



Published in final edited form as:

J Adolesc Health. 2017 February ; 60(2): 229–232. doi:10.1016/j.jadohealth.2016.10.003.

Effect of Exercise and Antidepressants on Skeletal Outcomes in Adolescent Girls with Anorexia Nervosa

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Abstract

Purpose—We examined the relation between malnutrition, lifestyle factors, and bone health in AN via dual-energy X-ray absorptiometry (DXA) and peripheral quantitative computed tomography (pQCT).

Methods—Seventy adolescent girls with AN and 132 normal-weighted controls underwent pQCT tibial measures including trabecular volumetric bone mineral density (vBMD), cortical vBMD, and cortical thickness. Participants with AN underwent DXA measures of the axial skeleton. We assessed the association of DXA and pQCT measures with clinical and lifestyle variables.

Results—BMI Z-score and ideal body weight percentage were positively correlated with trabecular vBMD, cortical CSA, and section modulus ($p < 0.04$). Exercise was associated with all pQCT measures, but only with hip BMD by DXA. In AN, use of antidepressants was associated with lower pQCT measures ($p < 0.03$).

Conclusions—Antidepressants may negatively, and exercise positively, influence BMD in adolescents with eating disorders. These findings offer a provocative look at two longstanding questions.

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Keywords

Anorexia nervosa; malnutrition; peripheral quantitative computed tomography; DXA; exercise; antidepressant

Introduction

Bone loss frequently complicates anorexia nervosa (AN)^{1,2}; patients have a seven-fold increased fracture incidence³. Studies using dual energy X-ray absorptiometry (DXA) demonstrate significant reductions in bone mineral density (BMD)¹. Several factors correlate with BMD in AN: body mass index (BMI), age at menarche, lean body mass, and illness duration¹. Less is known about the impact of modifiable factors, such as physical activity or medication use, on the peripheral skeleton or bone geometry of girls with AN. We sought to determine the association between these factors and skeletal health as measured by DXA and peripheral quantitative computed tomography (pQCT). We hypothesized that physical activity would be protective for skeletal health even in the setting of AN, while use of antidepressant medications would not significantly impact bone measurements in these patients.

Materials and Methods

Participant Selection/Measurements

Details have been published previously.⁴ We recruited female adolescents (ages 11–20 years) from two Eating Disorders Programs for participation in a clinical trial (Clinicaltrials.gov, NCT01343771). Eligible patients were post-menarchal or had a bone age 13 years, and met DSM-V diagnostic criteria for AN. Subjects were excluded if they had other medical conditions known to affect bone health (such as celiac disease or cystic fibrosis), or if they were receiving medications known to affect the skeleton (such as oral contraceptives). Control subjects were recruited from general adolescent medicine clinics at the same sites. Control subjects were normal-weighted, free of concomitant chronic diseases, and did not regularly use medications over the year prior to study enrollment. We report baseline data from the first research visit for 70 females with AN and 132 healthy control subjects (ages 11–18 years). The study was IRB approved; informed consent was obtained.

Bone measurements were completed at the baseline visit. DXA (Discovery A, Hologic, Inc.) measurements of bone mineral content (BMC, g) and BMD (g/cm^2) were obtained for the total body less head (TBLH), spine, and total hip. Body composition was measured by DXA. pQCT left tibial cross-sectional measurements were obtained (Stratec XCT 3000, Orthometrix) at tibial length percentages proximal to the growth plate (3%, 38%, 66%) for trabecular and cortical volumetric BMD (vBMD, mg/cm^3), cortical BMC (mg) and cross-sectional area (CSA, mm^2), cortical thickness (mm), and muscle CSA (mm^2). Results were converted to Z-scores.

