Published in final edited form as:

Osteoporos Int. 2008 March ; 19(3): 289–294. doi:10.1007/s00198-007-0476-z.

Low prevalence of vitamin D deficiency among adolescents with anorexia nervosa

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Abstract

Summary—Fifty adolescents with AN and 200 healthy girls underwent vitamin D screening. Girls with AN reported exceptional compliance with vitamin D supplementation and PTH concentrations were lower. Vitamin D deficiency was less common in the group with AN, but when race was considered, the trend was no longer significant.

Introduction—The objective of this study was to determine whether patients with anorexia nervosa (AN) are more compliant with supplementation and have a lower prevalence of vitamin D deficiency than healthy controls.

Methods—Fifty adolescents with AN and 200 controls were compared using anthropometric and lifestyle data, serum 25-hydroxyvitamin D (25OHD) and parathyroid hormone (PTH) concentrations, and prevalence of vitamin D deficiency.

Results—The prevalence of deficiency (<20 ng/mL) was 2% in the AN group vs. 24% among controls ($p=0.003$). 25OHD was similar among white participants with AN and white controls (39.5 vs. 36.0 ng/mL, $p=0.20$), but higher than in non-white controls (20.6 ng/mL). Significantly more girls with AN reported vitamin D supplementation (86%) than the full control (14%) or white subgroup (27%) ($p<0.001$). Participants with AN had lower PTH concentrations than controls, (27.8 vs. 47.4 pg/mL, $p=0.009$), a trend that lost significance after age and race adjustment (41.7 pg/mL, $p=0.12$).

Conclusions—Compared to healthy controls, adolescents with AN had a lower prevalence of vitamin D deficiency and PTH concentration. However, 25OHD and PTH concentrations were similar after adjustment for race and age. The trend of lower PTH levels in adolescents with AN, accompanied by exceptional compliance with supplementation, may have bone health implications for these patients.

Keywords

Adolescents; Anorexia nervosa; Calcium; Parathyroid hormone; Vitamin D

Introduction

Anorexia nervosa (AN) is a common cause of low bone mass among adolescents and young women [1-5]. By definition, young women with this disease have a low body mass index and reduced fat mass secondary to malnutrition [1-5]. They may also exhibit delayed puberty and poor growth related to disease-associated hormonal alterations [5]. Therefore, AN represents an important clinical model for the study of malnutrition's effects on the skeleton.

The vitamin D status of teenagers with AN, with its implications for bone health, has only been examined previously in small studies [4, 6-8]. Fonseca et al. measured serum vitamin D concentrations in 17 young adults with AN [6]. The participants' dietary intake was less than 50 IU daily and only one patient was receiving vitamin D supplementation; the median serum concentration of 25-hydroxyvitamin D (25OHD) was significantly lower than controls. Another study found no significant difference in serum vitamin D parameters among 20 female patients with AN compared to those of 10 lean and 10 normal weight controls [8].

More recent studies have examined the vitamin D status of patients with AN who were receiving vitamin D supplementation in the context of an observational or interventional study. Soyka et al. examined mechanisms of bone loss in adolescents with AN and found similar serum 25OHD concentrations among 19 adolescent girls with AN and 19 controls [4]. Kiriike et al. found that among 29 patients with AN, most had normal vitamin D concentrations (defined as 25OHD >16 ng/mL) [9]. Another study of 12 patients with AN found no significant difference in the serum 25OHD level between patients and controls [10]. Grinspoon et al. noted normal 25OHD and parathyroid hormone (PTH) concentrations among 60 women with AN who were participating in a clinical trial [11]. A small study that examined bone turnover in nine women with AN also found normal 25OHD and PTH levels [12]. Lastly, Aarskog et al. studied 12 pubertal girls with AN and found similar concentrations of 25OHD among young women with AN and healthy control subjects [7].

