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Bone Mineral Density in Male Schizophrenia Patients: A Review

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Background. *Decreased bone mineral density (BMD) has been documented frequently in female patients with schizophrenia receiving antipsychotic therapy with potent dopamine D_2 antagonists, but there has been much less coverage of this issue in male patients with schizophrenia despite the fact that older males who sustain osteopenia-related hip fractures have subsequently greater mortality than females.*

Methods. *A Medline search was performed for the years 1966–2004 using the following search terms: "osteopenia or osteoporosis or bone density or bone mineral density," combined with "schizophrenia or psychosis or antipsychotic."*

Results. *The search yielded 8 studies which provided data on bone mineral density in male patients with schizophrenia, of which 2 were case reports, and 3 were controlled studies. Hormonal measures were present in 6 studies. In every study where such information was provided, the patients with schizophrenia had significantly lower BMD than nonschizophrenic controls or population norms, with the prevalence of osteopenia ranging from 40–72%.*

Conclusions. *Low BMD and corresponding osteopenia or osteoporosis may be a highly prevalent but significantly underdiagnosed medical condition among male schizophrenia patients. Psychiatrists should consider BMD screening among older males who have received chronic antipsychotic therapy with antipsychotics expected to achieve high levels of postsynaptic D_2 antagonism.*

Keywords Schizophrenia, Bone mineral density, Osteopenia, Osteoporosis, Dexascan, Male

INTRODUCTION

There has been increasing interest in physical health problems among patients with schizophrenia, in part related to the concerns about metabolic adverse effects of antipsychotic treatment (1,2). One issue that has received less attention, but may be of increasing importance in the aging demographic of schizophrenia patients, is osteopenia and osteoporosis. In general, osteoporosis and osteopenia are major public health concerns, with an estimated 28 million persons in the United States, 80% of whom are female, having low bone density or overt osteoporosis (3). Postmenopausal females have traditionally been the demographic that is the focus of attention, with data showing that 50% of women over the age of 50 will sustain an osteoporosis-related fracture. Postmenopausal females are clearly at risk, yet the figure for males is also appreciable, with estimates that nearly one in eight will suffer osteoporosis-related fractures, with greater mortality rates after hip fracture than for females (3). Genetic factors (e.g., ethnicity) play a primary role in determining bone density during development into adulthood (4,5), but acquired conditions and environmental or lifestyle factors are largely responsible for subsequent bone density loss. Common causes of demineralization include inactivity, smoking, poor nutrition, low levels of vitamin D, hyperparathyroidism and low sex hormone levels (estradiol and testosterone), while obesity appears to be protective for decreased bone mineral density (4,5).

Schizophrenia patients are at risk for osteopenia and osteoporosis due to inactive lifestyles, high prevalences of smoking, and possibly lithium exposure (6) or polydipsia (7), although the mechanism by which the latter two may induce osteopenia is not known, and the data are not compelling (8,9). The greater source of risk for most patients with schizophrenia arises from the effects of antipsychotic therapy on sex hormone levels. The decrease in sex hormone levels is mediated through tubero-infundibular postsynaptic dopamine D_2 receptor antagonism by antipsychotics, and

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resultant increases in serum prolactin (6,10). Elevated prolactin does not by itself impact bone density, but does so indirectly through suppression of the pulsatile secretion of gonadotropin-releasing hormone (GnRH), leading to low serum levels of the sex hormones estradiol and testosterone. It is worth noting that in premenopausal women with hyperprolactinemia related to pituitary adenomas or antipsychotic treatment, BMD changes correlate best not with serum prolactin levels but with the extent of time spent amenorrheic (11,12). In premenopausal females, amenorrhea thus serves as a clinical marker for low serum estradiol, but in males, especially those with schizophrenia, low testosterone may be easily overlooked unlooked unless a patient complains of reduction in libido or other prolactin-related adverse effects such as gynecomastia. Amenorrhea serves as a clinical endpoint to base decisions concerning antipsychotic treatment and sex hormone levels in females with schizophrenia, but serum testosterone is rarely obtained in the clinical management of male patients with schizophrenia. Moreover, changes in libido may be difficult to track in male schizophrenia patients by those unused to quantifying this outcome measure, especially in a patient population who may be taking sedating medications or have other reasons for sexual dysfunction (e.g., negative symptoms, smoking). Given the strong correlation between amenorrhea and BMD loss, the literature is replete with data on the impact of antipsychotic treatment on prolactin levels and measures of bone density in females with schizophrenia (13–22), but clinicians are often less aware that male schizophrenia patients are also at risk. The purpose of this paper is to review the body of literature on bone density in male patients with schizophrenia to highlight the fact that this is a condition worthy of clinical attention, especially among older patients who may suffer significant complications after major osteoporosis related hip fractures.

