A Cross-Sectional Evaluation of the Effect of Risperidone and Selective Serotonin Reuptake Inhibitors on Bone Mineral Density in Boys

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Objective: The aim of the present study was to investigate the effect of risperidone-induced hyperprolactinemia on trabecular bone mineral density (BMD) in children and adolescents.

Method: Medically healthy 7- to 17-year-old males chronically treated, in a naturalistic setting, with risperidone were recruited for this cross-sectional study through child psychiatry outpatient clinics between November 2005 and June 2007. Anthropometric measurements and laboratory testing were conducted. The clinical diagnoses were based on chart review, and developmental and treatment history was obtained from the medical record. Volumetric BMD of the ultradistal radius was measured using peripheral quantitative computed tomography, and areal BMD of the lumbar spine was estimated using dual-energy x-ray absorptiometry.

Results: Hyperprolactinemia was present in 49% of 83 boys (n = 41) treated with risperidone for a mean of 2.9 years. Serum testosterone concentration increased with pubertal status but was not affected by hyperprolactinemia. As expected, bone mineral content and BMD increased with sexual maturity. After adjusting for the stage of sexual development and height and BMI *z* scores, serum prolactin was negatively associated with trabecular volumetric BMD at the ultradistal radius ($P < .03$). Controlling for relevant covariates, we also found treatment with selective serotonin reuptake inhibitors (SSRIs) to be associated with lower trabecular BMD at the radius ($P = .03$) and BMD *z* score at the lumbar spine ($P < .05$). These findings became more marked when the analysis was restricted to non-Hispanic white patients. Of 13 documented fractures, 3 occurred after risperidone and SSRIs were started, and none occurred in patients with hyperprolactinemia.

Conclusions: This is the first study to link risperidone-induced hyperprolactinemia and SSRI treatment to lower BMD in children and adolescents. Future research should evaluate the longitudinal course of this adverse event to determine its temporal stability and whether a higher fracture rate ensues.

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The overlap between psychiatric and medical conditions is increasingly appreciated as are the long-term sequelae of psychotropics on various bodily systems.[1] With preventive interventions playing an ever more central role in medical care, mental health professionals are called upon to investigate the potential effects of psychopharmacology, during extended use, in order to optimize patient safety.

Many diseases associated with high morbidity and mortality have their onset in childhood and adolescence. One such condition is osteoporosis, currently estimated to affect around 3%–4% of the US population with billions of dollars in annual costs related to fractures and disability.[2] In fact, most skeletal mass is accrued during the first 2 decades of life.[3,4] Moreover, age-related bone loss is directly associated with peak bone mineral density (BMD), with even a moderate reduction in it significantly increasing the incidence of fractures.[2,5]

As a result, investigating the effect of psychotropics on BMD in youths is important not only because failure to reach optimal bone mass by young adulthood may lead to osteoporosis[2] but also because, in children and adolescents with chronic psychiatric disorders, polypharmacy is common with any number of medications that can modulate various central and peripheral regulatory systems involved in bone mineralization.[1,6]

Low spinal BMD has been reported in patients with prolactin-secreting pituitary adenomas.[7,8] Consequently, due to the propensity of several antipsychotics to block the dopamine D_2 receptor in the anterior pituitary, thus leading to hyperprolactinemia, concerns have been raised about the potential for long-term antipsychotic-induced hyperprolactinemia to affect BMD. In fact, in adults with schizophrenia, hyperprolactinemia induced by typical antipsychotics and risperidone has been associated with reduced BMD and increased fractures.[9–13] However, despite the widespread use of antipsychotics in children and adolescents,[6] to our knowledge, this question has not been investigated in the pediatric population.

Compared to cortical bone, which is present in the shaft of long bones, trabecular bone appears more vulnerable to hormonal abnormalities (eg, hyperprolactinemia or menopause).[8,14,15] Trabecular bone is found at the end of long bones and in flat bones, like the vertebrae. Dual-energy x-ray absorptiometry (DXA) is the most commonly used technique to measure BMD, yet it does not isolate trabecular from cortical bone[8,14,15] and, as a result, might lack the sensitivity needed to detect the effects of hyperprolactinemia on BMD. In addition, DXA generates a bidimensional projectional image of a tridimensional structure,[8,14,15] which makes it susceptible to inaccuracies in children who have not reached their final height.[15] Both of these shortcomings do not apply to a relatively novel technique, peripheral quantitative computed tomography (pQCT), which can be used to estimate BMD in the limbs, exposing the subjects to negligible radiation.[8,14,15]

Because risperidone is commonly prescribed in youths with psychiatric disorders and is one of the antipsychotics that most often induce hyperprolactinemia,[16,17] we recruited children and adolescents in relatively long-term risperidone treatment to examine the effects of serum prolactin concentration on BMD. Since we collected their complete treatment history, we also investigated the effect of selective serotonin reuptake inhibitors (SSRIs) on BMD, as they have been associated with bone loss,[18] reduced BMD,[19] and increased fracture risk in older adults.[20]

METHOD

Subjects

Participants, 7 to 17 years old, treated with risperidone for ≥ 6 months, irrespective of diagnosis and indication, were recruited from psychiatry outpatient clinics between November 2005 and June 2007 for this cross-sectional evaluation. Subjects concomitantly treated with other antipsychotics were excluded as were patients with conditions that could interfere with normal pituitary function.[21]

Procedures

This study was approved by the University of Iowa Institutional Review Board. Written assent was obtained from children ≤ 11 years old, and consent was obtained from adolescents and all parents or legal guardians.

