Risperidone, but Not Olanzapine, Decreases Bone Mineral Density in Female Premenopausal Schizophrenia Patients

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Background: The hyperprolactinemia induced by conventional antipsychotics often leads to osteoporosis. The commonly used atypical antipsychotics risperidone and olanzapine vary in their hyperprolactinemic properties. Therefore, we compared hormone profiles and bone properties in female premenopausal schizophrenia patients treated with either risperidone or olanzapine.

Method: In a cross-sectional study, consecutive premenopausal, female, DSM-IV schizophrenia patients who were treated with either risperidone (N = 12) or olanzapine (N = 14) for at least 2 years were included. Dual energy X-ray absorptiometry evaluated bone mineral density, and multisite quantitative ultrasound measured bone speed of sound. In addition, profiles of urinary excretion of deoxypyridinoline and circulating levels of hormones and lipids were assessed.

Results: Serum prolactin levels were higher in the risperidone-treated group as compared with the olanzapine subjects (123 ± 144 and 25.9 ± 25.7, $p < .05$). Whereas bone mineral density was similar in the treatment groups, bone speed of sound was lower in the risperidone group as compared with the olanzapine-treated group. Expressed as age-adjusted Z score, bone speed of sound at the radius was –0.31 and 0.58, respectively, $p < .05$, and at the phalanx, –1.41 and 0.04, respectively, $p < .05$. The bone speed of sound in the risperidone-treated patients inversely correlated with urinary deoxypyridinoline excretion ($r = 0.73$, $p < .05$).

Conclusion: Risperidone treatment, as opposed to olanzapine, for female premenopausal schizophrenia results in hyperprolactinemia and clinically relevant decrease in bone mineral density. The calculated relative risk for fragility fracture of women treated with risperidone as compared to those treated with olanzapine is 1.78 when bone speed of sound was measured at the phalanx and 1.23 when measured at the radius.

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The cardinal, but not sole, side effect that distinguishes conventional from novel antipsychotics is iatrogenic extrapyramidal symptomatology.[1] It occurs less frequently using the novel antipsychotics as compared with the high-potency,[2,3] but not the low-potency, conventional antipsychotics.[3]

Hyperprolactinemia is another common adverse effect of many antipsychotics.[4] In comparison to extrapyramidal side effects, it has received less attention. Apparently, the novel antipsychotics affect the dopamine tuberoinfundibular tract that controls prolactin secretion to a lesser degree than do the conventional antipsychotics, and thereby induce less circulating prolactin.[5–9] Among the atypical antipsychotics, olanzapine treatment (like all other second-generation antipsychotics except risperidone), even at high doses, is not usually associated with persistent hyperprolactinemia.[5,6] In contrast, administration of another commonly prescribed novel antipsychotic, risperidone, usually results in hyperprolactinemia in both children and adults.[8,9] The marked hyperprolactinemia effect of risperidone is found to be higher than that induced by clozapine[10] or olanzapine[5,8] and may be related to higher dopamine-2 receptor occupancy by risperidone.[5,6] The reported risperidone-induced hyperprolactinemia is higher in women than in men.[11] The main manifestations of hyperprolactinemia in female patients with schizophrenia are menstrual irregularity, decreased libido, galactorrhea, occasional hirsutism, and higher long-term risk of osteoporosis.[12,13]

Several previous reports indicate a high prevalence of osteoporosis in patients treated with both conventional

