UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL
PROGRAMA DE PÓS GRADUAÇÃO EM CIÊNCIAS MÉDICAS:
ENDOCRINOLOGIA

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TERAPIA HORMONAL CRUZADA, DENSIDADE MINERAL ÓSSEA E COMPOSIÇÃO CORPORAL EM INDIVÍDUOS TRANSGÊNEROS

Porto Alegre – RS
2018

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Tese de Doutorado apresentada ao Programa de Pós-Graduação em Ciências Médicas: Endocrinologia da Universidade Federal do Rio Grande do Sul como requisito parcial para obtenção do título de Doutor em Endocrinologia.

Orientadora Profa. Dra. Poli Mara Spritzer

Porto Alegre – RS

2018

AGRADECIMENTOS

Agradeço à minha orientadora, Poli Mara Spritzer, que me ensinou pelo exemplo não apenas Endocrinologia, mas ética e comprometimento com a pesquisa.

À Victoria Zeghbi Cochenski Borba e Carolina Aguiar Moreira, que foram a inspiração para o estudo das doenças osteometabólicas. À Gisah Musialowski do Amaral e César Luiz Boguszewski, exemplos de médicos com quem tive a honra de aprender Endocrinologia.

Aos colegas da Unidade de Endocrinologia Ginecológica do Serviço de Endocrinologia do Hospital de Clínicas de Porto Alegre, Eliane Dias da Silva, Betânia Rodrigues dos Santos, Thaís Rasia da Silva, Lucas Bandeira Marchesan, Gislaine Casanova, Laís Lima Ferreira, Gustavo Borba e Ramon Bossardi. Aos que terminaram sua jornada neste Serviço, mas deixaram um pouco de si, Denise Rovinski, Guilherme Cardenaz de Souza e Cristiane Kopacek. Obrigada pela amizade, pelo aprendizado e pela convivência. À Miriam Sant'Helena e Natália Goulart, obrigada pelo apoio técnico, mas principalmente pelo carinho incondicional todos os dias.

Agradeço aos meus pais, Airton José Fighera e Tânia Carpes Muniz, à minha irmã, Tiziane Muniz Fighera Back, e minha afilhada querida, Manuella Fighera Back, que me incentivaram em todos os momentos, desde sempre, através de uma palavra, um gesto, ou simplesmente estando por perto nas incontáveis horas de estudo. Aos meus avós, Ivo Matteo Muniz e Clory Carpes Muniz, que acreditaram em mim quando nem mesmo eu acreditava. Ao meu marido, Lucas Giron Bernaud, obrigada por estar sempre ao meu lado e fazer de mim uma pessoa melhor.

Finalmente, e acima de tudo, agradeço à Deus.

Esta tese de doutorado segue o formato proposto pelo Programa de Pós-Graduação em Ciências Médicas: Endocrinologia: Faculdade de Medicina, Universidade Federal do Rio Grande do Sul. Será apresentada na forma de manuscritos sobre o tema da Tese:

- Artigo original: Impact of cross-sex hormone therapy on bone mineral density and body composition in transwomen. Clin Endocrinol 2018, 88 (6): 856-862.
- Artigo original: Bone mass effects of cross-sex hormone therapy in transgender people: updated systematic review and meta-analysis. **Artigo submetido** – jc.2018-02632, em dezembro de 2018.

LISTA DE ABREVIATURAS E SIGLAS

BMD / DMO = bone mineral density / densidade mineral óssea
CSHT = cross-sex hormone therapy / terapia hormonal cruzada
DXA = dual-energy X-ray absorptiometry / absorciometria de raio-X de dupla energia
GAS / CAS = gender affirmation surgery / cirurgia de afirmação sexual
TH = terapia hormonal

SUMÁRIO

RESUMO

A disforia de gênero é definida pela incongruência entre o sexo de nascimento e o sexo de identidade, com duração superior a 6 meses. Esta condição está associada a sofrimento pessoal e prejuízo em diferentes áreas, e os indivíduos submetidos à terapia hormonal (TH) cruzada podem apresentar melhora da qualidade de vida com o tratamento adequado.