The clinical diagnoses were based on chart review. In addition to the start and stop times of each medication, all changes in the dosage and formulation were recorded.[16,21] Upon recruitment, all participants were queried about adherence to their psychiatric medications, smoking, and calcium and multivitamin supplementation.

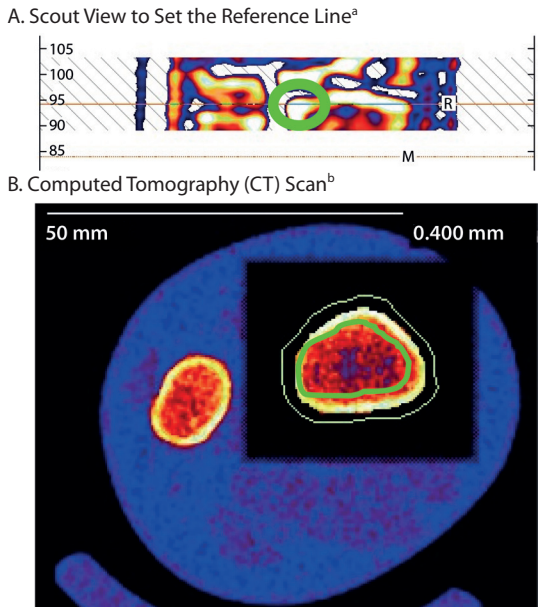
Daily calcium and vitamin D intake during the week prior to enrollment was estimated using the 2004 Block Kids Food Frequency Questionnaire.[22] This questionnaire includes 77 food items, based on the dietary recall data of the National Health and Nutrition Examination Surveys (NHANES; 1999–2002).[22] Physical activity was assessed by asking the parent to compare the child's usual level of physical activity to his peers' using a 5-point Likert scale.[23]

Upon enrollment, pubertal stage was evaluated by physical examination as well as a self-completed form that included pictures depicting Tanner stages I through V.[24] Interrater agreement between the physician and self-rating was high (weighted $\kappa = 0.81$, [95% confidence interval (CI), 0.74–0.88], n = 74). Height was measured to the nearest 0.1 cm using a stadiometer while the participant was standing erect (Holtain Ltd, Crymych, United Kingdom), and weight was recorded to the nearest 0.1 kg using a digital scale (Scaletronix, Wheaton, Illinois) while the participant was wearing indoor clothes without shoes. Age- and gender-specific *z* scores for height, weight, and body mass index (BMI) were calculated using the Centers for Disease Control and Prevention normative data.[25]

In 93% (n = 77) of the subjects, a morning fasting blood sample was obtained to measure thyroid-stimulating hormone (TSH), prolactin, testosterone, and risperidone concentrations. In the other 7% (n = 6), a nonfasting sample was collected. Prolactin was measured by electrochemiluminescence immunoassay. Based on the upper range of normal of this assay, hyperprolactinemia was defined as a prolactin level > 18.4 ng/mL. Patients with undetectable combined serum risperidone and 9-hydroxyrisperidone concentration, reflecting nonadherence (n = 2), were excluded from the analysis.

Volumetric BMD (vBMD) at the nondominant ultradistal radius was measured with pQCT using a Stratec XCT-2000 scanner (Stratec, Inc, Pforzheim, Germany). In the absence of a history of fracture, measurements were performed on the nondominant forearm. A scout view was obtained to determine the reference line. A virtual circle was then drawn to include the medial tip of the growth plate, when present, or of the endplate. The reference line bisected this virtual circle (Figure 1A). Next, a single computed tomography (CT) slice, of 2.4 mm thickness, at a voxel size of 0.4 mm, speed of translational scan movement of 30 mm/s, was obtained at a site proximal to the reference line by a distance corresponding to 4% of the forearm length (measured from the elbow to the ulna styloid process) (Figure 1B). Image analysis was performed using the manufacturer's software package, version 6.0, with the following parameters: contour mode 3, peel mode 4, and bone threshold 650 mg/mm^3. Trabecular vBMD was measured as the mean density of the 90% central area of the bone's cross-section (ie, 10% inward from the endosteum). Due to partial volume effect related to the thin cortical shell (< 2 mm), cortical bone was not analyzed.[26] However, total vBMD was determined. It combines cortical and trabecular bone, reflecting the mineral density of the entire bone volume at the 4% site (Figure 1B). A Hologic QDR DELPHI-4500A unit (Hologic, Inc, Bedford, Massachusetts) was used to estimate the total cross-sectional area, bone mineral content (BMC), and areal BMD (aBMD) in the lumbar spine (L1–L4).

Figure 1. Peripheral Quantitative Computed Tomography (pQCT) Measurement at the Ultradistal Radius (Right Forearm)



[a]A scout view is first obtained. A virtual circle (bright green) is then drawn to include the medial tip of the growth plate of the radius, when present, or of the endplate. The reference line bisects this virtual circle.
[b]A bright green circle is drawn on this CT scan to illustrate how pQCT isolates trabecular (central area) from cortical (yellow rim) bone. Total volumetric bone mineral density represents the mean mineral density of trabecular and cortical bone.

