebral height (defined as >15%), leading to a VF incidence of 2.5% by this method, including one subject whose fracture was also picked up by the semiquantitative method. Many of these subjects had restored body weight between baseline and the time of their fracture (Table 3).

Comparing those subjects who suffered a fracture to those who did not, we found no baseline differences in BMD Z-scores of the lumbar spine, total body, nor hip. At visits where we detected incident vertebral fractures (n=10), the change from baseline lumbar BMD was +0.003 (SE 0.011). In visits at which no incident fracture was detected, 174 lumbar BMD changes were measured, and mean significantly increased from baseline (+0.008 (SE 0.003)), adjusting for treatment arm and time of measurement, Anthropometric data, including BMI, lean mass, and percentage of median body weight, were not associated with fracture. Neither duration of anorexia nervosa diagnosis nor duration of amenorrhea was predictive of sustaining a vertebral fracture in this cohort.

Discussion

In the current study, we found that ill adolescents and young women with anorexia nervosa were at low risk for asymptomatic vertebral fractures. Vertebral fractures were not predicted by duration of illness, severity of malnutrition, or traditional measures of areal bone mineral density at the lumbar spine.

Other pediatric populations have shown similar rates of VF, ranging from 6% to 10%(7). In children initiating glucocorticoid therapy for nephrotic syndrome, the VF rate was low (8%), and consisted of a mild Grade 1 deformity in each instance(8). A higher prevalence (16% to 19%) has been demonstrated in pediatric patients with newly diagnosed acute lymphoblastic leukemia or with chronic rheumatic diseases(9, 19); these studies utilized lateral radiographs for spinal assessment. The lower rate of VF in our cohort may be related to the underlying illness in question, or to the method of VF screening utilized.

Contrary to our initial hypothesis, no correlation between BMD Z-scores and likelihood of vertebral fracture was seen. A similar lack of association between spinal BMD and the presence of VF has been reported in postmenopausal women(20). Fractures occurred in subjects with variable duration of malnutrition and amenorrhea as well, indicating that VF may present early in the clinical course, and not just in the most chronically ill patients. Given the lack of clinical symptoms of VFs, and the inability to predict likelihood of VF based on BMD measures, screening for VF should be considered in patients who would be at risk for fragility fracture regardless of aBMD or symptoms. While the non-fracture group appeared to have a greater degree of lumbar BMD change over the study, our small sample size in the fracture group precludes a direct comparison of the two rates of change.

The clinical significance of these vertebral fractures remains unclear. In adults, asymptomatic VF are associated with an increased risk for future VF(21). Whether this future fracture risk holds true for adolescents and young women with skeletal insults is presently unknown.

Study limitations should be acknowledged. DXA images are not optimized for VFA assessments. However, the effective radiation dose-equivalent experienced by the patient is far lower than that of conventional radiography. Additionally, the entire spine is acquired in a single image, rather than in serial images. Varying quality of the images and parallax distortion of the borders of the vertebral body may lead to difficulties with accurate placement of points on the vertebral body for measurement of vertebral height, particularly high in the thoracic spine. This midthoracic region (T6-T8) is the most frequent site for vertebral fractures in adults(22), children with leukemia,(9) and rheumatologic disorders(7). Thus, VFA may underestimate the VF frequency. However, the significantly higher radiation exposure associated with radiography and CT preclude their use as a screening tool in pediatric populations. Point placement is subjective; we attempted to minimize variation in technique by having one trained investigator place all the points for the current study. While the arbitrary 15% loss of vertebral height was used to define the incidence of fracture, concordant with previously published studies, this number may be too high for use in an adolescent and young adult population in whom patients should not be losing bone. A more conservative cut-off point should be considered and investigated in future studies.

Despite limitations, we have demonstrated that adolescents and young adults with anorexia nervosa are at low risk for vertebral fractures. The incidence of fracture was not predicted by BMI or BMD Z-scores in our cohort. These data illustrate the fact that VFA is a feasible technique that affords additional information from DXA assessments of bone health in a pediatric population.