A TH cruzada tem como objetivo principal suprimir os hormônios endógenos e as características sexuais secundárias do sexo biológico e induzir características sexuais compatíveis com o sexo de identidade. Em indivíduos submetidos à cirurgia de afirmação sexual (CAS), a TH cruzada é utilizada como forma de reposição hormonal, uma vez que o procedimento gera uma situação de hipogonadismo persistente. A TH cruzada inadequada ou irregular, neste contexto, poderia acarretar prejuízo à saúde óssea e maior risco de baixa massa óssea e/ou fraturas.

No que se refere às mulheres trans, os estudos mostram aumento ou preservação da densidade mineral óssea (DMO) na coluna lombar quando avaliada a massa óssea antes e após a terapia estrogênica. Quando comparadas aos controles do sexo masculino, a terapia estrogênica parece não afetar significativamente a DMO nos sítios avaliados. No presente estudo, uma elevada prevalência de baixa massa óssea foi observada em mulheres trans quando comparadas a controles de ambos os sexos. A maior parte das mulheres trans avaliada utilizava terapia estrogênica por longo período de forma irregular, e um terço já havia realizado CAS.

No que se refere aos homens trans, não foi observada diferença significativa na DMO considerando a massa óssea antes e após a terapia androgênica, ou quando comparado aos controles do sexo feminino.

As evidências atuais indicam que a TH cruzada não afeta a DMO em homens trans, e em mulheres trans está associada a aumento da DMO na coluna lombar. Contudo, as evidências são de baixa à moderada qualidade, e estudos com maior tempo de acompanhamento e uso regular da TH são necessários para confirmar estes dados.

ABSTRACT

Gender dysphoria is defined by the incongruence between the biological sex and the sex of identity, lasting more than 6 months. This condition may be associated with personal distress and impairment in different areas, and individuals undergoing cross-sex hormone therapy (CSHT) may have improvement in quality of life with appropriate treatment.

The main objective of CSHT is to suppress endogenous hormone secretion and the sex characteristics of the expressed gender and maintain sex hormone levels and sex characteristics consistent with the other gender. In individuals undergoing gender affirmation surgery (GAS), CSHT is used as hormone replacement, since the procedure generates a condition of persistent hypogonadism. Inadequate or irregular CSHT in this context could lead to bone health impairment and increased risk of low bone mass and / or fractures.

Regarding trans women, studies showed a preservation or increase in bone mineral density (BMD) in the lumbar spine when evaluated bone mass before and after estrogen therapy. When compared to male controls, estrogen therapy did not significantly affect BMD at any site evaluated. In our study, higher prevalence of low bone mass was observed in trans women compared to natal men and women. Most of the trans women evaluated used irregular estrogen therapy for long period, and a third had already performed CAS.

Regarding trans men, no significant difference was observed in BMD considering bone mass before and after androgen therapy, or when compared to female controls.

Current evidence indicates that CSHT does not affect BMD in trans men, and in trans women it is associated with increased BMD in lumbar spine. However, the evidence is of low and moderate quality and further studies with regular CSHT and longer follow-up are needed to confirm this data in trans women.

INTRODUÇÃO

Disforia/Incongruência de gênero

A disforia de gênero é definida pelo desconforto persistente e sensação de inadequação no papel do gênero expresso ao nascimento. É uma condição marcada pelo sofrimento psicológico que acompanha a incongruência entre o gênero de nascimento e o gênero desejado (1,2). Epidemiologicamente, a prevalência da disforia de gênero é difícil de ser avaliada. Dados da Holanda e Bélgica mostram que 1:11.900 homens e 1:30.400 mulheres apresentam disforia de gênero com desejo de tratamento hormonal e/ou cirúrgico, com uma razão de aproximadamente 3:1 (3,4). Em uma meta-análise sobre prevalência de transexualismo que incluiu 12 estudos, foi observada prevalência de 4.6 pessoas trans para cada 100.000 indivíduos (6.8 para mulheres trans e 2.6 para homens trans) (5). Com relação à etiologia, os dados ainda são limitados. Estudos com ressonância magnética estrutural e functional do cérebro de indivíduos transgêneros mostram diferenças na espessura cortical, substância branca e ativação de áreas distintas do sistema nervosa central quando comparados a controles (6). É possivel que estas diferenças sejam uma resposta adaptativa à diferentes comportamentos, mais do que uma etiologia para disforia de gênero (7).

