# Ultrasound bone mass in schizophrenic patients on antipsychotic therapy

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**Objective**  To determine bone mass using quantitative phalangeal bone ultrasound in institutionalized schizophrenic patients under chronic treatment with antipsychotic drugs.
**Methods**  A total of 73 patients with schizophrenia (25 women, mean age $59.84 \pm 17.01$ years; 48 men, mean age $61.89 \pm 12.95$ years) and 73 healthy subjects (25 women, mean age $60.37 \pm 17.16$ years; 48 men, mean age $61.24 \pm 13.09$ years) participated in the study. Bone status was assessed using an ultrasound device that measures the amplitude-dependent speed of sound (Ad-SoS) in metres per second. Measurements were made on the phalanges (II–V) of the non-dominant hand, and the mean value was computed.
**Results**  The schizophrenic women had higher levels of prolactin (PRL), parathyroid hormone (PTH), alkaline phosphatase (AlPh), and tartrate-resistant acid phosphatase (TRAP) (all $p < 0.0001$), and lower 25-hydroxyvitamin D(25(OH)D3) levels ($p < 0.0001$) and Ad-SoS values ($p < 0.05$) than controls. Ad-SoS was higher in schizophrenic men ($p < 0.05$).
**Conclusions**  Schizophrenic women in treatment with antipsychotic drugs had a loss of phalangeal bone mass that was associated with the levels of vitamin D or PTH, and increased bone turnover. Copyright © 2008 John Wiley & Sons, Ltd.

KEY WORDS — antipsychotic drugs; bone mass; parathyroid hormone; phalangeal bone ultrasound; prolactin; vitamin D

## INTRODUCTION

The association between mental disorders, the use of antipsychotic drugs, and reduced bone mineral density (BMD) or bone mass, may represent a potential public health problem. In recent years there has been recognition of the possible decrease in BMD in psychiatric patients (Halbreich *et al.*, 2003), although the evaluation of its prevalence has yet to be fully documented.

Schizophrenia is often associated with risk factors for low BMD, as also are inadequate exercise, unbalanced diet, smoking, and alcohol dependency (Kishimoto *et al.*, 2005). Hyperprolactinæmia is commonly induced by those antipsychotics whose principal mechanism of action is blocking dopamine receptors, and it often occurs with conventional and only with some atypical (risperidone and amilsupride) antipsychotics (Haddad and Wieck, 2004). During the treatment of schizophrenia with antipsychotics, pro-

lactin (PRL) levels may rise by a factor of 10 or more over the pre-treatment values (Haddad and Wieck, 2004). Moreover, the disease and the medication can both lead to a hypogonadal state in men and women, which is also a risk factor for bone loss (Misra *et al.*, 2004).

In recent years, we have been using quantitative ultrasound (QUS) techniques as useful tools with which to detect rapid changes in bone mass caused by drugs (Pedrera *et al.*, 2000). Measurements made on the phalanges provide the best discrimination of patients at risk for fractures (Damilakis *et al.*, 2003). They are also of low cost and radiation free.

We conducted a study on a group of patients under chronic treatment with antipsychotic drugs in order to observe the changes in bone mass as measured by ultrasound, and identify the possible mechanisms by which these drugs may affect the bone. The association between PRL-raising antipsychotic medication and hip fracture may have serious implications for public health (Howard *et al.*, 2007). So, it is necessary to carry out further studies to clarify if these patients present a higher risk of osteoporosis and, in consequence, a higher fracture risk.