METHODS

A Medline search was performed in December, 2004 for the years 1966–2004 using the following search terms: "osteopenia or osteoporosis or bone density or bone mineral density," combined with "schizophrenia or psychosis or antipsychotic." Included studies or case series for examination were those with BMD from densitometry measurements employing single or dual photon absorptiometry, or dual energy X-ray absorptiometry (dexascan), with BMD reported in T-scores or Z-scores. A Z-score is defined as the number of standard deviations from the mean bone density for age-, sex-, and ethnicity-matched controls, while quantitative BMD measurements in T-scores reflect the number of standard deviations from the mean bone density of women ages 20 to 29. Osteopenia is defined as BMD at least one standard deviation below the mean (T-score –1 to –2.5), while osteoporosis is a BMD 2.5 standard deviations or more below the mean (T-score < –2.5) (3).

RESULTS

The Medline search yielded eight studies which examined BMD specifically among males with schizophrenia (7,14, 15,17,18,20,22,23) and are presented in Table 1. Among these studies of male patients with schizophrenia only three studies utilized matched controls instead of population norms (14,17,23), while two were small case reports, and the remainder uncontrolled studies which used population norms as the reference group to examine BMD results.

Delva and colleagues (7) sought to understand the biological variables contributing to osteopenia among a group of 10 institutionalized white males with schizophrenia who also suffered from psychogenic polydipsia. For comparison, the investigators utilized a control group of 10 white males with schizophrenia from the same facility, matched for age, race, and illness duration, but who did not have polydipsia. The two cohorts were assessed on the basis of results from an extensive laboratory battery, including 24 hour urine collection for electrolytes and calcium, serum chemistries and hormonal measures, and bone densitometry employing single or dual photon absorptiometry with a gadolimiun-153 source.

The study found no significant differences between the groups on risk factors for low bone density such as daily cigarette consumption, daily neuroleptic dose, or proportion of patients who were current or former lithium users. The study also found no abnormalities on most of the laboratory measurements, including serum calcium, urinary calcium, or serum testosterone. Serum prolactin was elevated in both groups, and numerically, but not significantly, greater in the polydipsia cohort (33 ng/ml) than the matched controls (18.2 ng/ml) (normal range of 5–15 ng/ml). Mean lumbar BMD densitometry (at the L2-L4 level) for the polydipsia cohort was 83.8% of the comparable demographic US norm, and radial BMD 91.5% of the population norm, while the control group had lumbar and radial BMD measurements which were 102.90% and 97.6% of the population norm. The radial BMD differences between the cohorts were not significant, but the polydipsia cohort did have significantly lower mean lumbar spine BMD compared to the schizophrenia patients who did not have polydipsia. Of note, two of the polydipsia patients had clear evidence of prior lumbar compression fractures, an unusual finding possibly related to suicide attempts by jumping as inferred by prior history of calcaneal fractures, although the authors make no comment on this. Moreover, the control group was significantly heavier (76 ± 9 kg) than the polydipsia group (64 ± 9 kg) ($p < .05$), leaving some doubt whether the differences in lumbar BMD were artifactual.