Individual measurements were converted into age- and gender-adjusted *z* scores using the manufacturer-supplied software and normative values. Quality-control and calibration of the equipment were performed daily.

Statistical Analysis

Since BMD is under a strong gender effect[27] and since the number of females in our study was small (n = 12), we restricted the analysis to boys. Differences between boys with and without hyperprolactinemia in demographic and clinical variables were compared using the Student *t* test for continuous variables and the Fisher exact test for categorical ones. The Kolmogorov-Smirnov test was used to test the assumption of normality. If this was violated, we used Wilcoxon rank sum test.

Our primary hypothesis was that prolactin concentration will be inversely associated with trabecular vBMD, measured by pQCT at the distal radius with secondary analyses investigating the effect of prolactin on the other pQCT- and DXA-based variables. These variables included total vBMD and cross-sectional area at the ultradistal radius site and the cross-sectional area, total BMC, total aBMD, and total aBMD *z* score at the lumbar spine (L1–L4).

In order to test our hypotheses, multiple linear regression was used initially with individual pQCT- and DXA-based variables as the dependent variable and prolactin concentration and Tanner stage as predictor variables. These models sought to first establish the presence of a linear association between prolactin and bone metabolism while controlling for the stage of sexual development, a major determinant of BMD.[14,15] Next, additional covariates were added to each model. These were selected based on their known association with bone mineralization and included height, weight, and BMI *z* scores; estimated daily calcium and vitamin D intake; and physical activity. In addition, we used the duration of risperidone treatment as a surrogate for the duration of hyperprolactinemia. Among this group of covariates, we included in each regression model predicting individual bone-related variables those factors that were correlated with the dependent variable at a *P* value < .2. This lenient significance level was used so that potentially important covariates were not excluded while, at the same time, the number of covariates included in each model was restricted due to the limited sample size.

As noted earlier, SSRIs have been shown to interfere with bone mineralization.[18–20] Therefore, in a final set of analyses, we also controlled for SSRIs as a binary covariate, reflecting SSRI treatment status upon enrollment. In order to standardize the doses across the different SSRIs, to reflect each participant's daily dose, we defined one SSRI unit as being equivalent to a daily dose of 20 mg of fluoxetine, paroxetine, or citalopram; 50 mg of sertraline or fluvoxamine; 10 mg of escitalopram; or 12.5 mg of controlled-release paroxetine. All tests were 2-tailed. All analyses were conducted using SAS version 9.1.3 (SAS Institute, Inc, Cary, North Carolina).

RESULTS

Clinical Sample

Of 88 recruited boys, 1 refused the blood draw, 2 were nonadherent to risperidone (based on undetectable serum concentration), and 2 declined the bone measurements. Thus, 83 participants were included in the analyses. Their mean age was 11.9 years (SD = 2.8, range, 7.3–17.2 years) (Table 1). By enrollment, they had been in treatment with risperidone for an average of 2.9 years (SD = 1.9, range, 0.5–8.3 years) and were receiving 0.03 mg/kg (SD = 0.02, range, 0.002–0.11 mg/kg) of risperidone daily. Most participants carried more than 1 clinical diagnosis (median = 2, range, 2–3), including attention-deficit/hyperactivity disorder (ADHD; 87%, n = 72), disruptive behavior disorders (64%, n = 53), anxiety disorders (36%, n = 30), mood disorders (24%, n = 20), tic disorders (20%, n = 17), pervasive developmental disorders (18%, n = 15), and psychotic disorders (2%, n = 2). Risperidone was used to target irritability and aggression in 80% (n = 66) of the cases. Other indications included impulsivity and treatment-refractory ADHD (7%, n = 6), tics (8%, n = 7), obsessive-compulsive disorder (2%, n = 2), insomnia (1%, n = 1), and suicidality (1%, n = 1). In addition to risperidone, psychostimulants (67%, n = 56),

Table 1. Demographic and Clinical Characteristics of Subjects With Normal and High Prolactin Concentration

