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Low bone mass is prevalent in male-to-female transsexual persons before the start of cross-sex hormonal therapy and gonadectomy☆,☆☆,★,★★

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ABSTRACT

Objective: Cross-sex hormonal therapy and sex reassignment surgery (including gonadectomy) in transsexual persons has an impact on body composition and bone mass and size. However, it is not clear whether baseline differences in bone and body composition between transsexual persons and controls before cross-sex hormonal therapy play a role.
Design: A cross-sectional study with 25 male-to-female transsexual persons (transsexual women) before cross-gender sex steroid exposure (median age 30 years) in comparison with 25 age-matched control men and a male reference population of 941 men.
Main outcome measures: Areal and volumetric bone parameters using respectively dual energy X-ray absorptiometry (DXA) and peripheral quantitative computed tomography (pQCT), body composition (DXA), grip strength (hand dynamometer), Baecke physical activity questionnaire, serum testosterone and 25-OH vitamin D.
Results: Transsexual women before cross-sex hormonal therapy presented with less muscle mass ($p \leq 0.001$) and strength ($p \leq 0.05$) and a higher prevalence of osteoporosis (16%) with a lower aBMD at the hip, femoral neck, total body (all $p < 0.001$) and lumbar spine ($p = 0.064$) compared with control men. A thinner radial cortex ($p \leq 0.01$) and lower cortical area at the radius and tibia (both $p < 0.05$) was found in transsexual women vs. control men. Serum testosterone was comparable in all 3 groups, but 25-OH vitamin D was lower in transsexual women ($p \leq 0.001$).
Conclusions: Transsexual women before the start of hormonal therapy appear to have lower muscle mass and strength and lower bone mass compared with control men. These baseline differences in bone mass might be related to a less active lifestyle.

Introduction

Male-to-female transsexual persons, also named 'transsexual women', undergo drastic changes in body composition and bone mass due to cross-sex hormonal therapy and sex reassignment surgery (SRS, incl. gonadectomy, vaginoplasty) [1–10]. Up till now, conflicting results have been reported. Most published reports demonstrated a maintained areal bone mineral density (aBMD) after several years of cross-sex hormonal therapy and SRS [3,5,7,12] or even an increase in aBMD after minimum 2 years of treatment [1,6,8–10]. However, a decrease in aBMD in transsexual women using less than 2 years of cross-sex hormonal therapy has been observed [8] and after median 8 years of estrogen therapy transsexual women seemed to have a lower aBMD, volumetric bone mineral density (vBMD) and smaller bone size in relation to lower muscle mass and strength compared with male controls [4,11]. Next to insufficient compliance with estrogen substitution therapy after SRS, another possible reason for the lower aBMD in transsexual women compared with control men, could be the status of bone and body composition before the start of hormonal therapy and SRS. Only one study compared transsexual women before the start of cross-sex hormones and SRS with healthy control men [3]. Other research only described the rate of change of aBMD during hormonal therapy in retrospective [1,6,12] or, prospective [7] design and a few cross-sectional

Abbreviations: aBMD, areal bone mineral density; vBMD, volumetric bone mineral density; BMC, bone mineral content; pQCT, peripheral quantitative computed tomography.

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★★ Precis: Transsexual women before the start of hormonal therapy appear to have a lower bone mass and less muscle mass and strength. These baseline differences might be related to a less active lifestyle.

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studies compared transsexual women with control males after 8 months up to 12.5 years of cross-sex hormonal therapy [4,5,9,10]. Haraldsen and colleagues observed a lower aBMD and lean body mass and higher fat body mass in 21 transsexual women prior to hormonal therapy compared with control males [3]. This study and nearly all but two other studies [4,5] used classical dual X-ray absorptiometry (DXA), which has limitations due to its two-dimensional projection technique: i.e. larger bones and projection of soft tissue (i.e. fat mass) can lead to an overestimated aBMD [13].

In this study, we assessed the body composition and bone mass in a group of transsexual women before any kind of hormonal treatment and SRS compared with age-matched control men. In particular, we evaluated both areal bone density using DXA and volumetric bone parameters using peripheral quantitative computed tomography (pQCT).

Materials and Methods

Study Design and Population

All transsexual participants were diagnosed with gender identity disorder (DSM-IV, 302.85; ICD-10, F64.0) and were recruited from the center for Sexology and Gender Problems at the Ghent University Hospital, Belgium. Every patient was treated in accordance with the World Professional Association for Transgender Health standards of care [14].

This research is part of the 'European network for the investigation of gender incongruence' (ENIGI), a collaboration of four major West European gender identity clinics (Amsterdam, Ghent, Hamburg and Oslo) [15], a study group created to obtain more transparency in diagnostics and treatment of gender identity disorder.