Halbreich and colleagues (14) published one of the more comprehensive studies in which they obtained dexascan data for BMD at lumbar and femoral neck sites in 68 consecutively admitted psychiatric patients (35 males, 33 females) diagnosed with major depression ($n = 21$), schizophrenia ($n = 33$), schizoaffective disorder ($n = 7$), mania ($n = 2$), and adjustment disorder ($n = 5$). Related hormonal measures (prolactin,

Table 1 Summary of Studies on BMD in Male Patients with Schizophrenia

	Sample	Results for Males	Comments
Delva et al., 1989 (7)	10 males with polydipsia 10 nonpolydipsic controls (matched for diagnosis gender, duration of illness, age, and race)	Prolactin levels elevated but normal FSH and testosterone in both groups. Polydipsia cohort had significantly higher FSH.	Control group significantly heavier. 2 polydipsia subjects may have had prior L-spine compression fractures from trauma.
Halbreich et al., 1995 (14)	68 consecutively admitted psychiatric inpatients (51.5% male) of which 40 had schizophrenia or schizoaffective disorder. Data analyzed for 27 males compared to age- and gender-matched controls	79% of males had BMD >1 SD below population mean at L2 level, 72% for mean L2-L4 results, and 90% at femoral neck. 35%, 28% and 52% were more than 2 SD below normal at these same sites respectively. Hypogonadal males had significantly lower lumbar BMD than eugonadal males. BMD negatively correlated with prolactin for lumbar BMD.	Not all patients were diagnosed with schizophrenia and some were not treated with antipsychotics during this hospitalization. All patients were within 20% of ideal body weight.
Abraham et al., 1996 (15)	Case report: 1 male 1 female	BMD (vs. age-matched norms): −0.62 SD at left hip, −0.92 SD at femoral neck, −0.99 SD at L1-L4.	Normal prolactin FSH, LH, and testosterone in the male patient. Male patient had chronic history of polydipsia and heavy smoking.
Bilici et al., 2002 (17)	40 on conventionals (CN): 20 male 20 female 35 on atypicals (AN): 18 male 17 female 20 controls	BMD not significantly different between AN and controls, but was significantly lower for the CN group, even when adjusted for physical activity. Regression analysis found that neuroleptic dose, length of treatment and illness duration were significant predictors of BMD variance.	Patients on atypical antipsychotics had greater body mass index (33.4 ± 4.8 kg/m^2) than those on conventionals (27.2 ± 3.7 kg/m^2) or controls (26.7 ± 4.4 kg/m^2). Controls much more active than either schizophrenia cohort.
Abraham et al., 2003 (18)	11 males 5 females	Significant negative correlation between total BMD and serum prolactin when covaried for testosterone levels. Correlation not present at lumbar region.	Specific BMD measurements not reported, only correlation coefficients, and results not analyzed in gender-specific manner.
Meaney et al., 2003 (20)	Case report: 1 male 2 females	In the male, T-scores at L1–L4 ranged from −1.39 to −2.04 SD, and at L hip T-score of −2.04 SD.	Male subject on depot typical plus high dose risperidone. Elevated serum prolactin, with normal FSH, LH, and low normal testosterone.
Meaney et al., 2004 (22)	30 males 25 females	57% of males had reduced bone mineral density on at least one of the two sites used for measuring BMD in the hip and lumbar spine.	BMD values not reported in the paper. Males had marked hyperprolactinemia (3x ULN), but normal hormonal measures.
Lehman and Meyer, 2005 (23)	10 male patients 10 controls (matched for age, gender, and body mass index)	Lower mean BMD in the schizophrenia subjects in every matched pair except when discordant for African American ethnicity. 40% of schizophrenia patients had mean BMD > 1 SD below normal.	Higher smoking prevalence in the schizophrenia cohort. No hormonal measures or assessment of activity.

cortisol, thyroid indices, testosterone and estrogen) were also reported for a subgroup. The overall group demographic was 65% white, 34% African American, with 63% smokers. None of the patients were bedridden or in a wheelchair, and all were within 20% of ideal body weight.

