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# Cross-sex pattern of bone mineral density in early onset gender identity disorder

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**Abstract**

Hormonally controlled differences in bone mineral density (BMD) between males and females are well studied. The effects of cross-sex hormones on bone metabolism in patients with early onset gender identity disorder (EO-GID), however, are unclear. We examined BMD, total body fat (TBF) and total lean body mass (TLBM) in patients prior to initiation of sex hormone treatment and during treatment at months 3 and 12. The study included 33 EO-GID patients who were approved for sex reassignment and a control group of 122 healthy Norwegians (males, $n=77$; females, $n=45$). Male patients ($n=12$) received an oral dose of 50 μg ethinylestradiol daily for the first 3 months and 100 μg daily thereafter. Female patients ($n=21$) received 250 mg testosterone enantate intramuscularly every third week. BMD, TBF and TLBM were estimated using dual energy X-ray absorptiometry (DXA). In male patients, the DXA measurements except TBF were significantly lower compared to their same-sex control group at baseline and did not change during treatment. In female patients, the DXA measurements were slightly higher than in same-sex controls at baseline and also remained unchanged during treatment. In conclusion, this study reports that body composition and bone density of EO-GID patients show less pronounced sex differences compared to controls and that bone density was unaffected by cross-sex hormone treatment.


*Keywords:* Gender identity disorder; Bone metabolism; BMD; Estrogen receptors; Estrogen; Testosterone; Gonadotropin

## Introduction

Sex is the major predictor of and contributing factor to skeletal size and shape. Evidence from twin and family studies suggests that between 50 and 85% of the variance in peak bone mass (bony tissue present at the end of the skeletal maturation) is genetically determined (Gueguen et al., 1995; Krall and Dawson-Hughes, 1993). Many candidate genes have been identified that regulate bone mass and susceptibility to osteoporosis, but the full profile of such genes and their variants remain to be defined (Ralston and de Crombrugghe, 2006). Furthermore, bone mineral density (BMD) has also been found to be determined by environmental factors such as diet and lifestyle (Falch, 1982; Lewiecki, 2005). Nevertheless, gonadal hormones have an important modulating impact on bone physiology in both sexes (Turner et al., 1995). Prior to puberty, boys and girls gain BMD at similar rates. After puberty, men tend to acquire greater BMD than women (overview provided by the National Institute of Arthritis Musculoskeletal and Skin Disease at The National Institute of Health, www.niams.nih.gov).

The propose role of sex hormones, such as estrogens, in bone physiology is supported by the marked bone loss seen at menopause or after castration, a process mediated by increased osteoclastic bone resorption (Riggs et al., 1998). Menopause leads to accelerated bone loss that plateaus after 5 to 10 years (Gennari et al., 2002). Conversely, several studies have shown a significant effect of estrogen substitution on reduction of bone loss and fracture risk in postmenopausal women (Lindsay,

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2004). Moreover, estrogens have a strong influence on both fetal bone growth and on postnatally imprinted bone cells (i.e., pubertal growth or closure of the epiphyses) (Couse and Korach, 1999; Manolagas et al., 2002; Parfitt, 2002).

The role for androgens in bone physiology is supported by reduced BMD seen in androgen-deprived prostate cancer patients (Basaria et al., 2002; Wakley et al., 1991). Withdrawal of testosterone has been shown to increase osteoclast activity and thus increase bone loss (Bellido et al., 1995). Conversely, testosterone substitution increases BMD in cases of male hypogonadism (Katznelson et al., 1996), possibly by stimulating osteoblast proliferation and differentiation, thereby increasing matrix production and mineralization (Kasperk et al., 1989, 1997; Vanderschueren and Bouillon, 1995).

Estrogens and androgens appear to act synergistically on bone metabolism in both sexes (Kasperk et al., 1989; Zumoff et al., 1995). Patients with complete androgen insensitivity experienced pubertal growth when treated with estrogens, suggesting that estrogens are sufficient to induce pubertal growth in these patients when prematurely castrated (Zachmann et al., 1986). Furthermore, anabolic steroid treatment increases bone density in postmenopausal women (Kanis et al., 1992). Finally, hyperandrogenism appears to limit bone loss in female patients with polycystic ovary syndrome (Adami et al., 1998).

