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Bone mineral density and its relationship to prolactin levels in patients taking antipsychotic treatment

OD Howes, **MJ Wheeler**, **AM Meaney**, **V O'Keane**, **I Fogelman**, **G Blake**, **RM Murray**, and **S Smith**

INTRODUCTION

A previous report suggested that patients receiving long-term antipsychotics show reduced BMD, equivalent to osteopenia or osteoporosis in 57% of males and 32% of females[1]. Osteoporotic fractures were reported in 23% of males on psychotropics [2]. Low dietary calcium intake, smoking, polydipsia, and antipsychotic-related hyperprolactinaemia have been implicated[2]. BMD has been reported to be inversely related to prolactin levels in patients with schizophrenia[3]. High prolactin levels have been associated with elevated markers of bone turnover[4].

Few studies have compared BMD in patients with chronic psychotic disorders to normal values, and previous authors have concluded larger studies are needed[1;2;4]. We tested whether BMD in patients taking antipsychotic treatment is reduced to a clinically significant level and correlates with prolactin levels.

MATERIALS AND METHODS

Study design and setting

Consecutive outpatient clinic attendees at The Maudsley Hospital were invited to participate (20 declined, 7 were excluded and 102 participated, mean age: 46.0 (SD: 13.1), sex: 47% male, ethnicity: 46% white British, 54% black African/African-Caribbean). After complete description of the study, subjects provided written informed consent. Inclusion criteria: aged 18-65 years, stabilised on antipsychotic medication for >two years. Exclusion criteria: medical/psychiatric causes of low BMD[5].

Procedure

Clinical, demographic, and established risk factors for low BMD [5] were assessed using structured ratings as previously described[1].

BMD was measured in the lumbar spine and the hip by dual x-ray absorptiometry (DXA) scan using a Hologic QDR 4500A bone densitometer (Hologic Inc. Bedford, MA, USA). BMD measurements are reported as Z scores (a comparison with reference values of the same age, sex and ethnicity)[5]. The manufacturer's reference range was used for spine[6] and the NHANES III for hip BMD[7] as recommended[5].

Serum was taken to measure prolactin, osteocalcin levels (indicating bone formation[5]), and urinary deoxypyridinoline levels (indicating bone resorption[5]) using immunoassays (from ADVIA Centaur (for prolactin), and Metra Biosystems, California for osteocalcin and deoxpyridinoline (corrected for urinary concentration by creatinine) levels). Within- and between-assay precision was respectively 2.8%, and 1.8% for prolactin, <8% and <7.5% for osteocalcin, and <6.5% and <4.5% for deoxypyridinoline across the concentration ranges.

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Statistical analysis

The null hypothesis that the mean BMD in subjects is the same as the reference values was tested using a z-test, and two tailed t-tests were used to compare mean BMD between sub-groups. Correlations between measures of bone mineral density and factors influencing bone mineral density were tested using Pearson's product moment correlation.

RESULTS

Clinical

Subjects were taking the following antipsychotics: amisulpride (n=10), chlorpromazine (n=5), flupentixol (n=21), fluphenazine (n=5), haloperidol (n=9), olanzapine (n=19), pimozide (n=1), pipotiazine (n=2), quetiapine (n=1), risperidone (n=9), sulpiride (n=3), trifluoperazine (n=8), ziprasidone (n=1), zuclopenthixol (n=7). The mean dose of antipsychotic treatment expressed as chlorpromazine equivalents was 356mg (SD=318)), and the median treatment duration was 3.0 years (interquartile range=8.5). Subjects were taking the following additional medications: antimuscarinics (n=38), mood stabilisers (n=15), anti-depressants (n=23), antihypertensives (n=10), benzodiazepines (n=9), and others (n=15).

Structured rating scales indicated that compliance was good and subjects experienced low levels of side-effects, positive and negative symptoms (data on request). No subjects were underweight, polydipsic or eating disordered. In the women, 30.4% were post-menopausal, 8.7% amenorrheic, 13.0% oligomenorrheic, and 47.8% showed regular menstruation. No women were pregnant, although 65% had been pregnant at some time (median of 2.0 (interquartile range=4.0) pregnancies, and mean of 3.8 months (SD=8.7) breastfeeding).

Forty-six (45%) smoked (median=15 cigarettes/day (interquartile range=20), and forty-three (42%) drank alcohol (mean=6 (SD=11) units/week). Mean calcium intake, exercise levels, and BMI were 575mg/day (SD=415), 40 minutes/day (SD=65), and 30.8 kg/m^2 (SD: 6.2) respectively.