After excluding BMD data in eight of the male patients due to very high readings consistent with compression fracture, Halbreich reported significantly lower BMD Z-scores at the lumbar region (L2-L4), the L2 vertebra specifically, and the femoral neck ($p < .0001$ for all sites) compared to age- and gender-matched nonpsychiatric controls. Using the lumbar region reading as the most conservative reading of the three sites, 72% of the psychiatric patients were more than one standard deviation (SD) below normal compared with 33% for the control group, and 28% were >2 SD below normal compared to only 7% for the controls. At L2 specifically, 79% and 35% of patients were one and two SD below population norms respectively, with values of 90% and 52% respectively at the femoral neck. Interestingly, these trends were less robust among the female patients. Both mean testosterone (363.8 ng/ml, normal 360–990 ng/ml) and free testosterone (7.0 ng/ml, normal 5.1–41.0 ng/ml) for the male patients as a group were in the low normal range, and there was a significant correlation between the individual values and BMD measured in the lumbar region or at L2 (total testosterone $r = 0.54$, $p = .003$; free testosterone $r = 0.58$, $p = .003$), and at L2-L4 (total testosterone $r = 0.48$, $p = .009$; free testosterone $r = 0.53$, $p = .009$), while the correlation was significant only for free testosterone at the femoral neck site ($r = 0.52$, $p = .012$). When hypogonadal males (testosterone <250 ng/ml) were compared with eugonadal males, the hypogonadal group had significantly lower mean BMD at L2 ($t = 2.51$, $p = .0022$), and at L2-L4 ($t = 2.71$, $p = .015$), but not at the femoral neck ($t = -.41$, $p = .691$). There was also a negative correlation between serum prolactin and BMD for the males at the lumbar sites (L2 $r = -0.458$, $p = .048$; L2-L4 $r = -0.495$, $p = .031$), but not at the femoral neck ($r = 0.121$, $p = .631$), and not for any BMD measures among the female cohort. In a regression analysis using descriptive variables only (sex, gender, smoking status, use of ethanol, class of medication, past or current medication use, lithium use, years since diagnosis, number of hospitalizations) but not hormonal measures, only age was significantly related to the variance in BMD at lumbar and femoral regions.

Aside from a case review of two patients (one male, one female) by Abraham in 1996 (15), and a case review of three patients (one male, two female) by Meaney in 2003 there are only four other significant studies which report BMD data in males: one published by Bilici and colleagues in 2002 (17), an uncontrolled study by Abraham in 2003 (18), an uncontrolled study by Meaney in 2004 (22), and a small controlled study by Lehman and Meyer (23).

In the 2003 Abraham study, which consisted of 11 males and 5 females with schizophrenia, dexascan data were obtained at several sites on the left hip and lumbar region (L1 – L4) to study the correlation with serum levels of prolactin, estradiol and testosterone. The group had a mean prolactin level of 39.9 ng/ml (range of 5.8–157 ng/ml), mean testosterone level (normal for males 360–990 ng/ml, females <62 ng/ml) of 346.15 ± 272.11 ng/ml (range of 20–1000 ng/ml) and mean estradiol level (normal for males ≤50 pg/ml, premenopausal females 10–400 pg/ml) of 34.19 ± 19.04 pg/ml (range of 20–85.4 pg/ml). There was a significant negative correlation between total bone mineral density and serum prolactin ($r = -0.62$, $p < .05$), and at the femoral neck ($r = -0.54$, $p < .01$) and trochanter ($r = -0.51$, $p < .01$), but not lumbar spine. The correlation between total bone mineral density and serum prolactin remained significant when covaried for testosterone ($r = -0.56$, $p < .01$) or estradiol levels ($r = -0.61$, $p < .01$), but not so for the trochanter measurements, while the correlation between femoral neck BMD and prolactin remained significant when covaried for estradiol ($r = -0.52$, $p < .01$), but not testosterone. The specific BMD measurements were not reported in the paper, only the Spearman correlation coefficients.