In this study, we measured 25OHD and PTH concentrations in 50 patients with AN in comparison to 200 healthy adolescent control subjects. We examined the correlation between serum concentrations of 25OHD and PTH, and the relationship between 25OHD level and body mass index (BMI), compliance with vitamin D and calcium supplementation, and milk consumption. We tested the hypothesis that adolescent girls with AN would be more compliant with non-caloric vitamin supplements than healthy female control subjects, and that the prevalence of vitamin D deficiency would, therefore, be low among this patient group.

Materials and methods

The study sample consisted of 250 participants, including 50 patients (49 white), age 15–26 years (mean 18.4) from the outpatient eating disorders program within the Adolescent Medicine Division at Children's Hospital Boston. Participants were established patients within the program and each met criteria to be followed as outpatients (i.e., were without significant bradycardia or hypotension). Inclusion criteria included meeting DSM-IV criteria for AN, amenorrhea for greater than 3 months, and hemodynamic stability. At the time of study entry, patients with AN had been encouraged to consume 400 IU of vitamin D (ergocalciferol or cholecalciferol) daily in a multivitamin by their primary eating disorder provider, as is the standard of care in our program. Data from 200 control subjects (37 white) were used to provide the comparative information. The healthy adolescent girls (age

11–18 years, mean 14.9) were established patients and were recruited from the Adolescent/Young Adult Outpatient Program at Children's Hospital Boston, as included previously in a report of healthy adolescent girls and boys [13]. Exclusion criteria included having a chronic disease or receipt of medications known to affect bone metabolism. Per standard clinic recommendations, they had also been encouraged to consume a daily multivitamin as part of primary care recommendations.

Participants completed validated nutritional and exercise questionnaires, including a detailed assessment of calcium and vitamin D intake, and reported weekly participation in sports activities, as had been used previously [13–15]. In addition to information obtained on their dietary intake, participants were questioned separately about use of multivitamins, and supplementation with calcium and vitamin D. As multivitamins typically contain vitamin D, this information was included in the response regarding receipt of vitamin D. At the study visit, weight (kg) and height (cm) of the subjects (wearing only a hospital gown) were determined after voiding. All weights were obtained on the same scale; heights were obtained using the same stadiometer (Perspective Enterprises, Kalamazoo, MI). Body mass index (BMI) was calculated from these measurements in kg/m^2 . Random blood samples (15 cc) were obtained at the end of the health visit. Serum 25OHD concentrations for the controls were measured by competitive binding assay (Nichols Institute, San Clemente, CA), and intact PTH by two-site chemiluminescence immunoassay (Nichols Institute). Serum calcium and phosphorus were measured by endpoint assay in a Roche/Hitachi multichannel analyzer (Roche; Brachburg, NJ). The samples were analyzed in multiple assays. Interassay coefficients of variation were 5.4–7% for PTH, 9–15% for 25OHD, and 1.5–2.2% for the cations. For the patients with AN, a chemiluminescent assay was used (Liason®, Diasorin, Stillwater, MN), with an interassay precision of 8.6–10.0%. This study was approved by the Children's Hospital Committee on Clinical Investigation. Informed consent was obtained from all participants, including parental consent for participants less than 18 years of age.

Data analysis

Statistical analyses were performed using SAS (SAS Institute Inc., Cary, NC) and SPSS software (SPSS Inc, Chicago, IL). Analysis of variance was used to compare continuous measures between AN and normal subjects, controlling for potential confounding variables including age and vitamin D supplementation. Prevalence of vitamin D deficiency was compared among the participant groups by multiple logistic regression, again controlling for age and vitamin D supplementation. Other binary variables, including history of fractures, were analyzed similarly. The comparisons of 25OHD level and vitamin D deficiency were additionally adjusted for season, exercise level, and milk consumption. A p-value <0.05 was considered statistically significant.

Results

As expected, the young women with AN had a significantly lower weight and BMI than the healthy controls, despite being more than 3 years older on average (Table 1). Reported weekly exercise, fracture history, and milk consumption were similar among the group with AN and controls. Reported compliance with vitamin D supplementation (including multivitamins) and calcium supplementation were markedly and significantly greater in the AN patients (Fig. 1), with over 85% of AN patients reporting vitamin D supplementation in contrast with 14% in the comparison group.