O tratamento de afirmação sexual é multidisciplinar, focado na atenuação dos sintomas disfóricos relacionados à imagem corporal, incluindo abordagem psicosocial, TH cruzada e CAS, quando esta for desejada pelo indivíduo (8). Em homens e mulheres trans, a TH cruzada está associada à melhora da qualidade de vida do ponto de vista mental, psicosocial e auto-estima (9,10), redução de sintomas de ansiedade (10) e de sintomas dissociativos (11). As mudanças físicas induzidas pelo tratamento, compatíveis com o gênero de identidade, possivelmente reforçam a afirmação do gênero, melhoram o bem estar e a aceitação pessoal e social do indivíduo (12,13). Apesar das manisfestações clínicas desta condição ocasionalmente iniciarem na infância, apenas uma pequena parte persiste com disforia do gênero até a vida adulta. Por este motivo, o momento adequado para iniciar a transição deve ser individualizado, mas as evidências atuais suportam a indicação de tratamento com esteroides sexuais preferencialmente a partir dos 16 anos (8,14).

Terapia hormonal cruzada

A TH é realizada com o objetivo de suprimir os hormônios sexuais endógenos e as características sexuais secundárias do sexo biológico, e manter os níveis hormonais e características sexuais do sexo de identidade. Em mulheres trans não gonadectomizadas, a terapia estrogênica é utilizada em associação com anti-andrógenos. Não há uma recomendação unânime com relação à escolha do anti-andrógeno, sendo a espironolactona e o acetato de ciproterona os mais utilizados (15). As mudanças físicas podem ser perceptíveis já nos primeiros meses de tratamento. Entre 3 e 12 meses após o início da TH cruzada, pode ocorrer redução das ereções espontâneas, redução dos pelos corporais, aumento do tecido mamário e redistribuição da gordura com predomínio ginoide (16). Nos homens trans, o tratamento é baseado no uso de diferentes formulações de testosterona intramuscular ou transdérmica, com o objetivo de atingir concentrações fisiológicas deste hormônio, compatíveis com o gênero desejado (17). Nos primeiros 6 meses de tratamento ocorre já, com frequência, interrupção dos ciclos menstruais, aumento do desejo sexual e pelos corporais, aumento da massa muscular e redistribuição da gordura corporal com predomínio androide. Em 30% dos indivíduos os ciclos menstruais não cessam com o uso da testosterona e a associação com um progestágeno pode ser necessária. Alterações na voz, clitoromegalia e alopecia podem ocorrer após o primeiro ano de tratamento (16,17).

Para muitos indivíduos, a CAS pode ser uma etapa importante para satisfação plena com o gênero desejado. A remoção das gônadas em homens e mulheres afeta a fertilidade de forma irreversível e a TH cruzada neste contexto é necessária como reposição hormonal em indivíduos com hipogonadismo permanente após a cirurgia. A má aderência ou insatisfação do indivíduo com a TH cruzada durante o processo de transição são parâmetros que contra-indicam o procedimento de redesignação sexual (8).

Esteroides sexuais e a massa óssea

Os esteroides sexuais atuam diretamente na aquisição e preservação da massa óssea em ambos os sexos (18). As diferenças na formação óssea periosteal entre homens e mulheres são consideradas um reflexo da ação estimulatória da

testosterona nos homens, e da ação inibitória do estrogênio nas mulheres. Durante a puberdade, a aquisição de massa óssea é aproximadamente 10% maior em meninos do que em meninas. Esta diferença ocorre principalmente devido à maior expansão periosteal, estimulada pela massa muscular e atividade física, maior tempo de crescimento puberal e exposição direta aos androgênios (19,20). A testosterona pode agir diretamente no tecido ósseo através do receptor androgênico ou indiretamente via aromatização em estradiol (18). Além disso, ao aumentar a massa muscular, age de forma indireta estimulando a formação óssea (21). Contudo, estudos em modelos animais mostram que baixas concentrações de estrogênio são essenciais para a ação androgênica, considerando que a inativação do receptor estrogênico α ou da aromatase resulta em menor crescimento ósseo radial (22,23). Dessa forma, o processo de expansão óssea periosteal tipicamente associado ao fenótipo masculino, pode ser estimulado, em parte, pelo estrogênio. O estrogênio é o principal regulador da homeostase óssea, atuando em todo o processo de remodelamento que inclui osteócitos, osteoblastos e osteoclastos. Favorece a formação óssea por reduzir a apoptose de osteócitos e osteoblastos. Por outro lado, diminui a reabsorção óssea, inibindo a osteoclastogênese e induzindo apoptose e menor diferenciação dos osteoclastos (24).

