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Bone mineral density as a marker of cumulative endogenous estrogen exposure: Relationship to background genetic risk of psychotic disorder

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ABSTRACT

Background: Alterations in bone mineral density (BMD) in patients with psychotic disorder may reflect the effect of treatment (disease effect observed in patients but not their siblings) or, as an intermediate marker of cumulative endogenous estrogen exposure, alterations in the neuroprotective effect of estrogen in the brain (vulnerability effect observed in patients and siblings).
Methods: Dual X-ray absorptiometry (DEXA) scans were acquired in 62 patients with a psychotic disorder, 67 non-psychotic siblings of patients with a psychotic disorder, and 48 controls. BMD (g/cm^2), Z-scores and T-scores were measured in the lumbar spine and proximal femur. Associations between group and BMD were investigated with multilevel random regression analyses. Group × sex interactions and effects of antipsychotic medication (AP) on BMD were examined.
Results: Group was not associated with BMD outcome measures, although patients had consistently lower BMD measures compared to both siblings and controls. There were no significant group × sex interactions, but stratified analyses showed that BMD measures in female patients were significantly lower in comparison to female controls and siblings (e.g. total femoral BMD, P vs. C: $B = -0.100$, $p = 0.010$; P vs. S: $B = -0.104$, $p = 0.008$). After excluding female patients who used prolactin-raising AP, the effect was attenuated (e.g. total femoral BMD, P vs. C: $B = -0.073$, $p = 0.072$; P vs. S: $B = -0.085$, $p = 0.051$). In men, there were no significant BMD differences between patients and controls.
Conclusion: Familial risk of psychotic disorder was not associated with BMD. Instead, decreased BMD in the femur may reflect treatment effects or non-familial risk associated with low cumulative endogenous estrogen levels in women.

1. Introduction

In the past decade, an increased awareness of compromised skeletal status in patients with psychotic disorder has developed. This is based on findings of reduced bone mineral density (BMD) in this population, possibly resulting from a high prevalence of risk factors for osteoporosis (Haddad and Wieck, 2004; Halbreich, 2007). Some risk factors for osteoporosis may be inherent to positive and negative symptomatology such as polydipsia (Delva et al., 1989), diminished dietary intake, decreased physical activity and reduced sunlight exposure. In addition, comorbid substance abuse may further influence vulnerability for osteoporosis, as alcohol and cannabis have been shown to affect bone metabolism (Bab et al., 2009; Maurel et al., 2012). Hyperprolactinemia-induced hypogonadism, secondary to treatment with potent dopamine-2 receptor antagonists, has also been proposed as a factor contributing to loss of bone mass in schizophrenia (Bilici et al., 2002; Abraham et al., 2003a; Meaney et al., 2004; Meaney and O'Keane, 2007; Kishimoto et al., 2008). Notably, not all studies have found evidence for BMD reduction in patients (Howes et al., 2005), or for an effect of prolactin-raising antipsychotic drugs (AP) on BMD (Lee et al., 2010; Renn et al., 2010).

While there is evidence for decreased BMD specifically in male patients with schizophrenia (Hummer et al., 2005; Lehman and Meyer, 2005; Meyer and Lehman, 2006; Kishimoto et al., 2008), there are also studies suggesting that female patients are particularly vulnerable to compromised skeletal status (Partti et al., 2010), with some evidence for higher bone turnover, but normal bone mineral density (Abraham et al., 2003b; Bergemann et al., 2008).

The above mentioned studies (all cross-sectional, with the exception of two (Abraham et al., 2003b; Meaney and O'Keane, 2007)), differ with respect to cohort characteristics (e.g. sample size, stage of

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illness, male and/or female participants, women in pre- or postmenopausal phase) and correction for confounding factors, which may have contributed to an inconsistent pattern of results. Nevertheless, most studies are suggestive of reduced BMD in schizophrenia.

Loss of BMD may be a consequence of psychotic disorder or its treatment, but an alternative hypothesis is that a reduction in BMD, as a marker of cumulative endogenous estrogen exposure (Clemons and Goss, 2001), is an indicator of risk for and development of psychotic disorder (due to diminished neuroprotection of estrogen in the brain) (Maric et al., 2005). A primary low endogenous estrogen level may be associated with genetic risk of the disorder (intermediate phenotype) or, alternatively, represent a non-familial marker of risk.

The aim of the present study was to examine BMD in subjects at high genetic risk of psychotic disorder (patients with psychotic disorder) and subjects at higher than average genetic risk (unaffected siblings of patients with psychotic disorder) in comparison with individuals at average genetic risk of psychotic disorder (healthy controls). We hypothesized that BMD, as a marker of cumulative endogenous estrogen exposure, would be reduced in both patients and siblings, reflecting shared familial liability. The objective was not to identify a large, clinically relevant decline in BMD (e.g. to be able to pinpoint and reduce fracture risk), but to discern a difference, even small, that may be related to the (familial) etiology of schizophrenia and other psychotic disorders.