	Normal Prolactin (n = 42)	High Prolactin (n = 41)	Statistical Analysis	*P* Value[a]
Characteristic				
Race/ethnicity, % non-Hispanic white/African American/Hispanic/other	83/12/2/2	88/7/2/2	Fisher exact	.9
Age, mean ± SD, y	11.8 ± 2.8	11.9 ± 3.0	$t_{81} = .1$	.96
Pubertal status, % at Tanner stage I/II/III/IV/V	44/17/15/22/2	27/24/17/20/12	Wilcoxon = 1858	> .1
Height *z* score, mean ± SD	0.1 ± 0.9	0.3 ± 0.9	$t_{81} = 1.2$	.2
Weight *z* score, mean ± SD	0.4 ± 1.0	0.6 ± 1.0	$t_{81} = .9$	.4
Body mass index *z* score, mean ± SD	0.5 ± 1.0	0.6 ± 1.0	$t_{81} = .6$	.6
Cigarette smoking, n (%)	0	4 (10)	Fisher exact	***.06***
Calcium intake, mean ± SD, mg/d	1024 ± 400	1050 ± 340	$t_{80} = .3$	.8
Vitamin D intake, median (quartiles), IU/d	274 (179–365)	259 (203–373)	Wilcoxon = 1704	.7
Physical activity, median (quartiles)	4.0 (3.0–4.0)	3.0 (2.0–5.0)	Wilcoxon = 1695	.8
Elevated TSH, n (%)[b]	2 (5)	10 (24)	Fisher exact	**< .02**
Prolactin, median (quartiles), ng/mL	12.9 (8.3–16.0)	28.5 (23.2–42.4)	Wilcoxon = 2583	**< .0001**
Testosterone, median (quartiles), ng/dL	57.0 (6.0–313.0)	47.0 (15.0–382.0)	Wilcoxon = 1804	> .3
Pharmacotherapy				
Risperidone dose, mean ± SD, mg/kg/d	0.03 ± 0.01	0.04 ± 0.02	$t_{64} = 3.56$	**.002**
Risperidone treatment duration, median (quartiles), y	2.8 (1.1–3.9)	2.7 (1.7–3.8)	Wilcoxon = 1748	.8
SSRI treatment, n (%)	20 (48)	24 (59)	Fisher exact	.4
SSRI dose, median (quartiles)[c]	1.0 (0.5–1.5)	1.0 (0.8–1.9)	Wilcoxon = 422	.5
SSRI treatment duration, mean ± SD, y	2.9 ± 2.2	3.5 ± 1.6	$t_{42} = 1.03$	.3

[a]Statistically significant findings are in bold. Findings that are at a trend level are in bolded italics.
[b]The normal range for thyroid-stimulating hormone is 0.27–4.20 μIU/mL. In no cases was TSH > 7.0 μIU/mL.
[c]In order to compute a mean SSRI dose across the different medications available, we converted each patient's daily dose into an SSRI-unit equivalent (see text for details).
Abbreviations: SSRI = selective serotonin reuptake inhibitor, TSH = thyroid-stimulating hormone.

SSRIs (54%, n = 45), and α_2 agonists (27%, n = 22) were the most commonly prescribed medications. No differences were found between subjects with and those without hyperprolactinemia except for the former group receiving a higher daily dose of risperidone per kg of body weight and being more likely to have an elevated TSH concentration (normal range, 0.27–4.20 μIU/mL; see Table 1). These abnormalities were mild with no subject having a concentration higher than 7.0 μIU/mL. There was also a trend for subjects with hyperprolactinemia to smoke cigarettes more often. Of the 4 participants who smoked, 2 smoked 0.5 cigarette per day, 1 smoked 4 per day, and 1 smoked 20 per day. Excluding smokers and subjects with elevated TSH did not appreciably alter the findings.

Prolactin and Testosterone

Hypogonadism is thought to mediate hyperprolactinemia-related BMD loss in women with prolactin-producing tumors.[8] However, we failed to find a significant correlation between testosterone and prolactin (Spearman rank correlation test $r = 0.1$, $P = .3$, n = 94). In addition, using multiple linear regression to predict testosterone from prolactin concentration after controlling for Tanner stage, we found a strong effect for puberty ($F_{4,87} = 34.8$, $P < .0001$), whereby testosterone sharply increased with advancing sexual development but not for prolactin ($P > .7$). The results were similar when we restricted the analysis to pubertal participants (ie, Tanner stage ≥ II).

Bone Density Measurements

Correlates of pQCT-based measurements. Due to movement artifacts, 6 participants were excluded from the pQCT analyses (2 with hyperprolactinemia and 4 without; the Fisher exact test $P = .7$). Multiple linear regression was initially used to evaluate the association between trabecular vBMD at the ultradistal radius and prolactin concentration, while controlling for Tanner stage. Trabecular vBMD was negatively correlated with prolactin concentration (β = −0.73, 95% CI, −1.34 to −0.13; $P < .02$), which accounted for 7.4% of the variance. Of the potential covariates listed in the statistical analysis section, only height and BMI *z* scores were correlated with trabecular vBMD at a *P* value < .2. Therefore, these variables were entered, along with prolactin and Tanner stage, in the regression model predicting trabecular vBMD. The overall model was significant ($F_{7,68} = 3.5$, $P = .003$) accounting for 26.4% of the variance in trabecular vBMD. Prolactin and height *z* score were negatively associated (β = −0.66, 95% CI, −1.22 to 0.09; $P < .03$ and β = −13.14, 95% CI, −23.49 to −2.78; $P < .02$, respectively), and BMI *z* score was positively associated with trabecular vBMD (β = 14.92, 95% CI, 5.71–24.12; $P < .002$). Tanner stage was not significantly associated with Trabecular vBMD ($P = .13$). In this model, prolactin accounted for 5.9% of the variance in trabecular vBMD. When we also controlled for the duration of risperidone treatment ($P > .8$), a potential surrogate for the duration of hyperprolactinemia, the results remained unchanged.

Racial and ethnic differences in BMD have been well documented.[28] Thus, we repeated the analysis restricting it to non-Hispanic white boys, since they formed the majority of the sample (Table 1). Similar results were found except that, after controlling for the other covariates, the effect of prolactin concentration was more pronounced (Table 2).