Em indivíduos transgêneros, a TH cruzada pode influenciar a massa óssea diretamente ou indiretamente através de alterações na composição corporal (25). O uso de terapia estrogênica em mulheres trans parece ter efeito favorável sobre o tecido ósseo (26,27), porém a supressão prolongada da testosterona pode estar associada a redução da massa e da força muscular (28). Alguns trabalhos mostram maior prevalência de baixa massa óssea e menor tamanho de osso cortical em mulheres trans quando comparadas aos controles homens (29-31), sendo alguns destes trabalhos em indivíduos virgens de tratamento (31,32). Estes achados indicam que outros fatores não hormonais podem influenciar a massa óssea destes indivíduos. A terapia androgênica, por outro lado, está associada ao aumento da massa muscular (33-35), o que poderia explicar o discreto aumento do diâmetro de osso cortical (33,36) e da massa óssea observado em alguns estudos (26,37) (Figura 1). Independente do gênero, a idade de início da TH possivelmente é um fator determinante no impacto sobre a massa óssea, assim como o uso regular da reposição hormonal, principalmente em indivíduos submetidos a CAS (20).

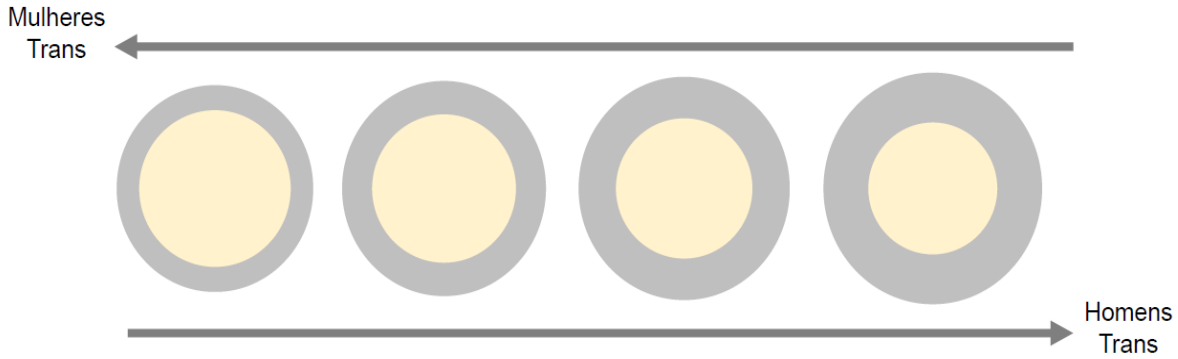

Figura 1: Adaptado de Van Caenegem and T'Sjoen (27)

TH cruzada e parâmetros de composição corporal

A composição corporal realizada por DXA é o método de escolha para avaliar os diferentes compartimentos corporais. A partir da aquisição de uma imagem de corpo total, permite a quantificação da massa magra e massa gorda do corpo inteiro e de regiões pré-definidas por linhas de referência. Além disso, é um método com baixo coeficiente de variação e mínima exposição a radiação (38).

Os esteroides sexuais são determinantes na distribuição de gordura e massa magra em diferentes regiões corporais. Desde a puberdade, as meninas apresentam acúmulo de gordura na região ginoide, enquanto os meninos apresentam maior desenvolvimento da massa muscular e concentração de gordura na região androide (39). Achados similares são observados com a TH cruzada em indivíduos transgêneros. Estas mudanças corporais nos compartimentos de massa gorda e massa magra permitem a melhor aceitação da imagem corporal, compatível com o sexo de identidade. Estudos em mulheres trans mostram que a terapia estrogênica está associada ao aumento da gordura corporal, com predomínio da gordura ginoide, e diminuição da massa magra. Efeito oposto é observado em homens trans durante a terapia androgênica, com redução da gordura ginoide e aumento da massa magra (35,40).