Table 1. Patient Characteristics

Patient	Age, y	BMI, kg/m^2	Schizophrenia		Treatment			Concomitant Therapy/Treatment[a]
			Onset Age, y	Type	R/O	Dose, mg/d	Duration, mo	
1	15	29.8	13	Unspecified	R	4	24	Electroconvulsive therapy
2	39	37.0	22	Paranoid	R	6	36	Clonazepam
3	32	28.8	17	Unspecified	R	6	36	
4	39	24.5	26	Paranoid	R	4	24	
5	27	23.0	22	Unspecified	R	4	24	Clonazepam
6	50	28.8	35	Paranoid	R	6	24	
7	30	27.6	19	Disorganized	R	6	36	
8	41	31.2	25	Paranoid	R	6	36	Valproic acid
9	49	28.6	28	Disorganized	R	4	24	
10	40	28.8	21	Unspecified	R	6	36	
11	35	30.1	24	Paranoid	R	4	24	
12	33	24.6	18	Unspecified	R	3	36	Clonazepam
13	55	28.8	35	Paranoid	O	20	36	
14	27	41.5	20	Unspecified	O	20	24	
15	19	19.3	15	Disorganized	O	15	36	
16	44	28.3	20	Unspecified	O	20	36	
17	21	16.5	16	Disorganized	O	20	24	
18	34	32.2	17	Unspecified	O	20	48	
19	49	39.5	28	Schizoaffective	O	20	48	Valproic acid
20	42	36.1	19	Paranoid	O	20	36	Clonazepam
21	49	28.7	30	Unspecified	O	15	30	
22	43	37.9	37	Unspecified	O	20	27	Clonazepam
23	47	27.5	28	Unspecified	O	15	36	
24	35	21.5	21	Paranoid	O	20	24	
25	47	26.0	20	Paranoid	O	20	48	
26	45	27.6	15	Disorganized	O	20	36	

[a]Missing data indicate no concomitant therapy/treatment.
Abbreviations: BMI = body mass index, O = olanzapine, R = risperidone.

antipsychotics and antidepressants.[14–19] However, we are not aware of any specific report of bone status in patients treated with recently introduced atypical antipsychotics.

Although the etiology of osteoporosis in schizophrenia patients is multifactorial,[17] the neuroleptic-induced hyperprolactinemia that disrupts the pituitary-ovarian axis is of importance.[13] Because the 2 most commonly used novel antipsychotics—risperidone and olanzapine—markedly differ in their hyperprolactinemic properties,[5–13] we hypothesize that they may differently affect bone mineral density. This study, therefore, compares hormone profiles and bone mineral density in female premenopausal patients with DSM-IV schizophrenia maintained on long-term treatment with either risperidone or olanzapine.

SUBJECTS AND METHOD

Subjects

The population study comprised 26 consecutive female, premenopausal, schizophrenia patients, aged 15 to 55 years, referred to 4 outpatient psychiatric clinics in the Ness Ziona catchment area (Table 1). To be included in the sample they had to have been continuously treated with either olanzapine (N = 14) or risperidone (N = 12) for at least the last 24 months. Most patients reported irregular menses but did not experience menopausal symptoms. None of the participants complained of polyuria or met the criteria for alcoholism or drug abuse. Each study group had only 2 nonsmokers. Schizophrenia or schizoaffective disorder was diagnosed according to DSM-IV criteria by a senior psychiatrist (D.B.). Candidates were excluded from the study if they had undergone a hysterectomy or suffered from metabolic, cardiovascular, pulmonary, hepatic, or renal diseases.

The local Helsinki Committee approved the study. All of the patients gave their informed consent to participate in the study.

Biochemical Evaluation

For determination of prolactin, estradiol, luteinizing hormone, follicle-stimulating hormone, cholesterol, and triglycerides, blood samples were collected between 8:00 a.m. and 8:30 a.m., following an overnight fast of at least 12 hours. This was done by venipuncture using routine laboratory radioimmunoassay kits. A commercial kit (Pyrilinks-D; TPC, Los Angeles, Calif.) measured urinary deoxypyridinoline in relation to creatinine in second morning postvoid specimens. The sensitivity of the assay is 1.1 nmol/mmol and the inter- and intra-coefficients of variation (not including that of creatinine) are 8.4% and 4.8%, respectively.

Bone Mineral Density

Dual-photon absorptiometry (Hologic QDR 4500 Elite, Waltham, Mass.) at the lumbar spine and proximal

Table 2. Patient Biochemical and Hormonal Levels by Treatment Group (mean ± SD)

Variable	Reference Range	Risperidone	Olanzapine
Follicle-stimulating hormone, IU/L	2–11	9.2 ± 7.4	7.7 ± 6.0
Luteinizing hormone, IU/L	2–11	4.7 ± 2.1	5.4 ± 4.2
Estradiol, pmol/L	110–1100	262 ± 209	281 ± 241
Prolactin, ng/mL	5–25	123 ± 144	25.9 ± 25.7*
Deoxypyridinoline, nmol/mmol	3.0–7.4	10.5 ± 4.8	8.8 ± 2.8
Cholesterol, mg/dL	100–200	168 ± 63	215 ± 35*
Triglycerides, mg/dL	100–250	114 ± 50	150 ± 73

*p < .05.

hip determined bone mineral density and was expressed as an age-adjusted Z score.