Anthropometrics were obtained in all participants. The Hamwi method for women was used to calculate percentage ideal body weight (% IBW) = 100 lbs for 60 inches tall, and 5 lbs/

inch for each inch over 5 feet^{5,6}. Participants provided health information, and completed the Youth/Adolescent Activity Questionnaire to quantify exercise.⁴

We used Pearson correlation and Student t-test to assess associations between clinical markers and measures, and analysis of covariance to compare groups for a given level of weekly exercise.

Results

Adolescents with AN differed from control subjects in BMI and %IBW (Table). Most subjects exercised regularly; all reported participation in weight-bearing activities such as running, walking, and use of equipment such as an elliptical machine. Controls who exercised reported less activity (mean \pm SD, 5.5 ± 4.4 hr/wk) than AN participants (8.5 ± 4.9 hr/wk, $p < 0.001$). Twenty-nine participants (41%) with AN used antidepressants regularly for a minimum of 3 months prior to study enrollment; no control subjects did. All 29 took a selective serotonin reuptake inhibitor (SSRI); of those, $n=7$ also took an antipsychotic and $n=2$ also took a tricyclic antidepressant. No subjects consumed alcohol or smoked.

BMI Z-score was positively associated with every BMD and BMC measure by DXA in AN (r range 0.44 to 0.57, $p < 0.001$). Illness duration inversely correlated with spinal BMD Z-scores only (Pearson $r = -0.32$, $p = 0.006$). Amenorrhea duration was negatively associated with TBLH and spinal Z-scores ($r = -0.26$ to -0.27 , $p = 0.04$). Peripherally, BMI Z-score correlated positively with trabecular vBMD, cortical BMC, cortical CSA, and muscle CSA Z-scores (r 0.35 to 0.50; $p < 0.005$). Correlations between these pQCT measures and %IBW were similar (r 0.22 to 0.42, $p < 0.07$). Neither the duration of illness nor duration of amenorrhea was associated with pQCT outcomes.

By DXA, only hip BMD Z-score was related to exercise in AN ($+0.06 \pm 0.03$ per hour of exercise/week, estimate \pm SE, $p = 0.02$). pQCT measures were associated not only with presence or absence of exercise, but amount of exercise performed. In AN, reported exercise positively correlated with trabecular vBMD ($p = 0.01$) and cortical BMC Z-scores (Figure; $p < 0.001$). Bone size was similarly impacted; more exercise was associated with higher cortical CSA and cortical thickness Z-score ($p < 0.001$). In contrast, cortical vBMD Z-scores were negatively associated with exercise in AN (Figure, $p = 0.007$). Weekly exercise impacted cortical BMC, CSA, and thickness Z-scores similarly between girls with AN and controls ($p > 0.40$ for group \times exercise interaction). Girls with AN showed consistently lower trabecular vBMD-Z scores and higher cortical vBMD Z-scores over the range of exercise (0–25 hr/wk).

Hip BMD Z-scores were lower with antidepressant use versus non-use in AN (-0.69 ± 1.3 vs. -0.05 ± 1.1 , $p = 0.03$). Hip BMC Z-scores were also negatively impacted (BMC Z-score -0.56 lower with antidepressants, $p = 0.02$). No differences were seen at TBLH or hip. With pQCT, cortical BMC (-0.57 ± 1.18), cortical CSA (-0.66 ± 1.20), and muscle CSA (-0.78 ± 1.04) Z-scores were lower with antidepressants compared to non-use, by differences of -0.60 to -0.61 units ($p < 0.03$). Trabecular vBMD, cortical thickness, and section modulus Z-

score differences were similar (-0.64 , -0.55 , -0.47) although marginally non-significant ($0.06 < p < 0.08$). Antidepressant use did not impact cortical vBMD Z-scores ($p=0.84$).

We adjusted the comparisons regarding antidepressant use in AN for BMI and exercise. BMI Z-scores were not different between anti-depressant users (BMI Z-score mean -0.64 ± 0.81) and non-users (BMI Z-score -0.57 ± 0.78 , $p=0.71$). Accordingly, BMI did not impact differences in skeletal measurements between the two groups. In contrast, adolescents with AN who used antidepressants reported significantly less exercise than those who did not (median 0 hr/wk versus 7 hr/wk, $p=0.002$). Adjusting for exercise did tend to attenuate the antidepressant differences for pQCT measures, particularly those at the 38% site.