Com base nestas considerações, o objetivo deste estudo foi avaliar a massa óssea e os parâmetros de composição corporal de indivíduos com disforia de gênero submetidos a terapia hormonal cruzada.

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PARTE 1

Impact of cross-sex hormone therapy on bone mineral density and body composition in transwomen

Artigo publicado na Clinical Endocrinology 2018, 88 (6): 856-862

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Article type : 4 Original Article - Americas

Impact of Cross-Sex Hormone Therapy on Bone Mineral Density and Body Composition in Transwomen

Running title: Impact of CSHT on BMD in transwomen

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Acknowledgments

This work was supported by grants from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq)/Brazilian National Institute of Hormones and Women's Health (CNPq/INCT 465482/2014-7). The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflict of Interest Statement

The authors declare no competing interests.

Summary

Objective: Cross-sex hormone therapy (CSHT) has been associated with changes in bone and lean/fat mass. This study assessed BMD, appendicular lean mass (ALM), and total fat mass in transwomen undergoing CSHT.

Patients and Design: We evaluated 142 transwomen (mean age: 33.7±10.3 years; BMI: 25.4±4.6; 86.6% with previous CSHT) during the first three months of regular estrogen treatment (with or without anti-androgens). A reference group including 22 men and 17 cis women was also studied.

Measurements: Clinical and hormonal evaluation and dual energy X-ray absorptiometry (DXA).

Results: BMD was similar in trans and reference women, and lower at all sites in transwomen vs. men. Low bone mass for age was observed in 18% of transwomen at baseline vs. none of the reference women or men. ALM and total fat mass were positively correlated with L1-L4 BMD, explaining 14.9% of the observed variation in lumbar spine BMD and 20.6% of the variation in total femur BMD. ALM was similar in trans and reference women, and lower in transwomen vs. men. Total fat mass was lower in trans vs. reference women. Densitometry was repeated after a mean of 31.3±6.5 months in 46 transwomen. There was a significant increase in total fat mass and a significant decrease in ALM. BMD remained stable over time.

Conclusions: The fairly high prevalence of low bone mass in this sample of transwomen from southern Brazil seems to be related to lower ALM. Non-pharmacological lifestyle-related strategies for preventing bone loss could be beneficial for transgender women receiving long-term CSHT.

Key words

Transsexualism, cross-sex hormone treatment, bone mineral density, lean mass, fat mass, DXA

Introduction

Gender dysphoria is defined as the desire to live and be accepted as a member of the opposite sex, often accompanied by the wish to make the body congruent with the sex of identity through cross-sex hormone therapy (CSHT) and gender-affirming surgery. The two major goals of CSHT are to reduce endogenous sex hormone levels and the secondary characteristics of the individual's assigned sex and to maintain sex hormone levels consistent with the individual's gender identity[1].

Sex steroids are important determinants of bone acquisition and bone homeostasis. In men, testosterone stimulates the process of periosteal apposition during puberty, producing ~~a~~ greater cortical bone size and wider bones as compared to women[2,3]. Male to female transsexual individuals (transwomen) undergo estrogen therapy associated or not

with anti-androgens, reducing endogenous testosterone and inducing feminization. While some studies report that transwomen undergoing testosterone deprivation are at risk of low bone mass[4,5], other studies show preservation of bone mineral density (BMD) in the first years of treatment[6-8]. Loss of bone mass has been reported as more likely after gender-affirming surgery in transwomen who are less compliant with estrogen therapy[9]. However, there are few data regarding long-term CSHT effects on bone in transwomen, with contradictory results from most studies, which are also limited by their small samples[4,6,10,11].

Both lean and fat mass have been positively correlated with BMD. However, the relative contribution of each type of mass remains to be established[12]. The positive relationship between BMD and lean mass[13,14] reported by some studies is usually stronger than that detected for fat mass[15]. Low lean mass has been suggested as a risk factor for fracture in older adults independently of BMD or other risk factors, but the clinical utility of this indicator to predict relevant endpoints, such as fractures, is also unclear[16,17]. In turn, the relationship between fat mass and bone health is more controversial[18,19], but recent evidence suggests a positive association between the two[20].