Quantitative Ultrasound

As previously described,[20] bone speed of sound was measured by the commercial version of Omnisense (Sunlight Medical, Ltd., Tel Aviv, Israel). The 3 bone speed of sound evaluation sites were the distal 1/3 of the radius, proximal phalanx of the third finger, and the midshaft tibia. In all cases, the probe was aligned along and parallel to the bone in accordance with the manufacturer's specific scan methodology for that site. The measurement was expressed as an age-adjusted Z score derived from a reference database of a healthy white population.[21] In all cases the right side limb was evaluated, but, according to the Omnisense operating manual, when the site of interest is not accessible, the left limb may be evaluated instead.

Statistical Analysis

The Mann-Whitney U test evaluated various parameters between the 2 study groups, and the Wilcoxon matched pair test determined variation within each group. The Spearman test evaluated possible corrections between variables. P values smaller than .05 were considered statistically significant. Statistica (StatSoft, Tulsa, Okla.; version 5.1) software was used to analyze the data.

RESULTS

The patients' characteristics are shown in Table 1. Whereas the treatment duration in the olanzapine group was somewhat longer than in the risperidone group (35.9 ± 8.2 vs. 30.0 ± 6.3 months, respectively, NS), all other variables were similar in both study groups. Except for a single patient (#1), all participants were previously treated with various conventional antipsychotics before the introduction of the atypical antipsychotics. The mean ± SD time of exposure to conventional antipsychotics was 11.66 ± 4.6 years for the risperdone group, and 13.82 ± 8.5 years for the olanzapine group (NS).

Biochemical and hormonal values are presented in Table 2. Serum prolactin levels were higher in the risperidone-treated group as compared with the olanzapine treatment group (Figure 1). Circulating follicle-stimulating hormone, luteinizing hormone, and estradiol and urinary excretion of deoxypyridinoline were comparable in both treatment groups. Of the serum lipids measured, only cholesterol levels were higher in the olanzapine-treated patients, while the serum triglyceride levels were similar in both study groups.

Similar age-adjusted bone mineral density scores for risperidone- and olanzapine-treated patients were noted at the lumbar spine (–0.12 vs. –0.13, respectively) and femoral neck (0.28 vs. 0.38, respectively). However, age-adjusted bone speed of sound (Figure 2) was lower in the risperidone-treated participants as compared with the olanzapine-treated patients when determined at the radius (–0.31 vs. 0.58, respectively, $p < .05$) and phalanx (–1.41 vs. 0.04, respectively, $p < .05$) but not at the tibia (–0.01 and –0.36, respectively, NS). Bone speed of sound Z scores of the risperidone-treated women determined at the site that was most affected, the phalanx (Figure 2), inversely correlated with urinary deoxypyridinoline excretion (Figure 3, $r = 0.728$, $p < .05$). Schizophrenia duration, length of treatment, body mass index, or hormone levels measured did not correlate with the bone speed of sound in any of the measurement sites in both treatment groups (data not shown).

DISCUSSION

Among our sample of female patients with schizophrenia, the risk of hyperprolactinemia and lower speed of sound in the skeleton was significantly higher in the risperidone-treated females than in the olanzapine-treated participants. The inverse correlation of urinary deoxypyridinoline excretion with the lower bone speed of sound indicates a high bone turnover state in this subset of patients.[22] It supports a previous report of a correlation between bone markers and quantitative ultrasound but not bone mineral density in postmenopausal women with severe osteoporosis.[23] The increased bone turnover is associated with increased risk of fragility fracture independently of bone mineral density.[24] Odds ratios derived from multiple logistic regression of fracture discrimination data suggest that the relative risk for fragility fracture in women treated with risperidone, as compared with those treated with olanzapine, is 1.78 when bone speed of sound was measured at the phalanx and 1.23 when measured at the radius.[25]