Discussion

While DXA cannot fully characterize skeletal wellness, pQCT provides additional insight into the density and structure of the peripheral skeleton. Herein, we revealed skeletal deficits by pQCT in adolescents with AN. The high levels of weight-bearing activity in this cohort may have led to some compensation despite low muscle mass. Bone size and BMD by pQCT at several sites were positively affected by exercise, supporting our hypothesis. The effect size of exercise on cortical BMC, CSA, and thickness Z-scores was similar between girls with AN and healthy adolescents. However, trabecular and cortical vBMD Z-scores differed between groups at a given exercise level. Our findings suggest that exercise strengthens muscles around bone to confer skeletal gains, particularly at cortical sites, even in the face of an eating disorder. Clinicians need to remain cautious in the endorsement of exercise recommendations. Skeletal benefits need to be weighed against medical risk, and considering caloric expenditure, fracture risk, and purging through hyper-exercise. Additionally, exercise does not appear to solve all skeletal aberrations that occur in AN; trabecular and cortical vBMD Z-score deficits persisted in AN compared to controls despite the observed associations.

Antidepressant use was inversely associated with hip BMD by DXA, but did not impact the spine. Adult investigations⁷⁻⁹ and studies of AN^{10,11} have shown similar skeletal effects of antidepressants. We found that trabecular vBMD, cortical CSA, cortical thickness, section modulus, and maximal muscle CSA by pQCT were negatively correlated with antidepressant use. The adverse effects of these medications on cortical bone, which comprises 80% of the skeleton, are particularly concerning. However, these differences in pQCT measures were attenuated at the 38% site by the association between antidepressant use and lower levels of exercise in AN. Our findings suggest that exercise may ameliorate some of the negative impact of antidepressants on the cortical skeleton.

Study limitations merit acknowledgement. The sample size was relatively small, and study design, cross-sectional. Our recruitment strategy aimed to examine bone health across a broader spectrum of disease than captured previously. Our results may not be generalizable to patients with severe disease.

In conclusion, we found that the impact of malnutrition and accompanying systemic alterations on the peripheral skeleton of adolescents with AN may be similar to that of the

axial skeleton. Our findings around exercise and antidepressant use offer a provocative new look at two longstanding management issues for these patients that should drive future trials.

Acknowledgments

The authors thank Alicia McAllister, RT, CBDT, Valerie Marsocci, RT, and Nicole DaSilva, RT, CNMT for expert technical assistance; the excellent care of the Boston Children's Hospital Clinical and Translational Study Unit (CTSU) nurses; and our patients and their families, who made this research possible. Our study was supported by NIH R01 AR060829, NICHD K23 HD060066, NIH UL1 RR-025758 (Harvard Clinical and Translational Science Center), the Boston Children's Hospital Department of Medicine and CTSU, and the Brown Alpert Medical School Department of Orthopaedics.

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Implications and Contribution

The impact of malnutrition and accompanying systemic alterations on the peripheral skeleton of adolescents with anorexia nervosa (AN) may be similar to that of the axial skeleton. While exercise positively influences BMD even in the setting of AN, antidepressant use appears to negatively impact the skeleton.