We, then, evaluated the effect of prolactin on total vBMD while controlling for Tanner stage. Total vBMD significantly

Table 2. Results of Multivariate Analyses Predicting Trabecular and Total Volumetric Bone Mineral Density in Non-Hispanic White Boys and Adolescents in Extended Risperidone Treatment[a]

Bone Measure	β Estimate	Standard Error	*P* Value[b]
Trabecular volumetric bone mineral density[c]			
Prolactin[d]	−0.82	0.28	**<.006**
Tanner stage I	−45.99	17.65	**<.012**
Tanner stage II	−33.38	17.97	***<.07***
Tanner stage III	−54.26	18.66	**<.006**
Tanner stage IV	−41.73	18.20	**<.03**
Tanner stage V	…	…	…
Body mass index *z* score	17.06	4.72	**.0006**
Height *z* score	−13.75	5.40	**<.014**
Total volumetric bone mineral density[c]			
Prolactin[d]	−0.85	0.41	**<.05**
Tanner stage I	−100.54	23.85	**<.0001**
Tanner stage II	−76.07	23.73	**<.003**
Tanner stage III	−124.92	24.81	**<.0001**
Tanner stage IV	−98.69	24.37	**<.0002**
Tanner stage V	…	…	…
Height *z* score	−35.77	9.42	**<.0004**
Weight *z* score	15.35	8.19	***<.07***
Physical activity	10.04	6.13	<.11

[a]As discussed in the Statistical Analysis section, the covariates included in each model were selected based on their zero-order correlation with the respective dependent variables having a *P* value <.2.
[b]Statistically significant findings are in bold. Findings that are at a trend level are in bolded italics.
[c]Volumetric bone mineral density at the radius was generated using peripheral quantitative computed tomography.
[d]The β estimate reflects the change in the dependent variables for every change in prolactin by 1 ng/mL.

increased with sexual maturation ($P = .002$). This finding was primarily related to Tanner stage V being associated with higher total vBMD compared to all other stages. In addition, prolactin was negatively associated with total vBMD (β = −0.86, 95% CI, −1.67 to −0.04; $P < .04$), accounting for 4.9% of the variance. The participants' level of physical activity as well as height and weight *z* scores were correlated with total vBMD at a *P* value <.2. When these variables were entered in the regression model, prolactin became nonsignificantly associated with total vBMD (β = −0.52, 95% CI −1.35 to 0.31; $P = .22$) with height *z* score being negatively associated with it (β = −27.43, 95% CI, −45.62 to −9.25; $P < .004$). There was a trend for physical activity to be positively associated with total vBMD (β = 9.87, 95% CI, −2.22 to 21.95; $P = .1$), but weight *z* score did not significantly contribute to the model ($P > .3$). Controlling for the duration of risperidone treatment ($P > .9$) did not alter the results. When this analysis was restricted to non-Hispanic white patients, the effect of prolactin became significant (Table 2).

Correlates of DXA-based measurements. We conducted similar analyses using the DXA-generated total lumbar cross-sectional area, BMC, aBMD, and aBMD *z* score. Prolactin concentration was not significantly associated with total lumbar BMC, neither in the reduced model that included only prolactin and Tanner stage nor in the full model that also included duration of risperidone treatment, estimated daily intake of vitamin D, and physical activity. When the analysis was restricted to non-Hispanic white patients, there was a trend for prolactin to be negatively associated with total lumbar BMC in the reduced (β = −0.09, 95% CI, −0.20 to 0.01; $P < .07$), but not full, model. Except for Tanner stage ($P < .0001$), none of the other covariates was significantly associated with total lumbar BMC.

Similarly, we found no association between prolactin and total lumbar BMD either in the reduced model involving prolactin and Tanner stage only or in the full model that also included duration of risperidone treatment and physical activity. This was also the case when the analysis was restricted to non-Hispanic white patients.

There was also no association between prolactin concentration and total lumbar BMD *z* score neither in the reduced model nor in the full one that included, in addition to prolactin and Tanner stage ($P < .04$), weight *z* score (β = 0.60, 95% CI, 0.33–0.87; $P < .0001$), physical activity (β = 0.25, 95% CI, 0.06–0.45; $P = .01$), total daily intake of calcium in grams (β = 0.0005, 95% CI, −0.00007 to 0.001; $P < .09$), and height *z* score (β = −0.19, 95% CI, −0.49 to 0.11; $P = .23$). We found similar results in non-Hispanic white patients.

Finally, we found no effect of prolactin concentration on the cross-sectional area of either the ultradistal radius or the lumbar spine ($P > .5$).

We report, in Table 3, the least square means (standard error) of the different pQCT- and DXA-based variables in non-Hispanic white boys generated by multiple linear regression, while controlling for the relevant covariates. These illustrate the differences in the predicted values of bone measurements across the various stages of sexual development in 2 hypothetical cases, 1 with normal prolactin concentration (12.2 ng/mL) and 1 with a prolactin of 34.4 ng/mL, which is the mean concentration of the individuals with hyperprolactinemia. As can be seen, the difference in trabecular vBMD across those with and without hyperprolactinemia is in the order of 8%–9%.

