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Use of SSRIs may Impact Bone Density in Adolescent and Young Women with Anorexia Nervosa

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Abstract

Objectives—Alterations in serotonin impact bone metabolism in animal models, and selective serotonin reuptake inhibitors (SSRI) have been associated with increased fracture risk in older adults. SSRIs are commonly used in anorexia nervosa (AN), a condition that predisposes to low bone mineral density (BMD). Our objective was to determine whether SSRI use is associated with low BMD in AN.

Methods—We examined Z-scores for spine, hip and whole body (WB) BMD, spine bone mineral apparent density and WBBMC/height (Ht) in females with AN 12-21 years old who had never been on SSRIs, on SSRIs for <6 months (<6M) or >6 months (>6M).

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Results—Subjects on SSRIs for >6M had lower spine, femoral-neck and WBBMD Z-scores than those on SSRIs for <6M. Hip BMD and WBBMC/Ht Z-scores were lowest in subjects on SSRIs for >6M. Duration of SSRI use, duration since AN diagnosis and duration of amenorrhea inversely predicted BMD, whereas BMI was a positive predictor. In a regression model, duration of SSRI use remained an independent negative predictor of BMD.

Discussion—Duration of SSRI use >6M is associated with low BMD in AN.

Conclusion—It may be necessary to monitor BMD more rigorously when duration of SSRI use exceeds 6M.

Keywords

Anorexia nervosa; SSRIs; serotonin; bone density; selective serotonin reuptake inhibitors

Introduction

Anorexia nervosa (AN), an eating disorder characterized by severe undernutrition, is known to have a significant negative impact on bone health [1-5], and this has been attributed to the associated hypogonadism [6], low IGF-1 levels [1, 7-9], relative hypercortisolemia [10, 11], alterations in other hormones such as adiponectin, leptin and peptide YY [12-14], and changes in body mass index [1, 3, 15, 16] and lean body mass [17-19]. However, these hormonal and body composition alterations do not account for all the variability in bone mineral density (BMD) in AN, and other determinants of low BMD remain to be determined.

While it is well known that hormones such as leptin and PYY work through neural systems to impact bone metabolism [20], there is an emerging interest in the neurotransmitter serotonin (5-Hydroxytryptamine, 5-HT), because of recent evidence of the presence of a functional serotonergic pathway in bone cells [21-23]. Serotonin is a monoamine neurotransmitter that exerts effects on the central nervous system (CNS), gastrointestinal (GI) tract, and cardiovascular (CV) system [24]. Inhibition of the serotonin transporter (5-HTT) with selective serotonin reuptake inhibitors (SSRIs) in mice has been associated with reduced bone accrual during growth, and mice expressing a null mutation in the gene encoding for the 5-HTT have evidence of decreased bone mineral accrual [25, 26]. Furthermore, a chronic deficiency of tryptophan, an amino acid precursor to serotonin, impairs bone metabolism and accrual in rats [27].

Manipulations of serotonin levels in the CNS affect behavior and cognition [19], and serotonergic pathways have been effectively targeted for pharmacological therapies. The SSRIs represent a class of widely prescribed anti-depressant medications that are commonly used in populations at risk of compromised bone health, including patients suffering from eating disorders [1-4, 7] and major depressive disorders [28]. Therefore, assessment of the impact of SSRI use on bone metabolism in these populations is important. Recent studies report increased fracture risk and lower bone density in older men and women on SSRIs for depressive disorders [29-31]. However, data are lacking in adolescents and young women taking these medications.

Importantly, the adolescent years are a common time for the onset of eating disorders, and SSRI use is very prevalent in adolescents suffering from AN [5]. The pubertal years are also very critical for bone accrual, and represent a very narrow window in time in which to optimize gains in bone mass towards attainment of peak bone mass, an important determinant of bone health and fracture risk in later life. Therefore, it is especially important to consider the effect of SSRI use on bone health in the adolescent population.

No studies to date have examined the effect of SSRIs, which potentially cause pharmacological alterations in serotonin levels, on bone in adolescents and young women. In this study, we examined the potential impact of SSRI use on BMD in girls and young women with AN 12-21 years old, and we show that duration of SSRI use is a significant and independent predictor of low BMD in AN.

Subjects and Methods

Subject Selection

Subjects included 137 girls and young women meeting DSM-IV criteria for diagnosis of AN [32] between 12 and 21 years old. Diagnosis of AN was confirmed by a clinical interview with the study psychiatrist. These women were recruited through referrals from primary care providers, nutritionists, psychiatrists and therapists, and also from day-treatment eating disorder programs in and around Boston. Informed consent was obtained from all subjects. For subjects younger than 18 years, consent was obtained from parents and assent from the subjects. Our Institutional Review Board approved the study.