In both sexes, estrogens act through estrogen receptors alpha and beta (ER and ER). Males homozygous for an inactivating mutation of the *ER* gene show increased osteoporosis (Smith et al., 1994). A similar effect is described in men with an inactivating mutation of the gene encoding aromatase, the enzyme that converts androgens to estrogens (Bilezikian et al., 1998; Carani et al., 1997; Morishima et al., 1995). It is therefore likely that gene polymorphisms in hormone receptors and relevant enzymes play an important role for bone density in normal males and females (Gennari et al., 2002; Niu and Rosen, 2005; Valero et al., 2005). Estrogens are known to act directly with their receptors on osteoblasts, bone marrow stromal cells and osteoclasts (Bland, 2000; Cutler, 1997; Fiorelli et al., 1995; Grumbach and Auchus, 1999). One effect of estrogens is an increase in the absolute number of osteoblasts present in the bone marrow (Majeska et al., 1994), another is an indirect effects on osteoclasts by suppressing the production of bone-resorbing cytokines from osteoblasts and bone marrow stromal cells (Pacifici, 1998).

Physical activity is an important factor in modulating bone density (Frost, 1987, 1990; Schiessl et al., 1998). It is difficult, however, to separate the direct effects of exercise on BMD from the indirect effects of exercise-associated improvements in mobility and balance, which simply decreases the risk of falling (Fiatarone et al., 1990; Gass and Dawson-Hughes, 2006). High-impact physical training correlates with increased BMD, but low-impact exercise, such as walking, neither increases BMD nor reduces fracture risk (Going et al., 2003). It is postulated that exercise during pre-pubertal years and adolescence builds a skeleton with a high bone mineral density (BMD) and possibly a larger skeleton with different skeletal architecture (Nordstrom et al., 2005; Seeman, 2005). However, unlike the BMD calculated by DXA ($g/cm^2$), the true volumetric bone mineral density ($g/cm^3$) does not appear to increase with size and/or age. Variations in bone parameters during childhood and adolescence reflect changing growth and increased size rather than increased bone mineral per unit volume.

Increased remodeling rate is physiologic for rapid growth during puberty but could be pathologic in the mature skeleton (Manolagas et al., 2002). Unfortunately, no randomized, prospective study has documented an activity-associated reduction of fracture frequency to date (Karlsson, 2004). Nevertheless, BMD loss as a result of changing gravity in long-duration spaceflight strongly implies that mechanical input is indeed required for its maintenance density (Iwamoto et al., 2005; Lang et al., 2006).

Lean body mass and adipose tissue distribution also differ between men and women (Ross, 1996; Ross et al., 1994; Vogel and Friedl, 1992), and cross-sex estrogen and testosterone treatment induce changes in the typical gender-specific fat and muscle distribution patterns (Elbers et al., 1997, 1999). Cross-sex hormone treatment, as a current mode of intervention in adult gender identity disorder (GID) patients, results in considerable somatic changes. Several authors have reported that BMD and lean/adipose tissue distribution might be altered in a "cross-sex manner" (in parallel with changes in sex hormone levels; males showing female and females male values) as a result of such treatment (Dittrich et al., 2005; Goh and Ratnam, 1997; Lips et al., 1996a,b; Reutrakul et al., 1998; Ruetsche et al., 2005; van Kesteren et al., 1998).

In this study, we investigated potential variations in BMD and lean/adipose tissue distribution in a representative group of untreated Norwegian early onset GID patients compared to a Norwegian young adult reference group. Furthermore, we studied the longitudinal effects of cross-sex hormone treatment on these parameters in this particular patient group.

## Subjects and methods

### *Inclusion criteria*

Thirty-three somatically healthy EO-GID patients with symptom onset at <12 years of age and who consecutively sought sex reassignment surgery (SRS) in Norway between 1996 and 1999 were included (21 females and 12 males). Patients' age ranged from 20 to 46 years of age (21 females, mean age (SD)=25.1 (4.8) years and 12 males, mean age (SD)=29.3 (7.8) years). All patients were evaluated according to the Harry Benjamin International Gender Dysphoria Association's Standards of Care [1990 and 1998 (Levine et al., 1998)]. In two independent comprehensive evaluations through structured interviews with two individual senior psychiatrists, all patients fulfilled criteria A to D in DSM-IV from childhood on (<12 years of age). From the perspective of their sex, their sexual preferences at the time of investigation were distributed as follows: (1) attracted to the same-sex only ($n$=30), (2) attracted to both sexes ($n$=2) or (3) attracted to neither sex ($n$=1).

### *Controls*

A group of 122 young persons in the same age range consisting of 77 males (age (SD)=33.9 (9.3)) and 45 females (mean age (SD)=38.6 (6.1)) were selected as controls from a Norwegian reference population for National BMD, total body fat and lean body mass determination ($n$=372) (Falch, 2004; Falch and Meyer, 1996; Faulkner et al., 1996).