Effect of SSRI treatment. As we report elsewhere, after adjusting for age (or Tanner stage), the oral dose of risperidone per kg of body weight (or its serum concentration), and the oral dose of psychostimulants per kg of body weight, we found no independent effect of SSRIs on prolactin concentration.[16] Nevertheless, treatment with SSRIs may still directly interfere with bone mineralization.[29,30] Therefore, we repeated the regression analyses, using the full model for each respective bone variable, while controlling also for SSRI treatment status.

When SSRIs were entered in the model predicting trabecular vBMD, while adjusting for prolactin, Tanner stage, and height and BMI *z* scores, the overall pattern of the

Table 3. Least Square Means[a] ± SE of pQCT- and DXA-Based Bone Measurements[b] as a Function of Pubertal Stage in Non-Hispanic White Boys and Adolescents Treated With Risperidone

Prolactin Status[c]	Tanner Stage	Total vBMD (mg/cm^3)[d]	Trabecular vBMD (mg/cm^3)[e]	Lumbar Total BMC (g)[f]	Lumbar Total aBMD (g/cm^2)[g]	Lumbar Total aBMD *z* Score[h]
Normal	I	327.0 ± 12.3	221.4 ± 8.5	26.5 ± 1.6	0.64 ± 0.02	0.25 ± 0.20
Normal	II	351.5 ± 12.6	234.0 ± 9.4	31.7 ± 1.8	0.70 ± 0.02	0.43 ± 0.22
Normal	III	302.7 ± 13.6	213.1 ± 9.5	34.7 ± 2.0	0.71 ± 0.03	−0.31 ± 0.25
Normal	IV	328.9 ± 13.0	225.7 ± 9.5	48.2 ± 1.7	0.86 ± 0.02	−0.16 ± 0.21
Normal	V	427.6 ± 22.1	267.4 ± 16.7	62.6 ± 3.5	0.99 ± 0.04	0.3 ± 0.44
High	I	308.1 ± 11.6	203.2 ± 8.7	24.8 ± 1.6	0.62 ± 0.02	0.32 ± 0.20
High	II	332.6 ± 11.9	215.8 ± 8.7	30.0 ± 1.7	0.67 ± 0.02	0.50 ± 0.21
High	III	283.8 ± 14.8	194.9 ± 10.4	33.0 ± 2.1	0.68 ± 0.03	−0.25 ± 0.26
High	IV	310.0 ± 13.0	207.4 ± 9.8	46.4 ± 1.8	0.84 ± 0.02	−0.09 ± 0.22
High	V	408.7 ± 20.8	249.2 ± 15.4	60.8 ± 3.3	0.97 ± 0.04	0.39 ± 0.42

[a]All least square means were adjusted for stage of sexual development.
[b]vBMD at the radius was generated using pQCT and bone mineral measurements at the lumbar spine were generated using DXA.
[c]The mean prolactin concentration in the group with high (34.4 ng/mL) and normal prolactin (12.2 ng/mL) was used to generate the respective least square means.
[d]Total vBMD at the radius was adjusted for height and weight *z* scores and physical activity.
[e]Trabecular vBMD was adjusted for height and BMI *z* scores.
[f]Lumbar spine BMC was adjusted for physical activity, daily intake of vitamin D, and duration of risperidone treatment.
[g]Lumbar spine aBMD was adjusted for physical activity and duration of risperidone treatment.
[h]Lumbar spine aBMD *z* score was adjusted for height and BMI *z* scores, daily intake of calcium, and physical activity (see text for details).
Abbreviations: aBMD = areal bone mineral density, BMC = bone mineral content, BMI = body mass index, DXA = dual-energy x-ray absorptiometry, pQCT = peripheral quantitative computerized tomography, vBMD = volumetric bone mineral density.

findings remained unchanged except that the estimate of prolactin became smaller (β = −0.52, 95% CI, −1.09 to 0.04; $P < .07$), failing to reach significance, while SSRI treatment was associated with lower trabecular vBMD (β = −19.15, 95% CI, −36.46 to −1.85; $P < .04$). This translated into a medium effect size of 0.55. When the analysis was restricted to non-Hispanic white patients, similar results were found with the effect of prolactin reaching statistical significance (β = −0.67, 95% CI, −1.24 to −0.10; $P < .03$).

We also found a tendency for SSRI treatment to be negatively associated with total vBMD (β = −19.25, 95% CI, −43.16 to 4.65; $P = .11$). This was equivalent to an effect size of 0.40. The results were similar when this analysis was restricted to non-Hispanic white patients except that the effect of prolactin on total vBMD became more prominent (β = −0.75, 95% CI, −1.58 to 0.09; $P < .08$), compared to the same regression analysis with the full model but without covarying for SSRIs (see results above).

SSRI treatment was not associated with total lumbar BMC or BMD. However, it was associated with significantly lower total lumbar BMD *z* score (β = −0.41, 95% CI, −0.82 to 0.01; $P < .05$), after accounting for Tanner stage, height and weight *z* scores, daily intake of calcium, physical activity, and prolactin.