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## METHODS

We studied 73 patients with schizophrenia, in treatment with antipsychotic drugs, 25 postmenopausal women (mean age $59.84 \pm 17.01$ years) and 48 men (mean age $61.89 \pm 12.95$ years). All the patients fulfilled the DSM-IV and CIE-10 schizophrenia criteria. We also studied 73 subjects considered normal (control group), 25 women (mean age $60.37 \pm 17.16$ years), and 48 men (mean age $61.24 \pm 13.09$ years). Controls were matched with patients by age, weight, height, and gonadal status. The characteristics of the groups (number, age, anthropometric, ultrasound, and biochemical data) are summarized in Table 1. Patients had been under treatment for at least 5 years, and had been selected at the "Adolfo Díaz Ambrona" Psychiatric Hospital in Mérida. Of the schizophrenic women, 51.8% were taking conventional antipsychotics, 14.8% atypical antipsychotics, 14.8% conventional with atypical antipsychotics, and 18.5% admitted to being occasionally non-compliant with treatment. Of the schizophrenic men, 30.4% were taking conventional antipsychotics, 49% atypical antipsychotics, 12.8% conventional with atypical antipsychotics, and 7.7% of patients admitted to being occasionally non-compliant with treatment. Most of the patients showed combined therapies with two or more drugs, both in the case of patients treated with typical as well as atypical antipsychotics.

All subjects from control group were from the health district of Mérida, in Spain. In this group, a complete medical history was taken and a physical examination made before each candidate was enrolled in the study. Normality was established on the basis of an interview and biochemical measurements of blood. None of the persons in this group was taking antipsychotic drugs or medication that could interfere with calcium metabolism. Neither group had any dietary restrictions.

Medical history showed, in both groups, the non-existence of low-trauma fractures and other causes of elevated PRL (cushing's disease, pituitary adenoma, etc.) were excluded. All participants gave written informed consent. The research was approved by the Office for Protection of Research Risks of the University of Extremadura in accordance with the Helsinki Declaration of 1975.

Height was measured using a Harpenden stadiometer with mandible plane parallel to the floor, and weight was measured using a biomedical precision balance. Both measurements were performed in pajamas without shoes. The body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in metres ($kg/m^2$).

### Ultrasound studies

Before the study, conventional radiographs of both hands were made to exclude pathological alterations at the sites of measurements. Bone status was assessed using an ultrasound device model DBM Sonic 1200[R] (IGEA, Capri, Italy), which measures

Table 1.  Characteristics of the groups studied

|  | Women | | Men | |
|---|---|---|---|---|
|  | Patients | Controls | Patients | Controls |
| *n* | 25 | 25 | 48 | 48 |
| Age (years) | $59.84 \pm 17.01$ | $60.37 \pm 17.16$ | $61.89 \pm 12.95$ | $61.24 \pm 13.09$ |
| Weight (kg) | $70.12 \pm 16.63$ | $62.90 \pm 7.25^*$ | $73.67 \pm 15.31$ | $75.01 \pm 11.16$ |
| Height (m) | $1.59 \pm 0.06$ | $1.54 \pm 0.07^{**}$ | $1.68 \pm 0.06$ | $1.68 \pm 0.07$ |
| BMI ($kg/m^2$) | $27.6 \pm 6.3$ | $26.4 \pm 3.5$ | $25.9 \pm 4.9$ | $26.5 \pm 2.6$ |
| Ad-SOS (m/s) | $2003 \pm 86$ | $2050 \pm 66^*$ | $2068 \pm 59$ | $2037 \pm 69^*$ |
| *T*-score | $-1.7 \pm 1.2$ | $-1 \pm 0.9^*$ | $-0.8 \pm 0.8$ | $-1.2 \pm 1^*$ |
| *T*-score (%) | $-21 \pm 15$ | $-12 \pm 11^*$ | $-10 \pm 10$ | $-15 \pm 13^*$ |
| *Z*-score | $0.07 \pm 1.2$ | $0.2 \pm 0.9$ | $0.9 \pm 1.3$ | $0.4 \pm 1^*$ |
| *Z*-score (%) | $3 \pm 23$ | $5 \pm 15$ | $19 \pm 25$ | $6 \pm 16^*$ |
| PRL (ng/ml) | $19.65 \pm 14.98$ | $6.76 \pm 3.22^{***}$ | $7.27 \pm 5.88$ | $5.45 \pm 3.15$ |
| 25(OH)D3 (ng/ml) | $20.42 \pm 26.05$ | $33.12 \pm 19.42^{***}$ | $15.12 \pm 11.96$ | $18.13 \pm 15.43$ |
| PTH (pg/ml) | $77.44 \pm 45.77$ | $52.23 \pm 38.59^{***}$ | $46.36 \pm 23.52$ | $40.16 \pm 30.15$ |
| TPr (g/L[1]) | $76 \pm 4$ | $72 \pm 4$ | $75 \pm 4$ | $74 \pm 4$ |
| AlPh ($\mu$kat/L) | $3.2 \pm 0.92$ | $1.60 \pm 0.62^{***}$ | $1.62 \pm 0.73$ | $1.51 \pm 0.60$ |
| TRAP (nkat/L) | $72 \pm 12$ | $58 \pm 8^{***}$ | $53 \pm 11$ | $48 \pm 7$ |
| AST ($\mu$kat/L) | $0.33 \pm 0.07$ | $0.37 \pm 0.08$ | $0.36 \pm 0.05$ | $0.37 \pm 0.07$ |
| ALT ($\mu$kat/L) | $0.21 \pm 0.05$ | $0.22 \pm 0.08$ | $0.24 \pm 0.05$ | $0.25 \pm 0.07$ |