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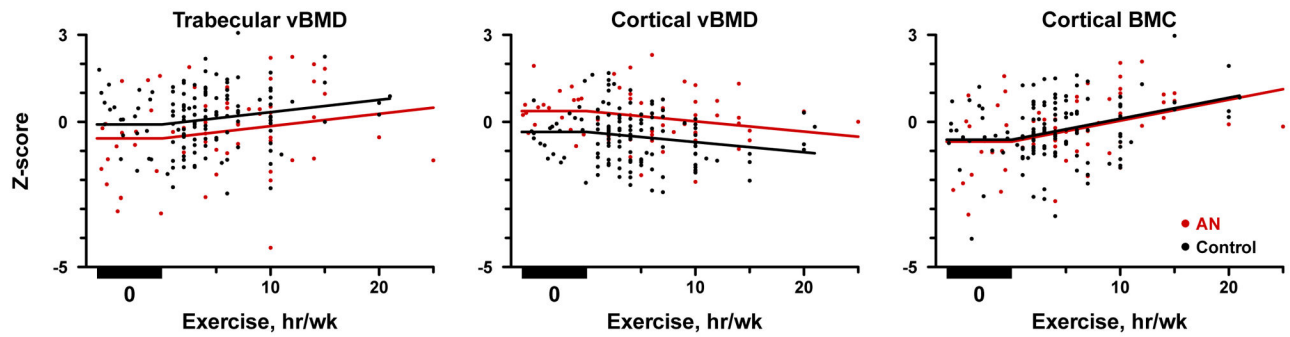


Figure.

Association of trabecular volumetric bone mineral density (vBMD) Z-scores (Panel A), cortical vBMD Z-scores (Panel B), and cortical bone mineral content (BMC) Z-scores (Panel C) with reported hours of exercise per week among adolescent girls with anorexia nervosa (AN, red lines) and healthy female control subjects (Control, black lines). In all 3 panels, a significant association between the number of hours of weekly exercise and the pQCT measure is observed ($p < 0.01$ for all), following a parallel course for AN and Control ($p > 0.40$ for group \times exercise interaction). Panels A and B: Significant differences between AN and Controls remain across the range of exercise for trabecular vBMD Z-score (AN-Control -0.48 ± 0.18 , estimate \pm standard error, $p = 0.008$) and cortical vBMD Z-score (0.71 ± 0.14 , $p < 0.001$). Panel C: No difference between AN and Controls for cortical BMC Z-score ($p = 0.66$).

Table 1
 Characteristics of 70 adolescent girls with anorexia nervosa and 132 female control subjects of comparable age.

Characteristic	AN*				Control			
	Mean ± SD	Min, Max	Mean ± SD	Min, Max	Mean ± SD	Min, Max	Min, Max	p-value
Age, yr	15.5 ± 1.9	11.5, 18.9	16.9 ± 2.3	11.0, 20.8	16.9 ± 2.3	11.0, 20.8	11.0, 20.8	<0.0001
Height, cm	160.5 ± 7.9	142.0, 178.0	161.9 ± 7.3	134.7, 178.4	161.9 ± 7.3	134.7, 178.4	134.7, 178.4	0.28
Weight, kg	48.4 ± 6.5	25.9, 59.4	59.4 ± 9.9	30.8, 81.4	59.4 ± 9.9	30.8, 81.4	30.8, 81.4	<0.0001
BMI, kg/m ²	18.7 ± 1.7	12.8, 22.4	22.6 ± 3.1	15.6, 29.7	22.6 ± 3.1	15.6, 29.7	15.6, 29.7	<0.0001
BMI Z-score	-0.60 ± 0.79	-3.13, 0.82	0.41 ± 0.74	-1.52, 2.01	0.41 ± 0.74	-1.52, 2.01	-1.52, 2.01	<0.0001
% IBW	91.0 ± 9.4	56.9, 111.0	109.6 ± 15.4	67.7, 146.2	109.6 ± 15.4	67.7, 146.2	67.7, 146.2	<0.0001
Lean mass, kg	34.5 ± 4.9	18.9, 50.0						
Fat mass, kg	11.9 ± 3.3	3.6, 18.6						
Body fat, %	24.4 ± 5.2	11.0, 33.5						
	Median	Min, Max						
Duration of AN, mo	4.5	1, 60						
Duration of amenorrhea, mo*	4	1, 18						
	N (%)		N (%)		N (%)		p-value	
Race								<0.0001
White	61 (87)		48 (36)		48 (36)			
Black	—		31 (23)		31 (23)			
Asian	2 (3)		22 (17)		22 (17)			
Other	7 (10)		28 (21)		28 (21)			
Native American	—		3 (2)		3 (2)			
Hispanic ethnicity	4 (6)		32 (24)		32 (24)		0.008	
Regular exercise	52 (74)		111 (84)		111 (84)		0.13	
Antidepressant use	29 (41)		0 (0)		0 (0)		P<0.0001	
Vitamin D insufficient (25OHD <30 ng/mL)	34 (49)		—		—			
Vitamin D deficient (25OHD <20 ng/mL)	7 (10)		—		—			