Polydipsia with obligatory hypercalciuria,[26] hypercortisolemia,[27] smoking, and alcoholism[17] are contributing factors to osteoporosis in schizophrenia patients.[19] However, the most important factor is neuroleptic-induced hyperprolactinemia resulting in secondary ovarian insuf-

Figure 1. Scattergram of Circulating Prolactin Levels in the 2 Treatment Groups

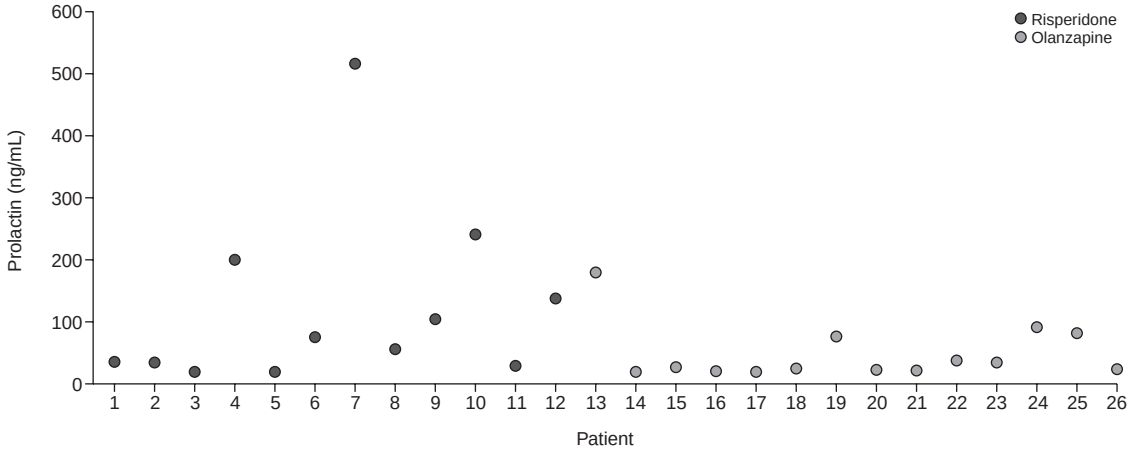


Figure 2. Multisite Bone Speed of Sound in the 2 Treatment Groups (mean ± SD)

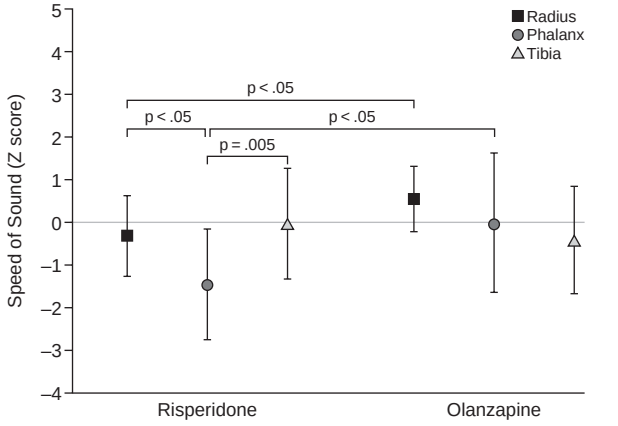
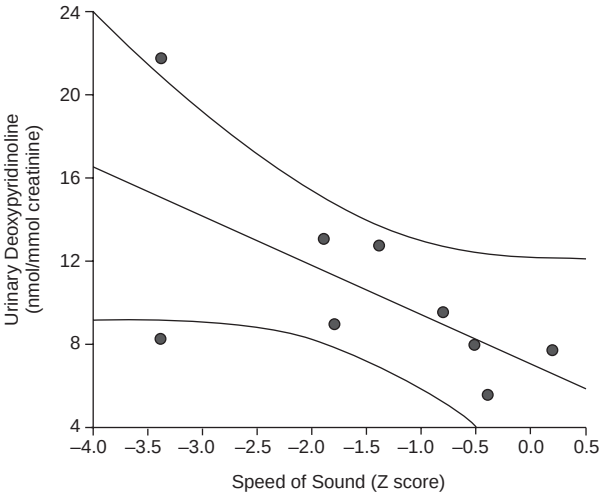