Mean serum 25OHD (Fig. 1), adjusted for age, supplementation and other predictors including season, was similar among the 49 white subjects with AN (39.6 ng/mL) and the 37

white controls (36.0 ng/mL, $p=0.20$), although higher than in the non-white controls (20.6 ng/mL). Serum calcium and phosphorus levels were similar in AN patients and controls. The subjects with AN had a significantly lower mean PTH level (27.8 pg/mL) than the entire control sample (47.4 pg/mL, $p=0.009$), but not significantly below the white subsample (41.7 pg/mL, $p=0.12$).

The prevalence of vitamin D deficiency (Table 2), defined as 25OHD concentration <20 ng/mL, was 2% in the AN group (1/50) as compared to 24% in controls (48/200), significant at $p=0.003$ after adjustment for age, vitamin D supplementation, season, and other confounders. No difference was seen between the AN sample and the white controls (1/37). Using an accepted optimal threshold of 30 ng/mL, we found that only 22% of the subjects with AN (11/50) had suboptimal levels, in contrast to 75% of controls (150/200), a greater than threefold difference ($p<0.001$). The difference in suboptimal 25OHD was twofold in the white subsamples (22% in AN, 43% in controls), but not statistically significant ($p=0.08$). Similar although statistically weaker results were found for severe deficiency, defined as 25OHD <15 ng/mL (Table 2).

Discussion

Confirming our anecdotal impression, we found that adolescents and young women with AN were significantly more compliant with multivitamin supplements, as well as calcium and vitamin D supplementation compared to healthy controls. The prevalence of vitamin D deficiency was only 2% among the adolescents and young women with the eating disorder in the face of exceptional compliance with these supplements. The prevalence of this problem was significantly lower than in healthy controls and vitamin D concentration higher until race was taken into account. These data may reflect the higher incidence of AN among white adolescents compared to other racial and ethnic groups. In addition, vitamin D deficiency is less common among whites, explained in part by more rapid cutaneous vitamin D synthesis in individuals of a fair complexion [13]. Thus, differences in prevalence and serum 25OHD concentration between the patients and controls became attenuated when race was considered. Few previous studies have examined directly the vitamin D status of adolescents with AN; therefore, these data fill a current gap in knowledge.

Our study replicates data from earlier reports in which young women with AN were noted to have normal vitamin D concentrations while receiving vitamin D through a multivitamin supplement [7-12]. As vitamin D is a fat soluble vitamin, it could be expected that patients with AN would have a lower 25OHD concentration, given the typical emaciated state of these patients. However, our participants with AN had higher 25OHD concentrations than controls of mixed race and ethnicity. This finding may be secondary to their strict compliance to what they perceive to be a non-caloric nutritional alternative. However, when compared to controls matched for age, gender, and race, their 25OHD concentrations were similar. This latter finding again likely reflects the higher prevalence of AN and lower prevalence of vitamin D deficiency among whites.

Although speculative, our findings may also be explained by the fact that these patients had a lower percentage body fat; therefore, they had decreased storage of vitamin D and higher circulating 25OHD concentrations. The association between vitamin D storage and fat mass has not been completely elucidated, but in a study by Wortsman et al., obese subjects had significantly lower basal 25-hydroxyvitamin D concentrations and higher PTH concentrations than did age-matched control subjects [19]. This was thought to be due to the decreased bioavailability of vitamin D from cutaneous and dietary sources because of its deposition in body fat compartments.