Taking these aspects into consideration, the aims of this study were to assess BMD and body composition over time in transwomen undergoing CSHT, and to analyze the relationship of bone mass with body fat and muscle mass in this group.

Material and Methods

Subjects and study protocol

Transwomen were recruited from the outpatient endocrine clinic of the Gender Identity Program at the Hospital de Clínicas de Porto Alegre (HCPA), Brazil. Individuals receiving CSHT for at least 3 months and who signed the informed consent form were enrolled. Transwomen receiving CSHT who had already undergone gender-affirming surgery were also eligible.

Considering that participants might have used some CSHT for variable periods of time before the study, the baseline assessment was performed 3 months after the start of the standard Gender Identity Program CSHT. After enrollment, assessments were performed according to the Program's usual protocol: clinical follow-up every 3 months in the first year and twice a year after that, with laboratory tests performed every 6 or 12 months,

depending on individual clinical conditions. BMD and body composition are evaluated by DXA at 3 months. For the present study, a second DXA was performed in all women with at least 1 year of follow-up.

Thirty-nine individuals (22 men and 17 cis women) aged between 18 and 40 years were selected after advertisement in the hospital's home page and served as a reference group. This group underwent the same protocol described for transwomen. Blood samples of cis women were obtained at the follicular phase of the menstrual cycle.

CSHT is provided free of charge by the public health care system to participants of the Gender Identity Program (estradiol valerate 1-4 mg/d or conjugated equine estrogen 0.625-2.500mg/d associated with spironolactone 50-150mg/d or cyproterone acetate 50-100mg/d, depending on availability). A few transgender women received transdermal 17β-estradiol 0.5-2mg/d for individual clinical reasons. Dosages were individualized according to clinical response. Most of the participants who had already been submitted to gender-affirming surgery received estrogen-only treatment.

The study protocol was approved by the Ethics Committee at Hospital de Clínicas de Porto Alegre (University Hospital), and all participants signed an informed consent form before joining the protocol.

Hormone measurements

Venous blood samples were obtained after a 12-hour fast. Blood samples were collected between 8 a.m. and 10 a.m. Total testosterone levels were measured by chemiluminescence immunoassay (CLIA, Siemens Advia, Centaur XP), with sensitivity of 10 ng/mL and intra and interassay coefficient of variation (CV) of 3.3 and 7.5% respectively. Estradiol was measured by electro-chemiluminescence immunoassay (ECLIA, Roche Diagnostics, Mannheim, Germany), with assay sensitivity of 5.0 pg/mL and intra- and interassay CV of 5.7 and 6.4% respectively. SHBG was measured by CLIA (Immulite 2000), with sensitivity of 0.02 nmol/L and intra- and interassay CV of 5.3 and 6.6% respectively. Free androgen index (FAI) was estimated by dividing total testosterone (TT) (in nanomoles per liter) by sex hormone binding globulin (SHBG) (in nanomoles per liter)×100.

BMD and body composition

Anthropometric data including weight, height and body mass index were assessed at the first visit. BMD and body composition were assessed by dual-energy X-ray absorptiometry (DXA) using a Lunar Prodigy Primo device (Encore version 14.10, Radiation

Corporation, Madison, WI). BMD was measured in lumbar spine (L1-L4), femoral neck and total femur of the left side and expressed as g/cm^2. In the presence of artifacts, a right femur scan was performed. Z-score for BMD was calculated using age-matched controls from the National Health and Nutrition Examination Survey III study group (NHANES III). Male reference values were used for transgender women and cis men, and female reference values were used for cis women. The coefficient of variation for lumbar spine and femur was 0.022g/cm² (1.8%) and 0.033g/cm² (1.9%) respectively. DXA quality control is performed daily by the same technician, with variation < 2%. Low bone mass was considered as Z-score ≤ -2.0 SD for age. Appendicular lean mass (ALM), obtained by measuring lean mass in both arms and legs, and total fat mass (FM) were expressed as kg and acquired with measurements of the whole body.