BMI, body mass index; Ad-SOS, phalangeal amplitude-dependent speed of sound; PRL, prolactin; 25(OH)D3, 25-hydroxyvitamin D; PTH, parathyroid hormone; TPr, total proteins; AlPh, total alkaline phosphatase; TRAP, tartrate-resistant acid phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase
$^*p < 0.05$; $^{**}p < 0.001$; $^{***}p < 0.0001$ vs. patients according to ANOVA and Student's *t*-test.

amplitude-dependent speed of sound (Ad-SoS) in metres per second. Measurements were made in the phalanges (II–V) of the non-dominant hand and an average value was computed. Coupling was achieved by means of standard ultrasound gel. Two 16 mm diameter, 1.25 MHz transducers were assembled on a high-precision calliper, which measured the distance between the probes. The probes were positioned on the mediolateral phalangeal surfaces using the phalanx head as a reference point. Positioning and repositioning of the instrument was easy because it used the prominences of the lower phalangeal epiphysis as reference for placing the clip just behind the prominences. To limit the influence of surrounding soft tissue, each measurement started with the determination of the speed of the sound through soft tissue in the interdigital region. These measurements were performed between thumb and index finger, as this site is considered representative for soft-tissue velocity in the hand. The measured value was used to calculate a correction factor that was applied automatically by the system to the subsequent speed-of-sound results for the whole phalanx. The instrument's precision was determined from three measurements in eight subjects made at time intervals not exceeding 21 days. The coefficient of variation (CV) was 0.77%. Inter-observer CV was 1.1%.

### Analytical studies

No smoking, coffee, tea, or alcohol intake, or exercise was permitted for 24 h before the day of investigation. Urine samples were collected in the morning after an overnight fast. Venous blood samples for hæmatological, biochemical, PRL, parathyroid hormone (PTH), and 25-hydroxyvitamin D (25(OH)D3) studies were obtained in a fasting state at 08:00 h. The biochemistry included: transaminases, creatinine, calcium, phosphorus, total proteins, bilirubin, alkaline phosphatase (AlPh), tartrate-resistant acid phosphatase (TRAP), and a coagulation study. In all cases, calcium was corrected for proteins according to Parfitt (1969). A biochemical study of calcium excretion and tubular phosphatase resorption was made on a 24 h urine sample. Serum concentrations were measured using a BM/Hitachi automated analyzer System 717 (Boehringer, Mannheim, Germany). Serum TRAP was quantified in the Hitachi automated analyzer with $\alpha$-naphthyl substrate, using a reagent from Boehringer Laboratories (Boehringer, Mannheim, Germany) that reacts specifically with isoenzyme $5\beta$ synthesized by osteoclasts (Rico and Villa, 1993). Twenty-four-hour urinary calcium excretion was determined by atomic absorption spectroscopy using a Perkin Elmer model 5000 spectrophotometer (Perkin Elmer, Norfolk, CT, USA). Blood samples were centrifuged and the serum was stored at $-20°C$ until assay. All samples were analyzed in the same assay to eliminate inter-assay variation. Assay reproducibility was determined by assaying four samples five times in different runs. The CV between runs was determined by components of variance (Descos et al., 1979). In every case, the CV was less than 6%. PRL was determined using the PROL-CTK-4 kit (DiaSorin, Saluggia-Vercelli, Italy). This kit establishes the following expected values of PTH as usual: men $< 18$ ng/ml and postmenopausal women $< 9$ ng/ml. PTH was determined using the Intact PTH IRMA kit (Nichols Institute Diagnostic, San Juan Capistrano, CA, USA). 25(OH)D3 was determined with the RIA test ($^{125}$I RIA Kit), of DiaSorin (Stillwater, Minnesota, USA). The intra-assay and inter-assay CV was $< 8\%$ in all cases.