2. Materials and methods

2.1. Subjects

Data was collected in the context of an ongoing longitudinal study in Maastricht, The Netherlands (Habets et al., 2011; Korver et al., 2012). In selected representative geographic areas in The Netherlands and Belgium, patients presenting consecutively at mental health services either as outpatients or inpatients were recruited for the study. Siblings were sampled through participating patients. Control subjects were recruited from the same population as the cases using random mailings in nearby municipalities and through advertisement in newspapers. Patients between the ages of 16 and 50 years with a diagnosis of non-organic, non-affective psychosis were included. Sufficient command of the Dutch language was an additional criterion for inclusion. Diagnosis was based on DSM-IV criteria (APA, 2000), assessed with the Comprehensive Assessment of Symptoms and History (CASH) interview (Andreasen et al., 1992). The CASH was also used to confirm the absence of a diagnosis of non-affective psychosis in the siblings, and absence of a diagnosis of any psychotic disorder in the control subjects. For the control subjects, the occurrence of any psychotic disorder in either the subject or any first-degree family member, assessed using the Family Interview for Genetic Studies, constituted an exclusion criterion.

The sample consisted of 62 patients with a psychotic disorder (of whom 50 patients had a diagnosis of schizophrenia, 4 patients had a diagnosis of schizoaffective disorder, 7 patients had a diagnosis of psychotic disorder not otherwise specified and 1 patient had a diagnosis of brief psychotic disorder), 67 non-psychotic siblings and 48 controls. The sample included 36 families, of which 24 families contributed one patient and one sibling and two families contributed one patient and 2 siblings. One family contributed two patients and one sibling; in one family one patient and 3 siblings participated. Two families contributed two siblings but no patients. In the control group, six families contributed two siblings. Thirty-three independent patients, 31 independent siblings, and 36 independent controls participated.

Nine controls and sixteen siblings had a history of major depressive disorder (MDD). In addition, one sibling was diagnosed with dysthymic disorder and one with mood disorder due to a general medical condition.

Prior to DEXA acquisition, participants were screened for the following exclusion criteria: 1) metabolic or endocrinologic disease, 2) dietary deficiency or eating disorder, 3) medication use: corticosteroids, thyroxin, anti-epileptics, heparin, lithium, cytostatic agents, 4) (semi-)professional athletes, 5) polydipsia (>3 l/day), 6) pregnancy, and 7) hormonal (infertility) treatment.

2.2. Measures

2.2.1. Substance use

Substance use was assessed using the Composite International Diagnostic Interview (CIDI) (WHO, 1990). Cannabis use was assessed as reported lifetime frequency of use. Other drug use, such as stimulants, sedatives, opiates, cocaine, PCP, psychedelics, inhalants or other (e.g. ecstasy, poppers) was assessed in the same way. Alcohol use was defined as the average number of weekly instances of consumption during the previous 12 months. Tobacco use was defined as the number of cigarettes, cigars or pipes per day, or number of daily occasions of use of chewing tobacco or snuff.

2.2.2. Physical activity and sunlight exposure

Physical activity and sunlight exposure were expressed in total minutes per week.

To quantify physical activity, the total amount of time spent on commuting by foot or bicycle, physical activity at work or school, household chores, active hobbies and sports was summed. Sunlight exposure was calculated by multiplying the number of days per week a person went outside by the average number of minutes spent outside on those days.

2.2.3. AP use

Current AP use was classified by AP type: “prolactin-raising”, i.e. first-generation APs, risperidone and amisulpride; or “prolactin-sparing”, i.e. second or third-generation APs with the exception of risperidone and amisulpride.

2.2.4. Use of contraceptive drugs (cumulative exogenous estrogen exposure)

Cumulative exogenous estrogen exposure in women was determined by multiplying the daily dose with the total days of use, expressed in micrograms.

2.2.5. Age at menarche and dysmenorrhea

Age at menarche and the occurrence of menstrual irregularity were assessed in women. Dysmenorrhea was defined as altered duration and/or frequency of menses or the absence of two or more menses during the previous three months. Amenorrhea was defined as the absence of menses for at least three months.

2.2.6. Familial osteoporosis

The occurrence of familial osteoporosis was documented.

2.3. DEXA acquisition and processing

DEXA scans were acquired at the Maastricht University Medical Center with a Hologic Discovery A (Tromp Medical, Castricum, The Netherlands) (NHANES and Ethnic Reference Data). DEXA scans of two anatomical areas were performed: the lumbar spine, vertebrae L2 through L4; and the proximal left femur, specifically the collum, trochanter major, intertrochanteric area and Ward's triangle. BMD was expressed in grams per square centimeter (g/cm^2), Z-scores and T-scores. The Z-score compares an individual's BMD with the mean BMD of a comparable population (with respect to gender, age and ethnicity). The T-score compares an individual's BMD to peak bone mass (PBM). Peak bone mass is the highest BMD an individual is expected to acquire during life. The T-score is used to diagnose osteopenia and osteoporosis. The World Health Organization employs the following criteria: T-scores in osteopenia lie between −1.0 and −2.5; T-scores in osteoporosis are equal or less than −2.5.