Figure 3. Correlation Between Bone Speed of Sound at the Phalanx and Urinary Deoxypyridinoline Excretion in Risperidone-Treated Patients[a]



[a] $r = 0.728$, $p < .05$.

ficiency.[12] Bone speed of sound in the risperidone-treated women as compared with that in the olanzapine group was lower at the phalanx as opposed to the radius, but not at the tibia. This is in accordance with the rate of decline in bone speed of sound observed in hypoestrogenic early postmenopausal healthy women, which is maximal at the phalanx, intermediate at the radius, and minimal at the tibia.[21,28] The lack of statistical correlation between circulating prolactin levels and bone speed of sound is in accordance with a previous report measuring bone mineral density in hyperprolactinemic schizophrenia patients.[15,16] Indeed, a previous report suggested a correlation between the duration of hyperprolactinemia, but not the degree of hyperprolactinemia, with bone mineral density.[29] As the duration of treatment with the atypical antipsychotics in our report spans a relatively short range, one may not expect to find a correlation between bone properties and the duration of hyperprolactinemia in our sample. Our data showing no correlation between estradiol levels and bone properties are in accordance with some reports[15,16] but in contrast to others.[19,30] This inconsistency may result from lack of correlation between circulating prolactin, follicle-stimulating hormone, and estradiol levels in hyperprolactinemic women.[31] Quantitative ultrasound of bone provides information on bone characteristics that correlates with bone quality.[32,33] The reported correlation with bone mineral density is especially low in premenopausal women and increases with age.[34] In our premenopausal patients, we also found discrepancy between bone speed of sound and bone mineral density data. In contrast to

bone speed of sound, the bone mineral density was similar between the 2 treatment groups, independent of the circulating prolactin levels. Better correlations between metabolic surrogates and bone properties in secondary osteoporosis were reported by using quantitative ultrasound, as compared with bone density measurements. In hyperthyroidism, bone speed of sound, not lumbar spine bone mineral density, was lower, as compared with euthyroid controls.[34,35] In patients with hyperparathyroidism, amplitude-dependent bone speed of sound, not bone mineral density, correlated with circulating parathyroid hormone levels.[36,37] In glucocorticoid-induced osteoporosis, the age-adjusted ultrasound scores are lower than those of bone densitometry.[38]

Based on our findings, it seems that female patients with antipsychotic-induced hyperprolactinemia should be monitored for the possible emergence of osteoporosis. Currently, our patients with signs of decreased bone mineral density are receiving follow-up assessments measuring whether further decline occurs. The monitoring will be performed once a year, after which bone parameters will be evaluated and antireabsorptive treatment will be given if required.

It is of note that findings such as higher cholesterol levels in the olanzapine-treated women may implicate a risk factor for cardiovascular diseases, and this, in turn, demonstrates the complexity of the choice of an antipsychotic agent.

The major limitation of our study is its cross-sectional design rather than the preferred prospective, double-blind study. The relatively small number of patients in the 2 study groups is also a drawback. Most patients in the study had previously received various conventional antipsychotics; however, it seems unreasonable that this would explain the difference in bone mineral density between the 2 groups, since the duration of the illness and the exposure to the atypical neuroleptic (risperidone or olanzapine) was similar for both groups. In addition, we did not determine the contribution of confounding factors such as polydypsia, hypercortisolemia, smoking, and alcoholism for the lower speed of sound.

The issue of the prevention and therapy of antipsychotic-induced osteoporosis merits further investigation, especially in premenopausal women. It will require a replication of our study using a prospective approach in a larger sample of women.

In conclusion, the atypical antipsychotic medication risperidone, in contrast to olanzapine, adversely affects bone mineral density resulting in increased osteoporosis-related fracture risk, probably due to risperidone-induced persistent hyperprolactinemia.

Drug names: clonazepam (Klonopin and others), clozapine (Clozaril and others), olanzapine (Zyprexa), risperidone (Risperdal), valproic acid (Depakene and others).

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