### Statistical studies

All values were expressed as mean $\pm$ SD. The normal distribution of data was confirmed by calculating the skewness and kurtosis before applying standard tests. The groups (patients and controls) were compared using analysis of variance to determine the differences. A maximum $p$-value of $< 0.05$ was the condition necessary for statistical significance. Regression and correlation analyses were used as appropriate to examine relationships betweens continuous variables. These studies were carried out with the Stat View 5.0.1 program (SAS Institute Inc., Cary, NC, USA) on a Macintosh computer.

### RESULTS

The results obtained for the variables analyzed are listed in Table 1. The schizophrenic women had higher values of weight, height, and PRL and PTH levels than controls ($p < 0.05$, $p < 0.001$, $p < 0.0001$, and $p < 0.0001$, respectively), but lower Ad-SoS and 25(OH)D3 values ($p < 0.05$ and $p < 0.0001$, respectively). The schizophrenic men had higher Ad-SoS values than controls ($p < 0.05$).

In the group of schizophrenic women, 67.9% had PRL values above 9 ng/ml, 74.1% had 25(OH)D3 values below 15 ng/ml, the lower limit of the accepted normal range which defines vitamin D deficiency by convention (Scharla, 1998), and 72.4% had PTH levels above 65 pg/ml, the accepted upper limit. In the group of schizophrenic men, 30.6% had PRL values
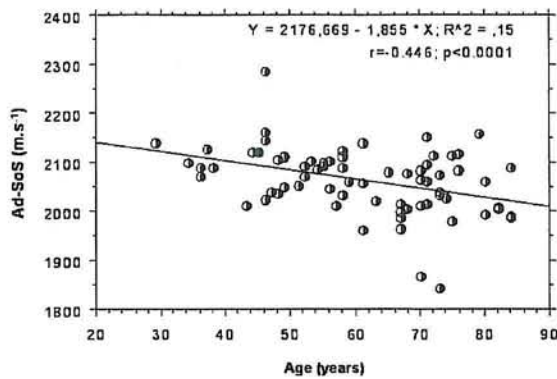
Figure 1. Simple linear regression of phalangeal amplitude-dependent of sound (Ad-SOS m/s) with age (years) in schizophrenic patients



Figure 3. Simple linear regression of 25(OH)D3 (ng/ml) with PTH (pg/ml) in schizophrenic patients

above 9 ng/ml, 69.56% had 25(OH)D3 values below 15 ng/ml, and 86.0% had normal levels of PTH.