We obtained detailed information regarding the type of SSRI medication used, duration of use, and medication dosage. Subjects were divided into three groups based on the duration of SSRI use, resulting in 95 subjects who had never taken an SSRI at the time of data collection (SSRI-0), 38 subjects who had been on an SSRI for less than six months at the time of data collection (SSRI<6M), and 22 subjects who had been taking an SSRI for longer than six months at the time of data collection (SSRI>6M). Medications recorded in subjects' histories and classified as SSRIs were fluoxetine, fluoxetine with olanzapine, paroxetine, duloxetine hydrochloride, sertraline hydrochloride, citalopram, escitalopram, venlafaxine and fluvoxamine maleate.

Experimental Protocol

All subjects were evaluated during a single outpatient visit to our Clinical Research Center. A complete history and physical examination was performed, and blood drawn for FSH and TSH levels to ensure that amenorrhea was not a consequence of thyroid dysfunction or premature ovarian failure. A single Harpenden stadiometer was used to measure heights of subjects, using an average of three measurements. Weight was measured on a single electronic scale, with the subject in a hospital gown. BMI was calculated using the formula [weight (in kilograms)]/ [height (in meters)] ^{2}. Bone age (obtained for subjects ≤ 18 years old) was assessed using the methods described by Greulich and Pyle [33] by a single investigator (a pediatric endocrinologist) to reduce interobserver variation. Nutritionists at the Clinical Research Center obtained exercise history from subjects using the Modified

Activity Questionnaire, and information regarding calcium and vitamin D intake using a Calcium Food Frequency Questionnaire.

Measurements of lumbar spine (L1-4), hip, and whole body (WB) BMD were obtained using dual-energy x-ray absorptiometry (DXA) (4500A fan-beam densitometer, software version 11.2; Hologic, Waltham, MA). We also calculated height-adjusted measures of bone density including bone mineral apparent density (BMAD) of the lumbar spine (L2-4) [34] and WB BMC/height (WB BMC/Ht). Body composition measures, including lean and fat mass values, were measured using the same equipment. Z-scores for BMD were calculated using reference databases available to Hologic [35], while Z-scores for BMAD of the spine and WB BMC/Ht were obtained using an online applet (http://www-stat-class.stanford.edu/pediatric-bones/). Coefficients of variation for spine BMD and WB BMD were 1.1% and 0.8% respectively. Coefficients of variation for fat and lean mass were 2.1% and 1.0%.

Statistical Methods

Data were analyzed using the statistical software JMP 5.0.1 (SAS institute, Inc, Cary, NC), and are reported as means ± S.D. P values of <.0.05 were considered significant and trends (p values between 0.05 and 0.10) are also reported. Analysis of variance was used to determine differences between groups (based on duration of SSRI use) and a Tukey-Kramer test was employed to correct for multiple comparisons. We performed simple correlation analysis to determine associations between bone density measures and duration of SSRI use, duration since diagnosis of AN, BMI, and duration since last menses. Because subjects with longer duration since diagnosis of AN may be more likely to be on SSRIs, we considered this variable to be a potential confounder of any detected associations between bone density measures and duration of SSRI use. BMI was used as an indicator of nutritional status, and duration of amenorrhea as an indicator of hypgonadism, both of which are important determinants of low BMD in AN.

We next performed mixed model stepwise regression analysis to determine independent predictors of bone density measures (p=0.10 to enter and leave the model), and variables included in the regression model were age, BMI, duration since diagnosis of AN, duration of amernorrhea, and duration of SSRI use. This analysis was selected in order to account for potentially confounding variables and to minimize the masking of associations of various independent variables with dependent variables from confounders.

Results

Baseline Characteristics

No difference was observed in bone age, percent ideal body weight, Tanner stage or duration of amenorrhea between subjects who had never been on an SSRI (SSRI-0), subjects who had been on an SSRI for less than 6 months (SSRI<6M), and subjects who had been on an SSRI for longer than 6 months (SSRI>6M) (Table 1). Subjects in the SSRI-0 group were younger than those in the SSRI>6M group, while there was no difference in age between SSRI<6M and the other two groups. Compared with SSRI-0, subjects in the SSRI<6M group had a higher BMI. However, the BMI of subjects in the SSRI>6M group did not differ

significantly from either group. Finally, duration since diagnosis of AN was significantly longer in SSRI>6M than for SSRI-0 or and SSRI<6M. Exercise activity, calcium and vitamin D intake did not differ between the groups (data not shown).