Fifty-eight transsexual women were included in the study. After screening by thorough medical history and determination of serum sex steroids, 8 of them had been using or still used anti-androgens or estrogen substitution therapy. Those participants were excluded from the study. We selected all transsexual women at the age of peak bone mass (between 24 and 46 years old) and compared this group with age-matched control men and with a previously described male reference population, a cohort of young healthy male siblings at the age of peak bone mass (n = 941) [16]. Peak bone mass was considered the stable bone mass in men at the ages between 25 and 45 years [17].

A final number of 25 transsexual women who had never used any kind of cross-sex hormonal treatment nor anti-androgen therapy, and thus before SRS, was included. Serum testosterone, SHBG and estradiol levels of the 25 included transsexual women were comparable to that of age-matched control men. All participants were Caucasian. The male control population, matched for age (±2 year, median 1 year), were healthy men recruited from suburban communities around Ghent or who responded on posters spread at the Ghent University Hospital and on its website and in schools.

Exclusion criteria for both groups were defined as illnesses or medication use known to affect body composition, hormone levels or bone metabolism such as current, prolonged or previous use (in the last 2 years) of glucocorticosteroids, (anti)androgens, estrogens, calcium and/or vitamin D supplements, antiepileptic drugs, calcitonin, bisphophonates; presence of hypogonadism, untreated hyperthyroidism, cystic fibrosis, malabsorption, eating disorders or disorders of collagen metabolism or bone development, chronic renal failure and autoimmune rheumatoid disease.

All participants were currently in good physical health and completed questionnaires about previous illness and medication use, current and past smoking habits and physical activity by recording the weekly frequency of sports, recreational and/or working activities (using the Baecke questionnaire [18]). Fracture prevalence in the participants was recorded after exclusion of finger, toe, and cranial fractures (a criterion used in previous literature on the male cohort) [19]. Family history on fractures was available by the prevalence of significant fractures in the participants' parents.

The study protocol was approved by the ethics review board of the Ghent University Hospital and all participants gave written informed consent.

Body Composition, Muscle Strength and Areal Bone Parameters

Body weight and anthropometrics were measured in light indoor clothing without shoes. Standing height was measured using a wall-mounted Harpenden stadiometer (Holtain, Ltd., Crymuch, UK).

Grip strength at the dominant hand was measured using an adjustable hand-held standard grip device (JAMAR hand dynamometer, Sammons and Preston, Bolingbrook, IL, USA). The maximum strength of 3 attempts was assumed to best reflect the current status and history of their musculoskeletal adaptation and was expressed in kilograms (kg).

Body fat and lean mass, bone mineral content (BMC), bone area and areal bone mineral density (aBMD) at the lumbar spine and left proximal femur (total hip and femoral neck region) were measured using dual X-ray absorptiometry (DXA) with a Hologic Discovery device (Software Version 11.2.1, Hologic, Inc., Bedford, MA, USA). The coefficient of variation for both spine and whole-body calibration phantoms was less than 1%, as calculated from daily and weekly measurements, respectively.

Volumetric Bone Parameters and Cross-sectional Muscle and Fat Area

A pQCT device (XCT-2000. Stratec Medizintechnik, Pforzheim, Germany) was used to evaluate the cortical volumetric bone parameters at the dominant midradius and tibia (at 66% of bone length) and trabecular bone parameters at the metaphysis (at 4% of bone length) of the dominant radius. Procedure details were as described previously [16].

Serum Analysis

Serum testosterone was determined by liquid chromatography tandem mass spectroscopy (AB Sciex 5500 triple-quadrupole mass spectrometer; AB Sciex, Toronto, Canada) and 25-OH vitamin D by electrochemiluminescence immunoassay, ECLIA (Modular, Roche Diagnostics, Mannheim, Germany). Seasonality was ruled out as all participants were recruited throughout the entire year.

Statistical Analysis

Descriptives are expressed as mean and standard deviation or median [1st to 3rd quartile], when criteria for normal distribution were not fulfilled. *P*-values <0.05 were considered to indicate statistical significance, all tests were two-tailed. Comparison of general characteristics and body composition between groups was made with an independent t-test or Mann–Whitney-U-test when variables were not normally distributed (Table 1). In qualitative variables, chi-square test or, when appropriate, Fisher's exact test was used. Multiple regression analysis was used to compare bone parameters in transsexual women and male controls (Tables 2–4) and used models included height, weight and a grouping variable (transsexual or control group) as independents. The p-value of this grouping variable is indicated in the tables. Correlations were performed using Pearson's correlation coefficient (r) or Spearman's rank correlation coefficient (r_s) when variables were not normally distributed. Data were analyzed using SPSS-software, version 19 (SPSS Inc., Chicago, IL).