Correlation studies (Fisher's $r$-to-$z$) of the overall group of patients, revealed significant positive correlations between Ad-SoS and both weight and height ($r = 0.246$, $r = 0.386$, respectively; $p < 0.05$ in both), between PRL and PTH levels ($r = 0.347$, $p < 0.05$), and between 25(OH)D3 and BMI values ($r = 0.653$, $p < 0.0001$). There were statistically significant negative correlations between Ad-SoS and age (Figure 1), BMI, and PTH (Figure 2) ($r = -0.446$, $p < 0.0001$; $r = -0.304$, $p < 0.05$; $r = -0.290$, $p < 0.05$; respectively), between the 25(OH)D3 and PTH levels ($r = -0.472$, $p < 0.0001$) (Figure 3), and between the PTH and BMI values ($r = -0.418$, $p = 0.0001$). Similar correlations were observed when patients were separated by sex. In the control group there was a significant positive correlation between Ad-SoS and height ($r = 0.365$, $p < 0.05$), and significant negative correlations between Ad-SoS and both, age and BMI
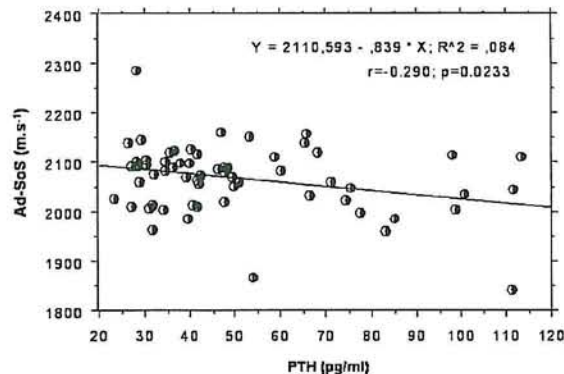
($r = -0.553$, $p < 0.0001$; $r = -0.235$, $p < 0.05$; respectively).

By means of a stepwise analysis, stratifying the patients according to the type of antipsychotics that they consume, and taking the Ad-SoS as the dependent variable and the rest of the variables (anthropometric, biological and biochemical) as independent variables, in the group of patients under treatment with conventional antipsychotics, we found a significant negative correlation with serum PRL levels ($\beta = -3.812$, $p = 0.0005$).

Other baseline biochemical values are listed in Table 1. The only significant differences found were for the AlPh and TRAP levels between the schizophrenic women and their controls ($p < 0.0001$ in both).

## DISCUSSION

Phalangeal bone ultrasound measurements seem to be appropriate techniques to test bone mass in normal and pathological circumstances. In fact, several authors have used these techniques for evaluation (Ventura *et al.*, 1996; Durosier *et al.*, 2007; Gemalmaz *et al.*, 2007). QUS measurements have been proven to be effective in the screening of osteoporosis in postmenopausal women (Benitez *et al.*, 2000). QUS also has several advantages compared to the radiological devices: these are non-invasive methods, which are safe, simple, free of radiation, portable, and relatively inexpensive (Wüster and Hadji, 2001).

The weight gain induced by antipsychotic drugs has been extensively described, and may be responsible for an increase in morbidity and mortality in patients with schizophrenia (Kurzthaler and Fleischhacker, 2001). It has been suggested that moderate increase in weight may improve bone mineralization (Bainbridge *et al.*,



Figure 2. Simple linear regression of phalangeal amplitude-dependent of sound (Ad-SOS m/s) with PTH (pg/ml) in schizophrenic patients
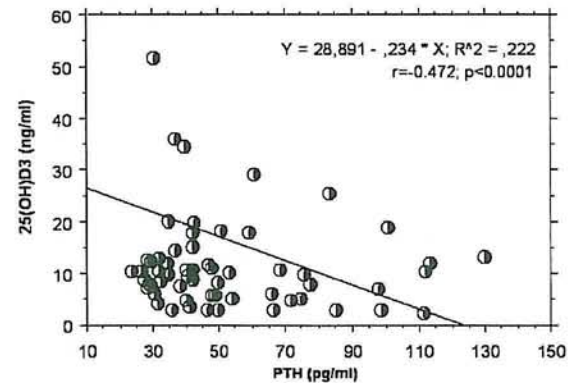
2004), and indeed osteoporosis is found to be less common in obese individuals who also show higher BMD (Yilmazi *et al.*, 2005). The schizophrenic women of our study, however, showed less bone mass than the controls as assessed by ultrasound, despite being significantly weightier—a finding that was therefore contrary to what would have been expected from the protective effect of weight on bone mass.