In Bilici's study, 75 schizophrenia patients with mean age 30 receiving typical or atypical antipsychotic monotherapy (38 males, 37 females), were compared with 20 age-matched normal controls (10 males, 10 females). The conventional neuroleptic cohort (CN) (20 males, 20 females) had mean illness duration of 5.3 ± 2.2 years, and mean duration of neuroleptic treatment 14.2 ± 3.1 months, comparable to the atypical neuroleptic group (AN) (18 males, 17 females) with average 5.8 ± 2.7 years illness, and 12.8 ± 2.9 months of antipsychotic exposure. The study excluded individuals receiving medications with known effects on BMD (e.g., corticosteroids), women with menstrual irregularities, and any control who was a heavy smoker. In addition to dexascan measurements at the lumbar region (L1 – L4), data on physical activity were obtained, but no hormonal measures. The cohorts were demographically similar, although the control group was significantly more active on all measures, and the AN group significantly heavier (mean BMI 33.3 kg/m^2 compared to 27.2 kg/m^2 and 26.7 kg/m^2 for CN and controls respectively). Bilici found that BMD was not significantly different between AN and controls, but was significantly lower for the CN group compared to either of these, and the between group differences were still significant when adjusted for physical activity using an analysis of covariance. Interestingly, BMD was not significantly different between male and female schizophrenia patients. There was, however, a negative linear correlation between BMD and duration of illness ($r = -0.38$; $p = .001$), length of antipsychotic exposure ($r = -0.47$; $p = .001$), and age ($r = -0.29$; $p = .005$), and a positive linear correlation with BMI ($r = 0.38$; $p = .004$) and physical activity ($r = 0.29$; $p = .01$). The multiple linear regression analysis found that neuroleptic dose, length of treatment and duration of illness were significant predictors of BMD variance.

Meaney and colleagues (22), studied 55 patients (25 women and 30 men) with long-term antipsychotic exposure, primarily to typical antipsychotics, and obtained BMD data from dexascans as well as prolactin and sex-hormone level measurements.

Fifty-seven percent of the men and 32% of the women had reduced bone mineral density on at least one of the two sites used for measuring bone density (hip and lumbar), but the definition of "reduced" is not explicit, and actual mean BMD values were not reported in the paper. The males had hyperprolactinemia, with mean serum prolactin levels at 3 times the upper limit normal for the laboratory, but other hormonal measures (thyroid indices, sex hormones, and cortisol) were in the normal range. Correlation was found between extent of antipsychotic exposure (measured in chlorpromazine equivalence scores) and extent of bone loss with both lumbar scores ($r = 0.4$, $p = 0.002$) and combined lumbar- and hip-weighted scores ($r = 0.35$, $p = 0.009$). The only other variable which correlated with low bone mineral density (specifically in the lumbar region) was low serum free testosterone levels in the male cohort ($r = 0.50$, $p = 0.03$).