The current participants with AN had significantly lower PTH concentrations compared to the healthy control subjects. This finding may be explained by their compliance with calcium supplementation as PTH secretion is exquisitely sensitive to circulating calcium concentrations. Differences in vitamin D consumption and status may have also contributed. In adults with established osteoporosis, magnesium deficiency has been shown to blunt PTH response [20]. Although serum levels of this cation were not measured in the current study, this possibility is an important consideration in a malnourished group with AN. PTH also stimulates osteoclast function [16]; therefore, lower PTH levels could ultimately affect bone resorption, resulting in skeletal benefits for these patients. Exercise is another factor that can modulate PTH secretion [17] and this patient group is known to overexercise. Interestingly, the reported exercise among our participants with AN was not significantly different from controls, an unexpected finding. However, several of our patients were on relative activity restriction at the time of study enrollment. The patients' reported weekly exercise prior to this restriction is not known, but we suspect would have been higher than that of the controls. The relation between exercise, PTH and bone turnover in these patients would be important to explore longitudinally to determine implications of this finding for bone health.

Robinson et al. surveyed 394 physician members of the Society for Adolescent Medicine. Among the membership, 72.8% reported that they prescribed hormone replacement therapy, often as oral contraceptives, for girls with AN, although there is a lack of data to support this practice. However, only 19.5% of the group surveyed prescribed vitamin D supplementation [18]. Our findings suggest that vitamin D supplementation is effective in maintaining normal vitamin D levels in adolescent girls with AN. This intervention is an inexpensive and safe method to improve bone health in this patient population, and our findings suggest that this strategy is currently underutilized. Although not examined in this study, given the low bone mass that is commonly seen among these patients [4], this simple intervention (i.e., administration of supplements to a patient) could have positive implications for bone health in youth with this common chronic disease. Further research should also explore the relationship between percentage of body fat and circulating vitamin D levels among these patients to clarify their baseline needs. In addition, studies that evaluate the correlation between PTH and bone turnover markers would be informative in these patients. Finally, health outcome studies would be important that examine the relationship between vitamin D and calcium supplementation, and both peak bone mass and fracture risk in adolescent girls with AN.

This study also raises interesting questions about standard supplementation recommendations for both healthy adolescents and those with chronic disease. The American Academy of Pediatrics currently recommends routine daily vitamin D supplementation, including 200 IU for most infants from age 2 months, and continued throughout childhood and adolescence [21]. Data are accumulating that vitamin D has important effects on both bone and muscle, as well as extraskeletal effects, including regulation of the immune system and cell proliferation, and suppression of autoimmune reactions; this vitamin may confer protection against specific malignancies, tuberculosis infections, type 1 diabetes mellitus, and other common diseases [22]. Because of these potential beneficial effects on multiple tissues, there is heightened awareness regarding routine vitamin D supplementation to all children and adolescents, and not only those deemed at risk for deficiency. Our findings highlight the high prevalence of vitamin D deficiency among healthy teenagers across ethnicity, and interestingly, a low prevalence of this problem among one group of adolescents with a common chronic disease: AN. A low prevalence of vitamin D deficiency in the adolescents with this eating disorder was accompanied by extraordinary compliance with vitamin D supplementation; these data can be viewed as an endorsement for routine supplementation.

Limitations of our study must be considered. We had a relatively small sample size, especially when examining ethnicity-matched control subjects, which may have limited our statistical power to control for potential confounding variables, and detect important relationships between some variables of interest. It must also be acknowledged that a different serum 25OHD assay was used for the patients with AN compared to the controls. The variability among vitamin D assays could introduce heterogeneity such that direct comparisons between the two groups is more complex. In addition, because the prevalence of vitamin D deficiency was based on a within-group calculation, between-group differences in prevalence should be emphasized over between-group comparisons of serum 25OHD concentration. Finally, nutritional and exercise data were obtained via self-report, with its inherent limitations, especially among a group of adolescents with an eating disorder.

We report a low prevalence of vitamin D deficiency among an outpatient, clinic-based sample of white girls with AN. These girls had circulating 25OHD concentrations that were higher than healthy non-white control subjects, in the face of exceptional compliance with vitamin D and calcium supplementation. However, when race was taken into account, the differences in 25OHD concentration were attenuated. Lastly, a better understanding of the lower PTH concentrations observed among the participants with AN could have therapeutic implications with respect to appropriate calcium and vitamin D supplementation, and the overall bone health of these patients.