We analyzed three factors possibly responsible for the absence of any positive effect of increased weight on the bone mass of these patients: hyperprolactinæmia, and the high levels of PTH and low levels of 25(OH)D3 in serum.

It is known that antipsychotic drug treatment is related to high levels of PRL (Halbreich *et al.*, 2003; Haddad and Wieck, 2004; Howes *et al.*, 2005), and that its long-term consequences include bone loss (Haddad and Wieck, 2004; Meaney *et al.*, 2004). We found that 67% of the schizophrenic women in our study had PRL levels that were significantly higher than the women in the control group. This may be linked to their lower bone mass, as their Ad-SoS values were significantly lower than the controls. Conventional antipsychotics, which most of the schizophrenic women in the present study were taking, cause greater increases in PRL than atypical antipsychotics (Misra *et al.*, 2004). We would thus associate their lower bone mass to this cause, especially as it was corroborated by the significant negative correlation between bone mass and PRL levels that we observed in these patients. This correlation was not observed in men, probably because 49% of them were taking atypical antipsychotics and only two men were treated with risperidone on monotherapy. It is described that the combination of risperidone with other atypical antipsychotics causes lower PRL levels then when it is used on monotherapy (Henderson *et al.*, 2001).

In a study carried out in 2006 with schizophrenic patients treated with haloperidol, Jung *et al.* (2006) obtained results similar to those obtained by us. This way, female patients, but not male, showed significantly lower BMD, using densitometry techniques by DEXA (dual-energy X-ray absorptiometry), than the normal controls as seen in all bone regions studied. Therefore, BMD loss in patients with schizophrenia tended to differ by gender.

Bone loss in schizophrenic patients has principally been attributed to the hypogonadism caused by the hyperprolactinæmia associated with the chronic consumption of antipsychotic drugs (Haddad and Wieck, 2004; Lean and De Smedt, 2004; Meaney *et al.*, 2004). There are probably two mechanisms for the bone loss caused by the œstrogen deficiency resulting from hyperprolactinæmia in women: activation of new bone re-modeling sites, and worsening of the imbalance between bone formation and resorption (Lindsay and Cosman, 2001).

Serum levels of 25(OH)D3 and 1,25(OH)2D3 are lower in psychiatric patients who are schizophrenics and with severe depression than in healthy subjects (Schneider *et al.*, 2000). This is coherent with the present results in which 74% of the schizophrenic women had low serum levels of 25(OH)D3 and high levels of PTH. There was also a significant negative correlation between the two parameters in both men and women schizophrenics, also in agreement with the results reported in studies in other groups (Kudlacek *et al.*, 2003; von Muhlen *et al.*, 2005; Need, 2006).

The ultrasound techniques used in the present study showed a negative correlation between the Ad-SoS and the serum levels of PTH. This is coherent with the negative correlation between BMD and serum PTH levels observed using densitometry techniques by DEXA (Carnevale *et al.*, 2004; von Muhlen *et al.*, 2005). Also, PTH preferentially increases resorption at the cortical bone level (Cormier, 2006), which is the bone compartment that we evaluate with phalangeal ultrasound techniques and with which we observed a negative relationship between bone mass and PTH in the schizophrenic patients. Although we observed no correlation between 25(OH)D3 and Ad-SoS in our study, we believe that there must exist a relationship between vitamin D and bone mass in these patients since we found biochemical evidence of osteomalacia—low 25(OH)D3 levels and high PTH levels—with increased bone turnover in those women with low serum levels of 25(OH)D3.

Nevertheless, we consider necessary to make further studies in order to deepen in potential factors of confusion which could affect negatively to schizophrenic patients' bone mass: inadequate exercise, unbalanced diet, smoking, alcohol dependency, etc.

## CONCLUSION

The women in our study, both patients and controls, presented accelerated bone turnover consistent with their gonadal status. The schizophrenic women, however, in response to their 25(OH)D3 insufficiency associated with secondary hyperparathyroidism, hyperprolactinæmia, and faster bone turnover than the women in the control group, showed bone loss probably due to the effect of their antipsychotic drugs. The men did not show this effect.

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