Lastly, Lehman and Meyer (23) reported BMD data on 10 matched pairs of ambulatory male schizophrenia patients and normal controls who were entered in a pilot study of visceral adiposity. For this reason, the pairs were matched for age and measures of adiposity including body mass index, but not for other variables (e.g., smoking), and 3 of the controls were using low doses of antipsychotic for post-traumatic disorder related symptoms (risperidone – 2, quetiapine – 1). Aside from differences in antipsychotic exposure, the only demographic difference was in the prevalence of smoking: 100% for schizophrenia cohort versus 60% for the matched controls ($p = .037$). Mean BMD T-score was $0.530 \pm .497$ for controls and -0.390 ± 1.50 for the schizophrenia patients. The Z-scores revealed a similar pattern, and were higher for the control group ($0.730 \pm .6237$) than the schizophrenia group (-0.100 ± 1.479). For the sample as a whole, bone mineral density was significantly correlated with diagnosis of schizophrenia using T-score ($r_S = .460$; $p = .041$) with a trend towards significance for the Z-score ($r_S = .426$; $p = .061$). The paired t-test for BMD was not significantly different for the two groups using either T-score ($p = .110$) or Z-score ($p = .117$); however, two pairs were discordant for African American ethnicity, an important mismatch as African Americans have significantly greater BMD than Caucasians or Asians. When these two pairs were removed from the analysis, mean BMD T-score was significantly lower among the schizophrenia patients (-0.825 ± 1.17) compared to the controls ($.413 \pm .638$) ($p = .013$), as were the Z-scores ($p = .010$). In every matched pair except one, in which the schizophrenia patient was African American while the matched control was not, the individual with schizophrenia had lower bone density than the matched control. Four of the schizophrenia cohort also had BMD T-scores in the range of either osteopenia (n = 3) (T-score –1.0 to –2.5) or osteoporosis (n = 1) (T-score <–2.5). There was a trend towards a significant correlation between smoking status and BMD using T-scores ($p = .088$), and a significant result ($p = .049$) with Z-scores. In a linear regression model with bone mineral density as the dependent continuous variable, the best fit was found for the model including schizophrenia diagnosis, age, and BMI as variables ($r^2 = .432$, adjusted $r^2 = .325$; $p = .025$). Neither addition of smoking to the model nor the substitution of smoking for schizophrenia status improved fit. As the intended primary outcome was visceral adiposity, the authors did not obtain hormonal measures, nor did they quantify duration of illness, activity level, use of alcohol or prior neuroleptic exposure.

DISCUSSION

Depending on the site of analysis (lumbar, femoral neck, hip, total body), the data indicate that males with schizophrenia may have high prevalences of decreased BMD that reach the level of osteopenia in a significant proportion, based upon the estimates from Halbreich, and Lehman and Meyer. Despite these findings, the paucity of controlled studies is surprising considering that the limited available data reveal that male patients with schizophrenia may have subnormal BMD, especially with exposure to typical antipsychotics. Atypical antipsychotics do have less affinity for postsynaptic dopamine D_2 receptors, and the results from Bilici suggest that patients receiving atypical agents may have similar BMD as matched controls, though other studies, including the small series from Lehman and Meyer which included subjects primarily receiving atypical antipsychotics, document significantly lower BMD than controls or expected population norms. Clearly, the prior long term use of typical agents may contribute to BMD loss in the years before exposure to an atypical antipsychotic, as was noted by Bilici (17), who found a significant negative correlation between BMD and illness duration; however, it should be noted that illness duration was not a significant contributor to variance in BMD among Halbreich's sample of 68 patients (14).

Bone demineralization is often reversible upon restoration of normal hormonal balance, but this process may take years, with no currently available data to outline whether switching osteopenic male patients with schizophrenia from high potency D_2 antagonists to lower potency agents results in meaningful improvements in BMD, or what role hormone, vitamin or calcium supplementation might play in this process. Moreover, BMD changes will certainly be influenced by the ongoing risk imposed by smoking and inactivity. Smoking in particular, is an important risk factor for osteopenia, and is much more prevalent in schizophrenia patients (75–90%) than the general population (25%)(24).

CONCLUSIONS

The studies reviewed here likely reflect the fact that cumulative insults to mineralization are incurred over the lifetime of exposure to higher levels of D_2 antagonism, with the resultant impact on serum testosterone levels mediated by elevation of serum prolactin levels. The time course of

improvement in BMD after restoration of normal serum sex hormone concentrations is at present not known for male patients with schizophrenia, but the data from these studies suggest that even in this era of widespread atypical antipsychotic usage, osteopenia may be a highly prevalent, but rarely recognized problem in males with schizophrenia. More research is clearly needed to understand the scope of this problem among males with schizophrenia, especially among the elderly demographic which is at highest risk for hip fracture-related mortality. The results of such studies will provide valuable guidance for clinicians on rational BMD monitoring schemes in males with schizophrenia by better defining the age cohort of interest, and the minimum necessary dexascan and laboratory parameters to be evaluated in such patients.

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