Bone fracture history. We queried the families about bone fractures and reviewed the pediatric records. Of the boys included in the analysis, 13 (16%) had a history of bone fractures (skull, nose, clavicle, and upper and lower extremities). These fractures sometimes occurred in toddlerhood, involving more than 1 skeletal site, as a result of physical abuse. Nine of these fractures occurred before any psychopharmacological treatment was initiated, and 1 occurred 2 years after psychostimulant treatment had been started but before either SSRI treatment or risperidone treatment was started. One left radius fracture occurred 1 month after an SSRI treatment was started but before risperidone treatment was started, another one involving the left radius occurred 5 and 12 months, respectively, after an SSRI and risperidone treatment was started, and 1 fracture involving the distal phalanx of the left ring finger occurred 3.5–4 years after an SSRI and risperidone treatment was started. The latter 3 fractures took place during a football game, a fall from a monkey bar, and a fall off of a chair, respectively. The 2 subjects who sustained fractures while taking risperidone had a normal prolactin concentration upon study enrollment, which took place 14 and 40 months, respectively, following the fractures.

DISCUSSION

To our knowledge, this is the first study to investigate the impact of antipsychotic-induced hyperprolactinemia on BMD at the radius in children and adolescents, finding a negative association. This effect appears more specific to trabecular bone. In further analyses, we also found a prominent effect of SSRI treatment on BMD at the lumbar spine and the ultradistal radius. This, to our knowledge, has also never been reported in youths.

A unique feature of this study is the use of pQCT. The strengths of this technique, as opposed to the traditional DXA, include isolating trabecular from cortical bone and measuring volumetric, rather than areal, BMD.[14,15] These 2 characteristics are important since hormonal abnormalities, such as hyperprolactinemia, initially affect trabecular bone and since volumetric measurements are less susceptible to body size compared to those generated by projectional

methods like DXA.[8,14,15] The limitations of DXA, in this context, perhaps underlie the inconsistent findings from studies investigating the consequences of antipsychotic-induced hyperprolactinemia on BMD in adults.[31,32] It is possible that pQCT is more sensitive than DXA to detect early differences in trabecular vBMD and that, over a more extended duration of hyperprolactinemia, DXA-based measurements will be similarly affected.

As hypothesized, pQCT-generated trabecular vBMD was more sensitive to the negative effect of prolactin on bone mineral accrual, even after taking into account significant confounders. Since total vBMD combines trabecular and cortical vBMD, it is not surprising that it was somewhat less markedly affected by prolactin. In fact, we failed to consistently find a statistically significant association between prolactin and total vBMD after controlling for relevant covariates, though the trend remained in the negative direction. This might reflect a heterogeneity related to the racial/ethnic diversity, albeit small, in our sample since, when the analyses were restricted to non-Hispanic white patients, the findings were more prominent. However, while race and ethnicity are well known to influence BMD,[28] to our knowledge, there is no evidence that they also differentially moderate the effect of prolactin on BMD.

In females with prolactin-secreting tumors, hypogonadism mediates the impact of hyperprolactinemia on BMD.[7,8,33] This was not the case in our sample, in which we found no association between prolactin and total testosterone. Similar results have been reported in males with prolactinomas, the majority of whom progressed through puberty normally, yet had low BMD.[34] This is also consistent with most, but not all, studies in antipsychotic-treated adults with schizophrenia where no correlation was found between prolactin and sex hormones.[9,12,35,36] Moreover, BMD does not necessarily recover following the normalization of gonadal status.[33,34] These findings, combined, suggest that mechanisms other than hypogonadism might be implicated. In fact, a direct effect of hyperprolactinemia on bone turnover in males has been postulated.[34] In addition, recent animal work has not only identified prolactin receptors in osteoblasts, but has also shown that hyperprolactinemia activates the phosphoinositide 3-kinase pathway, through these receptors, to suppress alkaline phosphatase activity.[37] Prolactin also disturbs the expression ratio of receptor activator of nuclear factor κB ligand (RANKL) and osteoprotegerin, which play a critical role in the regulation of bone resorption.[38,39] Such a mechanism would also be in agreement with findings in males with prolactin-secreting tumors of negative correlations between aBMD and osteocalcin on the one hand and prolactin on the other, but not with testosterone.[40] Another potential mechanism involves parathyroid hormone-related peptide, a bone-resorptive agent, which is elevated in lactating women and in patients with prolactin-producing tumors and is negatively associated with lumbar aBMD.[41,42]

Like others,[9,35] we could not find an independent effect of duration of risperidone treatment on BMD. It is possible that this variable does not accurately reflect the duration of hyperprolactinemia due to differences in individual susceptibility to this dose-related side effect and the changes in the dose of risperidone during the course of the treatment, as well as the potential for spontaneous resolution of hyperprolactinemia.[43] On the other hand, it is possible that the duration of hyperprolactinemia is not a critical determinant of bone loss, just as the duration of amenorrhea in patients with prolactin-secreting tumors has not been consistently found to influence the degree of bone loss.[42,44] Others[10,36,45] have found a negative association between BMD in adults and the duration of illness or treatment. However, these analyses did not control for age, which is usually positively associated with duration of illness and treatment and negatively associated with BMD.