No clinical factors correlated with BMD other than BMI (spine: r=0.24, p=0.02; hip: r=0.34, p=0.001; femoral neck: r=0.28, p=0.005 respectively).

Bone mineral density

Mean Z-scores are shown by gender and ethnicity in table 1. The Z-score was less than −1.0 for one or more measure in 53.7% of men and 29.2% of women. There was no significant difference in BMD (spine: t=-0.57, df=100, p=0.6; hip: t=-1.3, df=97, p=0.2) between patients taking antipsychotics grouped as previously described [1] into prolactin-raising or prolactin-sparing categories (mean prolactin levels: 802 mIU/l (SD= 1092), and 565 mIU/l (SD=688) respectively). Prolactin was not correlated with total spine (r=0.08, p=0.42) or hip (r=0.1, p=0.29) BMD for the whole sample, or when sub-grouped by sex, menopausal status or taking prolactin-raising or sparing antipsychotics.

Men—White men showed no evidence of reduced BMD at the total spine (mean Z-score: −0.24, p=0.2), total hip (mean Z-score: +0.26, p=0.16), and femoral neck (mean Z-score: +0.38, p=0.04). Black men showed reduced BMD in the total spine (mean Z-score: −0.88, p=0.00001), but not in the hip (mean Z-score: +0.49, p=0.016), or femoral neck (mean Z-score: +0.43, p=0.035).

Women—Black and white women showed no evidence of reduced BMD in the total spine (mean Z-scores: −0.04, p=0.83; +1.06, p<0.0001 respectively), total hip (mean Z-scores:

+0.52, p=0.006; +1.07, p<0.0001 respectively), and femoral neck (mean Z-scores: +0.46, p=0.015; +1.07, p<0.0001 respectively).

Bone metabolism

Men—Osteocalcin levels (mean=10.9 ng/ml (SD: 2.4)) exceeded the upper limit of the normal range (3.4-9.1). Mean deoxypyridinoline levels were 3.09nmol/mM creatinine (SD: 1.7), within the normal range (2.3-5.4).

Women—Osteocalcin (mean=8.7ng/ml (SD: 3.6) and deoxypyridinoline (mean: 4.9 nmol/mM creatinine (SD: 2.2)) levels were within the normal ranges (3.6-10.0 and 3.0-7.4 respectively).

DISCUSSION

Our key finding, in the largest sample of patients taking antipsychotics studied to date, is BMD is not clinically decreased compared to normal values and not correlated with prolactin levels. The biochemical measures of bone metabolism do not indicate increased bone turnover, supporting the main finding.

These findings contrast with earlier reports of decreased BMD, possibly due to sample differences: compared to previous studies subjects showed shorter treatment duration (although still a median of three years), and lower levels of prolactin, smoking, and alcohol use, and higher BMI [1;2]. Elevated BMI is protective against low BMD[5], and this may be a significant factor in the negative finding. The findings support reports of no significant difference in BMD (measured by DXA) between female patients taking 'prolactin-raising' and 'prolactin-sparing' antipsychotics [4]. The reduced spinal BMD in black men warrants further investigation, but is unlikely to indicate that antipsychotics are associated with reduced BMD as this would require a selective mechanism. It may be artefactual as reference data are less precise for spinal BMD in black men[5-7].

The major limitation of the study is it uses population data for comparison, although this aids interpretation as the clinical significance of reductions in BMD compared to population norms is well established[5].

The results do not exclude effects on BMD with longer-term treatment or sub-groups with marked hyperprolactinaemia, warranting further investigation[1;5]. The study was powered to detect BMD reductions ≥1 S.D (equivalent to age adjusted osteopenia or osteoporosis [5]) in a sample of 17 subjects but may have missed more subtle changes.

The finding that BMD is not clinically reduced or related to prolactin levels is reassuring for patients taking antipsychotics.

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Table 1

Mean bone mineral density expressed as Z-scores (standard deviations compared to the reference values).

	White Men, n=29 (SD)	White Women, n=18 (SD)	Black Men, n=25 (SD)	Black Women, n=30 (SD)
Total Spine Z score	−0.24 (1.22)	+1.06 (1.55)	−0.88 (1.29)	−0.04 (1.24)
Total Hip Z score	+0.26 (1.05)	+1.07 (1.12)	+0.49 (0.85)	+0.52 (0.82)
Femoral neck Z score	+0.38 (0.84)	+1.07 (1.03)	+0.43 (0.96)	+0.46 (0.99)