Bone Density Measures

Subjects who had been on an SSRI>6M had significantly lower spine, femoral neck and WB BMD Z-scores than subjects who had been on an SSRI<6M (Table 2.). Spine BMAD Z-scores did not differ between the groups. Hip BMD and WB BMC/Ht Z-scores were lower in subjects on an SSRI>6M compared with subjects in the other two groups.

Predictors of Bone Density Measures

Table 3 shows data from simple correlation analysis examining associations between bone density measures and co-variates of interest for the group as a whole. Overall, BMI was a positive predictor of BMD Z-scores, while duration since diagnosis of AN, duration of amenorrhea and duration of SSRI use were negative predictors of BMD Z-scores.

Regression Modeling

We next performed regression modeling to determine independent predictors of bone density Z-scores for the group as a whole. We first entered BMI, age, duration of amenorrhea and duration of SSRI use in the regression model (Table 4). An alternate regression model was next created in which we replaced duration of amenorrhea with duration since diagnosis of AN (Table 5). In both models, duration of SSRI use was a significant negative predictor of BMD Z-scores at most sites, while BMI was the most significant positive predictor. Finally, we ran an alternate regression model in which we substituted BMI with lean mass. Independent predictors of BMD Z-scores did not change significantly in this model.

Discussion

We have demonstrated that girls and young women with AN between the ages of 12 and 21 years who have taken an SSRI for longer than six months have lower BMD Z-scores than those who have either never used an SSRI or used this for less than six months. We have also shown that duration of SSRI use is a negative predictor of BMD Z-scores, independent of other predictors such as age, BMI, duration since diagnosis of AN or duration of amenorrhea.

Although a functional serotoninergic pathway has been demonstrated to exist in a variety of bone cells including osteoblasts, osteocytes, and osteoclasts [26], a definitive explanation for the observed effects of SSRIs on bone remains elusive at this time, and the origin and regulation of the serotonin in bone remain largely unknown. Data indicate that inhibition of the serotonin transporter 5-HTT (either from a mutation in the transporter or from use of an SSRI) is associated with decreases in bone mineral accrual via a reduction in bone formation [26], and increased levels of circulating gut serotonin caused by inhibition of the LDL-receptor related protein 5 (LRP5) are associated with reduced bone mass [36]. However, serotonin is known to be produced and function in the CNS, the GI tract, and the

cardiovascular system, and the extent to which serotonin in each of these systems affects bone remains unclear.

Normalizing blood serotonin levels in lrp5 knockout mice with a reduced tryptophan diet can normalize bone function and restore bone mass in these knockout mice [36]. The reduced tryptophan diet decreases circulating serotonin levels 8 to 10 fold, but does not affect serotonin content in the CNS. These findings suggest that brain serotonin may not be a major factor in the observed effects of serotonin on bone. However, SSRIs are assumed to mainly affect serotonin reuptake in the brain. It is unclear at this time whether SSRIs have a more widespread effect on the activity of 5-HTT in the body, especially at peripheral sites.

An important finding in our study is that duration of SSRI use, and not SSRI use alone, predicts reduced bone density. This is contrast to studies in older men and women, in whom SSRI use *per se* has been associated with lower bone density and increased fracture risk [29-31]. Interestingly, Gustafsson *et al.* showed *in vitro* that administration of an SSRI (fluoxetine) at a low concentration (0.01 micromoles) had a stimulatory effect on MC3T3 – E1 (osteoblastic lineage) cell proliferation. However, when administered at high concentrations (1-10 micromoles) a marked inhibitory effect was seen [37]. This bimodal effect of SSRI therapy may explain the difference in BMD Z-scores observed in subjects using SSRIs for varying durations. As an example, spine, femoral neck and WB BMD Z-scores were slightly higher in subjects who had been on SSRIs for less than six months as compared to subjects who had never been on an SSRI, although this was not statistically significant (Table 2). In contrast, BMD Z-scores were significantly lower in girls and women who had been on higher cumulative doses of SSRIs from having used these for longer than six months.

One large study of adults 17 years and older found no association between use of antidepressants and low bone density. However, a dose or duration effect was not examined [38]. In contrast, some studies in adults have demonstrated a dose effect [39, 40], and one study suggested a duration effect [41] of SSRIs on bone density. Importantly, in our study, SSRI use was associated with a greater impact on bone density at non-vertebral sites than vertebral sites, and increased risk of low bone density at the hip has been reported in some [29, 39, 42], but not all studies in adults [43].