Rounded down; premenarcheal participants excluded.
* BMI, body mass index; AN, anorexia nervosa; 25OHD, 25-hydroxy-vitamin D

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Correlation between tibial pQCT Z-scores or DXA measures with markers of disease severity in 70 adolescent girls with anorexia nervosa

Table 2

Site	DXA Z-score	Correlation with BMI Z-score	Correlation with duration of illness
TBLH	BMD Z-score	0.53*	-0.21
	BMC Z-score	0.57*	-0.19
Spine	BMD Z-score	0.53*	-0.32 [†]
	BMC Z-score	0.49*	-0.26 [†]
Hip	BMD Z-score	0.47*	-0.17
	BMC Z-score	0.44*	-0.03
Site	pQCT Z-score	Correlation with BMI Z-score	Correlation with duration of illness
3%	Trabecular vBMD	0.42*	-0.16
38%	Cortical vBMD	-0.05	-0.13
	Cortical BMC	0.46*	-0.15
	Cortical CSA	0.47*	-0.13
	Cortical thickness	0.35 [†]	-0.07
	Polar section modulus	0.45*	-0.15
66%	Maximum muscle CSA	0.50*	0.03

DXA, dual energy X-ray absorptiometry; pQCT, peripheral quantitative computed tomography; BMD, bone mineral density; BMC, bone mineral content; CSA, cross sectional area.

* p<0.0001.

[†] p<0.05.

Table 3

Comparison of skeletal measures by DXA and pQCT between adolescents with anorexia nervosa who use anti-depressants and those who do not

		Anti-depressant use N=29	No anti-depressant use N=41	p-value
DXA Measurements				
Site	Z-score	Mean ± SD	Mean ± SD	
Hip	BMD	-0.69 ± 1.3	-0.05 ± 1.1	0.03
	BMC	-0.18 ± 0.98	0.39 ± 0.91	0.02
TBLH	BMD	-0.49 ± 1.2	-0.08 ± 1.2	0.17
	BMC	-0.50 ± 0.98	-0.15 ± 0.98	0.14
Spine	BMD	-0.79 ± 1.4	-0.35 ± 1.3	0.18
	BMC	-0.39 ± 1.2	0.08 ± 1.1	0.09
pQCT Measurements				
Site	Z-score	Mean ± SD	Mean ± SD	
3%	Trabecular vBMD	-0.69 ± 1.51	-0.04 ± 1.30	0.06
38%	Cortical vBMD	0.20 ± 0.99	0.16 ± 0.87	0.84
	Cortical BMC	-0.57 ± 1.18	0.02 ± 1.10	0.03
	Cortical CSA	-0.66 ± 1.20	-0.04 ± 1.09	0.03
	Cortical thickness	-0.49 ± 1.18	0.05 ± 1.18	0.06
	Polar section modulus	-0.59 ± 1.08	-0.13 ± 1.07	0.08
66%	Maximum muscle CSA	-0.78 ± 1.04	-0.17 ± 0.87	0.01

DXA, dual energy X-ray absorptiometry; pQCT, peripheral quantitative computed tomography; BMD, bone mineral density; BMC, bone mineral content; CSA, cross sectional area.