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Table 1

Baseline Participant Characteristics

		All Subjects (n=80)	
		Mean ± SD	***Minimum, Maximum***
Age, yr		18.1 ± 2.7	13.3, 27.1
Height, cm		164.0 ± 7.0	148.3, 180.1
Weight, kg		48.6 ± 5.8	37.4, 67.9
BMI, kg/m^2		18.0 ± 1.5	14.8, 22.9
BMI, % of median for age		86 ± 7	68, 109
Fat mass, kg		8.6 ± 2.7	3.7, 17.4
Lean mass, kg		37.4 ± 4.5	27.2, 47.9
25(OH)D, ng/mL		38.3 ± 14.4	9, 83
PTH, pg/mL		29.7 ± 11.2	10.2, 70.2
Lumbar spine:	**aBMD, g/cm^2**	0.89 ± 0.10	0.67, 1.15
	Z, SD	–0.90 ± 1.00	–3.3, 1.2
Total hip:	**aBMD, g/cm^2**	0.89 ± 0.11	0.66, 1.19
	Z, SD	–0.36 ± 0.92	–2.2, 2.0
Whole body:	**aBMD, g/cm^2**	1.06 ± 0.07	0.92, 1.28
	Z, SD	0.07 ± 0.94	–2.0, 2.2

		Median (Q1–Q3)	***Minimum, Maximum***
Duration of AN, mo		12 (4–28)	1, 132
Months amenorrhea[†]		11 (5–20)	1,144
		N (%)	
White		71 (89)	
Hispanic		2 (3)	
Lumbar spine:	**Z ≤ –1 SD**	41 (51)	
	Z ≤ –2 SD	13 (16)	
Total hip:	**Z ≤ –1 SD**	19 (24)	
	Z ≤ –2 SD	3 (4)	
Whole body:	**Z ≤ –1 SD**	11 (14)	
	Z ≤ –2 SD	1 (1)	

[†]Excludes five participants with primary amenorrhea; includes six participants who were on COCs at time of recruitment and discontinued use of the medication for at least 1 month before the baseline visit.

Table 2

Characteristics of Participants with Prevalent Vertebral Fractures (n=3)

Fracture location/Grade		**T9, Grade 2**	**L1, Grade 1**	**T11, Grade 1**
Age, yr		20.5	20.9	17.4
Height, cm		168.2	167.3	177.0
Weight, kg		50.7	50	59
BMI, kg/m^2		17.9	17.9	18.8
BMI, % of median for age		83	82	89
Duration of AN, mo		36	31	4
Months amenorrhea		---†	20	11
History of previous fracture?		Yes	No	No
Family history of osteoporosis?		No	No	No
Medications?		No	Yes, SSRI	Yes, SSRI
Lumbar spine:	**aBMD, g/cm^2**	0.824	0.886	1.054
	Z, SD	-1.8	-1.2	0.6
Total hip:	**aBMD, g/cm^2**	0.795	0.874	1.09
	Z, SD	-1.2	-0.6	1.2

SSRI: Selective serotonin reuptake inhibitor

†Participant was on COCs at time of recruitment and discontinued use of the medication for at least 1 month before the baseline visit.

Table 3

Characteristics at Time of Fracture Diagnosis of Participants with Incident Vertebral Fractures (n=10)

		Median ± SD or Number	Range or %
Fracture location:			
T9		1	10%
T10		1	10%
T11		4	40%
T12		1	10%
L1		1	10%
L2		2	20%
Fracture Grade:			
Grade 1		9	90%
Grade 2		1	10%
Time after Baseline Visit:			
6 mo		2	20%
12 mo		6	60%
18 mo		2	20%
Age, yr		19.7 ± 1.9	17.5 to 22.1
Weight, kg		57.5 ± 8.5	49.8 to 74
BMI , kg/m^2		20.6 ± 2.7	18.5 to 25
BMI, % of median for age		96.2 ± 0.1	83.7 to 116.2
Duration of AN, mo†		22.6 ± 26.2	1 to 84
Months amenorrhea†		12.6 ± 11.6	1 to 36
History of previous fracture?		4	40%
Family history of osteoporosis?		3	30%
Medications?*		4	40%
Lumbar spine:	**aBMD, g/cm^2**	0.87 ± 0.07	0.78 to 0.99
	Z, SD	-1.4 ± 0.9	-2.9 to 0
Total hip:	**aBMD, g/cm^2**	0.86 ± 0.05	0.79 to 0.92
	Z, SD	-0.6 ± 0.4	-1.3 to -0.2

† data from baseline study visit

* Two subjects were prescribed selective-serotonin reuptake inhibitors at the time of VF; one subject was taking a proton-pump inhibitor; one subject was taking thyroid replacement.