Importantly, it is difficult to rule out the phenomenon of confounding by indication in cross-sectional studies, and given that depression is an independent risk factor for low bone density, it is unclear whether low bone density is a consequence of the underlying disorder necessitating SSRI use i.e. depression, or a consequence of the treatment for depression i.e. use of SSRIs. However, at least one study in adult men indicates that SSRI use is associated with low bone density independent of associated depression [31]. Of importance, similar studies to ours are necessary in patients with major depressive disorders to determine the impact of SSRIs on bone density in patients receiving SSRIs for depression. Prospective studies are also necessary to determine whether it is important to monitor bone density over time in patients with major depressive disorders receiving SSRIs. Another consideration is the important therapeutic role of SSRIs in the treatment of major depressive disorders, and

that the benefits of these medications likely outweigh the potential risk of low bone density at this time.

Limitations of our study include its cross-sectional nature and our inability to measure serotonin levels centrally or peripherally. In addition, our study did not assess fracture risk associated with SSRI use. However, our study does indicate the need for future prospective studies examining the impact of SSRIs on bone in adolescents and young adults. This is particularly important because patients commonly prescribed SSRIs often suffer from conditions such as depression or eating disorders that potentially predispose them to low bone density. It is also essential to study the impact of SSRIs on bone mass accrual in adolescents given the prevalence of use of these medications in this age group, and because the adolescent years are critical for attainment of peak bone mass.

Conclusion

We thus demonstrate lower BMD Z-scores in girls and young women with AN between 12-21years old who have been on an SSRI for more than six months, when compared with subjects who have taken an SSRI for less than six months or have never been on an SSRI. Duration of SSRI use is a significant independent predictor of reduced BMD Z-scores even after controlling for duration since diagnosis of AN, duration of amenorrhea, BMI and age. These findings support the current evidence for the presence of a functional serotonergic pathway in bone, and the potential of SSRI medications to affect bone density when given for a prolonged period. More studies are necessary to determine whether it will be important to monitor bone density in patients receiving SSRIs for long periods of time.

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Focus Points

- Use of SSRIs for more than six months is associated with low bone density at multiple sites in anorexia nervosa
- A longer duration of SSRI use, a longer duration of anorexia nervosa and low weight may be deleterious to bone health
- Prolonged SSRI use affects bone health independent of duration of anorexia nervosa and low weight
- Clinicians should consider monitoring bone density closely in women who have been on SSRIs for longer than six months

Table 1

Baseline Characteristics of Low Weight Females Never on SSRI, on SSRI Less than 6 Months, and on SSRI Greater than 6 Months

Baseline Characteristics	Subjects Never on SSRI N=95	Subjects on SSRI <6M N=38	Subjects on SSRI >6M N=22	P value
Age (years)	16.6 ± 1.8[a]	17.0 ± 2.3	17.9 ± 2.1	0.03
Bone age (years)	15.9 ± 1.4	16.2 ± 1.8	16.0 ± 1.1	NS
BMI (kg/m^2)	16.98 ± 1.17[b]	17.50 ± 1.03	17.27 ± 1.69	0.05
% Ideal Body Weight	82.8 ± 5.1	84.8 ± 4.1	83.2 ± 6.2	NS
Tanner Stage	4.6 ± 0.7	4.5 ± 0.8	4.7 ± 0.6	NS
Duration since diagnosis (months)	13.8 ± 17.1[a]	11.1 ± 11.7[a]	31.3 ± 31.2	0.0003
Duration of amenorrhea (months)	7.6 ± 8.5	8.6 ± 8.8	11.6 ± 21.9	NS

NS indicates not significant

Mean ± SD

ANOVA followed by the Tukey-Kramer test to adjust for multiple comparisons

[a] $p < 0.05$ compared with females on SSRI > 6M

[b] $p < 0.05$ compared with females on SSRI <6M

Table 2

Bone Density Measures for Low Weight Females Never on SSRI, on SSRI less than 6 months, and on SSRI greater than 6 months

	Never on SSRI (N=95)	On SSRI <6M (N=38)	On SSRI >6M (N=22)	P
Lumbar BMD Z-score	−1.16 ± 1.05	−0.83 ± 0.82 [a]	−1.70 ± 0.77	0.006*
Lumbar BMAD Z-score	−1.38 ± 0.89	−1.19 ± 0.85	−1.62 ± 0.67	NS
Hip BMD Z- score	−0.67 ± 0.94 [a]	−0.45 ± 0.73 [a]	−1.31 ± 0.91	0.003*
Femoral Neck BMD Z-score	−0.81 ± 1.03	−0.59 ± 0.79 [a]	−1.35 ± 0.83	0.02*
WB BMD Z-score	−0.49 ± 1.03	−0.17 ± 0.90 [a]	−0.85 ± 1.07	0.05*
WB BMC/Ht Z-score	−0.84 ± 0.72 [a]	−0.59 ± 0.60 [a]	−1.41 ± 0.75	0.0002*