Acknowledgments

We wish to acknowledge and thank the expert nursing staff in the General Clinical Research Center at Children's Hospital Boston; the excellent technical assistance of Diane DiFabio, Katie Clegg, Suzanne Muggeo, and Jessica Sexton; and our study participants who made this work possible.

Research Support: Funded by NIH Grants RO1 HD043869 and MO1-RR-2172 to the Children's Hospital General Clinical Research Center; Department of Defense (US Army, Bone Health and Military Readiness); and Project S-T71-MC-0000-10-S1-R0 from the Maternal and Child Health Bureau.

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Fig. 1.

Upper panel: Anorexic subjects showed far more frequent vitamin D supplementation than normals. Bars indicate percentage $\pm$ standard error. *Lower panel:* 25OHD levels, even after adjustment for supplementation, differed between anorexic and normal participants but not between white normals and the predominantly white (49/50) anorexics. Bars indicate mean $\pm$ standard error adjusted for vitamin D supplementation, season, exercise level, and milk consumption

Table 1

Anthropometric, biochemical and hormonal characteristics of participants with anorexia and controls^a

	Anorexic	Normal			p, AN vs. normal	p, AN white vs. normal white
		White	Non-white	All		
Participants	50	37	163	200		
	Mean ± s.d					
Age, yr ^b	18.4±2.7	15.0±2.1	14.9±2.0	14.9±2.0	<0.001	<0.001
Weight, kg	48.8±6.1	61.1±18.1	62.8±16.5	62.5±16.8	<0.001	0.001
Height, cm	164.7±7.2	161.1±6.3	160.5±6.1	160.6±6.1	0.02	0.08
BMI, kg/m ²	18.0±1.6	23.4±6.2	24.3±5.9	24.2±6.0	<0.001	<0.001
25OHD, ng/mL ^c	39.6±14.3	36.0±15.0	20.6±8.7	23.5±11.8	<0.001	0.20
Serum phosphorus, mg/dL	3.9±0.5	4.0±0.5	3.9±0.7	3.9±0.7	0.08	0.26
Serum calcium, mg/dL	9.6±1.3	9.5±0.4	9.5±0.9	9.5±0.8	0.66	0.73
PTH, pg/mL	27.8±9.1	41.7±19.2	48.7±24.0	47.4±23.3	0.009	0.12
Exercise, hr/wk	4.7±4.4	6.2±7.7	4.9±4.4	5.1±5.2	0.32	0.16
Milk intake, cups/day	1.7±1.4 n (%)	1.9±1.4	1.5±1.2	1.6±1.3	0.13	0.62
Past fractures	15 (30)	16 (43)	30 (19)	46 (23)	0.65	0.36
Vitamin D supplementation ^d	43 (86)	10 (27)	17 (10)	27 (14)	<0.001	<0.001
Calcium supplementation ^d	23 (46)	3 (8)	3 (2)	6 (3)	<0.001	0.04

^a Testing hypothesis of equal mean or percentage across categories. Means compared by analysis of variance, percentages by multiple logistic regression, adjusted in both cases for age and vitamin D supplementation except as noted

^b Unadjusted comparison by analysis of variance

^c Additionally adjusted for season, exercise level, and milk consumption

^d Adjusted for age only

Table 2

Prevalence of hypovitaminosis D among participants with AN and controls*

	Anorexic	Normal		p, AN vs. Nnormal		p, AN white vs. normal white	
		White	Non-white	All			
Participants	50	37	163	200			
		n (%)					
25OHD < 15 ng/ml	1 (2)	1 (3)	47 (29)	48 (24)	0.07		0.98
25OHD < 20 ng/ml	1 (2)	3 (8)	83 (51)	86 (43)	0.003		0.20
25OHD < 30 ng/ml	11 (22)	16 (43)	134 (82)	150 (75)	<0.001		0.08

* Testing for equal prevalence of deficiency across categories. Adjusted comparison by multiple logistic regression, controlling for age, vitamin D supplementation, season, exercise level, and milk consumption