Equally significant was our finding that SSRI treatment was associated with reduced BMD both at the ultradistal radius site and in the lumbar spine. SSRIs may increase prolactin, thereby hindering bone mineralization.[46] However, 2 findings from our work suggest that this might not be the case. First, after controlling for development and the dose of risperidone and psychostimulants, we found no independent effect of SSRIs on prolactin concentration.[16] In addition, the negative association between SSRIs and BMD emerged after adjusting for several covariates, including prolactin. Rather, it is likely that SSRIs act directly on the serotonin transporter or, indirectly, on any of the other functional serotonergic receptors that have been identified in osteoblasts, osteoclasts, and osteocytes.[29,47,48] In fact, the serotonin system appears to be implicated in bone metabolism, with in vitro studies revealing that serotonin regulates osteoclast differentiation and activity, promotes preosteoblasts proliferation, and modulates the interaction between osteoblasts and osteoclasts by regulating the release of RANKL and osteoprotegerin.[47,49] Moreover, controlled experiments in mice have associated the use of SSRIs with reduced BMD, altered bone architecture, and inferior mechanical properties.[30] This effect involved both cortical and trabecular bone, although the latter was impacted to a larger extent and appears to be secondary to reduced bone formation rather than accentuated resorption.[30,50,51]

By design, all our participants received risperidone, which itself interacts with serotonin receptors.[52] Therefore, we could not rule out the possibility of an interaction between SSRIs and risperidone, resulting in reduced BMD. In light of the widespread prescribing of SSRIs to children and adolescents,[53] the need for their prolonged use,[54,55] and the epidemiologic evidence associating SSRI treatment in adults with reduced BMD and increased fracture risk,[18–20] it is necessary to investigate the impact of SSRIs on BMD in youths without the confounding effect of antipsychotic treatment. With the medium effect size that we found, the clinical implications of such research can be significant because this

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effect would substantially increase the risk for osteoporotic fractures.[5] In addition, a thorough psychiatric assessment would be pivotal to avoid the pitfalls of confounding by indication. This refers to the fact that mood disorders, for which SSRIs are often prescribed, can themselves interfere with BMD and, consequently, confound the association between SSRIs and BMD.[56,57] In our study, we did not start administering psychiatric measures until the majority of our participants had been recruited. Nevertheless, in order to address the possibility that participants receiving SSRIs had a lower BMD due to the effect of an underlying depressive disorder (ie, confounding by indication), we controlled, in the regression models, for the clinical diagnosis of a mood disorder. The results remained virtually unchanged with the depression diagnosis not significantly contributing to the model ($P > .6$).

Our findings should be interpreted in light of several important limitations. The temporal stability of hyperprolactinemia cannot be verified due to our cross-sectional design. Thus, the results should be viewed as preliminary, rather than reflecting irreversibly low BMD. In fact, longitudinal studies have revealed that risperidone-induced hyperprolactinemia resolves in many patients during extended treatment.[43] Since BMD continues to accrue during adolescence, it is possible that once prolactin concentration normalizes, either spontaneously or following the discontinuation of risperidone, its effect on bone mineralization will subside. The impact of hyperprolactinemia and SSRIs on BMD will be clinically relevant only if it leads to increased bone fragility and fractures. It is reassuring that we did not find any history of fractures in our subjects with hyperprolactinemia; however, longer-term investigations with much larger samples are necessary to thoroughly investigate this outcome. In order to address these shortcomings, our group is currently conducting a follow-up assessment to prospectively monitor the change in BMD and the incidence of fractures. This will better establish the role that long-term hyperprolactinemia and SSRI treatment may play in hindering bone mineral accrual. In addition, we are seeking additional funding support to investigate the effect of hyperprolactinemia on bone turnover markers, though these can be highly variable in puberty.[58] It is premature, at this point, to make any definitive conclusions regarding the effect of psychotropics on bone mineralization based on a single measurement using one research modality (ie, pQCT or DXA). Measuring bone turnover markers would potentially complement our findings, especially that they reflect the dynamic aspect of bone metabolism across the entire skeleton in contrast to radiologic techniques that measure BMD at selected sites.[59] In fact, our findings cannot be extended to other bone structures, such as the hip, since we did not collect BMD measurements at those sites. However, measuring BMD at the hip in growing children is of questionable reliability due to limited reproducibility.[60] We focused our study on risperidone since it is most consistently associated with hyperprolactinemia. However, other psychotropics can alter prolactin secretion or directly affect bone metabolism and deserve investigation.[30,46] Finally, we did not correct for multiple comparisons since our primary analysis was hypothesis-driven. Nevertheless, it is necessary to replicate this finding in a larger and more ethnically/racially diverse sample that would also include females and a comparative control group.

CONCLUSION

In summary, we have found preliminary evidence that risperidone-induced hyperprolactinemia and SSRIs might, independently, hinder bone mineralization in boys, preventing a child from reaching his genetically determined peak bone mass. If this effect is sustained over time, it can have worrisome lifelong consequences.[2] Due to the widespread use of SSRIs and antipsychotic medications in children, additional research is necessary to confirm our findings, investigate the contribution of the duration of hyperprolactinemia or of SSRI treatment to this side effect, determine its actual impact on fracture risk, and, if indicated, develop preventive interventions.

Drug names: citalopram (Celexa and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), paroxetine (Paxil, Pexeva, and others), risperidone (Risperdal and others), sertraline (Zoloft and others).

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