NS indicates not significant

Mean ± SD

ANOVA followed by the Tukey- Kramer test to adjust for multiple comparisons

[a] $p<0.05$ compared with females on SSRI > 6M (Tukey- Kramer test to adjust for multiple comparisons)

* Significant after controlling for duration since diagnosis or duration of amenorrhea

Table 3

Correlation coefficients for association of bone mineral density Z-Scores with BMI, duration since diagnosis of AN, duration of amenorrhea, and duration of SSRI use

	BMI		Duration since diagnosis		Duration of amenorrhea		Duration of SSRI use	
	r	p	r	p	r	p	r	p
Lumbar BMD Z-score	0.26	0.01	−0.35	0.001	−0.28	0.01	−0.35	0.0008
Lumbar BMAD Z-score	0.30	0.005	−0.25	0.03	−0.23	0.05	NS	NS
Hip BMD Z-score	0.36	0.0006	−0.47	<0.0001	−0.31	0.006	−0.49	<0.0001
Femoral Neck BMD Z-score	0.33	0.002	−0.40	0.0002	−0.26	0.02	−0.46	<0.0001
WB BMD Z-score	NS	NS	−0.35	0.001	NS	NS	−0.25	0.02
WB BMC/Ht Z-score	0.24	0.02	−0.41	0.0002	−0.26	0.02	−0.5	<0.0001

NS indicates not significant

Table 4

Regression modeling to determine independent predictors of BMD Z-scores (Parameters entered in model: Duration of amenorrhea, BMI, age, duration of SSRI use)

	Parameter estimate	F ratio	p value	r^2	Cumulative r^2
Lumbar BMD Z score					
SSRI Duration	−0.025	9.59	0.001	0.14	
BMI	0.145	4.44	0.04	0.05	0.19
Lumbar BMAD Z score					
BMI	0.161	4.92	0.03	0.06	0.06
Hip BMD Z score					
SSRI Duration	−0.031	22.19	<0.0001	0.26	
BMI	0.191	11.78	0.001	0.11	0.37
Femoral Neck BMD Z score					
SSRI Duration	−0.030	18.50	<0.0001	0.23	
BMI	0.189	10.11	0.002	0.10	0.33
Femoral Neck BMAD Z score					
BMI	0.175	4.36	0.02	0.08	
SSRI Duration	−0.018	3.07	0.08	0.04	0.11
WB BMD Z score					
SSRI Duration	−0.030	9.88	0.01	0.09	
Age	0.114	4.14	0.046	0.05	0.14
WB BMC/Ht Z score					
SSRI Duration	−0.028	20.52	<0.0001	0.26	
BMI	0.118	5.02	0.03	0.05	0.31

Table 5

Regression modeling to determine independent predictors of BMD Z-scores (Parameters entered in model: Duration since diagnosis, BMI, age, duration of SSRI use)

	Parameter estimate	F ratio	p value	r^2	Cumulative r^2
Lumbar BMD Z-score					
SSRI Duration	−0.031	15.81	<0.0001	0.21	
BMI	0.142	5.83	0.02	0.06	0.26
Lumbar BMAD Z-score					
SSRI Duration	−0.020	5.21	0.007	0.09	
BMI	0.144	5.14	0.03	0.06	0.15
Hip BMD Z-score					
SSRI Duration	−0.022	5.28	<0.0001	0.30	
BMI	0.184	12.66	0.002	0.08	
Duration Since Dx	−0.011	4.88	0.03	0.04	0.42
Femoral Neck BMD Z-score					
SSRI Duration	−0.034	19.49	<0.0001	0.24	
BMI	0.159	7.73	0.007	0.07	0.31
Femoral Neck BMAD Z-score					
BMI	0.148	3.82	0.03	0.06	
Duration since Dx	−0.012	4.90	0.09	0.03	
Age	0.126	4.69	0.03	0.05	0.15
WB BMD Z score					
SSRI Duration	−0.040	18.06	0.0003	0.16	
Age	0.107	4.20	0.04	0.04	0.20
WB BMC/Ht Z-score					
SSRI Duration	−0.035	30.77	<0.0001	0.33	
BMI	0.098	4.41	0.04	0.04	0.37

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