Statistical analysis

Data were expressed as means ± standard deviation (SD) for variables with normal distribution and medians and interquartile range for variables with non-Gaussian distribution. Comparisons between groups were performed by one-way ANOVA followed by the Tukey post hoc test and the chi-square (χ^2) test for categorical variables. Variables without normal distribution were log-transformed for statistical analysis and back-transformed into their original units for presentation. Paired-sample t-test was used to compare variables from the same transgender women over time. Correlations were assessed using Pearson's correlation coefficient. Two multiple linear regression models were carried out with age, estradiol, total fat mass and ALM as independent variables and BMD of lumbar spine and total femur as dependent variables. The Statistical Package for the Social Sciences (SPSS version 18) (Chicago, IL, USA) was used for analysis. A p-value < 0.05 was considered to be statistically significant.

Results

We evaluated 142 transwomen receiving CSHT. Regarding skin color, 96% of participants were white and the remaining subjects were of mixed African/European ancestry. Regarding formal education, 54% had completed high school and 10% had a university degree. CSHT had been used previously by 123 (86.6%) participants for variable periods of time. Thirty-three (33%) participants had already undergone gender-affirming surgery. This group was older than those with no surgery (37.1±10.6 years vs. 32.6±9.9 years, p=0.029). Concerning other clinical variables, no differences were found between participants with or without surgery.

Table 1 shows baseline hormone levels, BMD, and body composition in transwomen and reference participants. Age and BMI were similar in both groups. Transwomen had intermediate median estradiol and serum TT levels when compared to reference men and women. SHBG and FAI levels were similar in trans and reference women. However, these levels were significantly lower in transwomen when compared to reference men. ALM was similar in transgender women as compared to reference women, but lower than in reference men. Conversely, total fat mass was lower in transwomen vs. reference women, and similar in transwomen and reference men.

Regarding bone mass, BMD was similar in trans and reference women at the three sites considered, but trans women had significantly lower L1-L4 BMD, femoral neck BMD, femoral neck Z-score, total femur BMD, and total femur Z-score in comparison to reference men. The frequency of low bone mass for age in transwomen was 18.3%, while in the reference groups all individuals had normal bone mass for age (p=0.001). A positive correlation was observed between ALM and L1-L4 BMD (r=0.327, p=0.0001) (Figure 1A), which remained significant after adjustment for TT (r=0.300, p=0.001). The correlation between total fat mass and L1-L4 BMD was also positive (r=0.334, p=0.0001) (Figure 1B), even after adjustment for estradiol (r=0.345, p=0.000).

Multiple linear regression analysis was performed to examine the independent contribution of age, estradiol, total fat mass, and ALM to BMD in transgender women (Table 2). In model 1, fat mass and ALM were independent predictors of L1-L4 BMD, explaining 14.9% of the variance at this site. In model 2, age and fat mass were predictors of total femur BMD, explaining 20.6% of the variance (Table 2).

In order to assess the effect of CSHT over time on BMD and body composition, a sub-sample of 46 transwomen with at least 1 year of follow-up underwent a second densitometry after a mean of 31.3±6.5 months (12 to 40 months). Estradiol and testosterone levels were similar to baseline in this subgroup. BMD also remained stable over time at all sites. A significant increase in total body fat was observed, along with a slight but significant decrease in ALM (Table 3).

Discussion

In the present study, transwomen had lower lumbar spine and femur BMD when compared to men. In addition, 18% of transwomen had low bone mass (z-score < -2 SD). Still, no changes in BMD were observed in a subgroup that was followed up for a mean of 31

months. BMD was also positively correlated with muscle and fat mass, which in turn contributed to variation in bone mass. These results provide novel evidence that bone mass may be, at least in part, influenced by changes in body composition secondary to CSHT.

Data regarding the effect of CSHT on BMD in transwomen are conflicting. While some studies report that estrogen therapy is able to maintain bone mass[21,22], others have observed a significant decrease in BMD despite CSHT[6,23]. In addition, some of the studies reporting an increase in bone mass with estrogen therapy were in fact performed over a short-term period of less than 2 years[2,10,24,25]. Indeed, Wiepjes et al[2] have recently described an increase in lumbar spine (+3.67%), total hip (+0.97%), and femoral neck (+1.86%) BMD in the presence of estrogen and antiandrogen therapy in a multicenter study including 231 transgender women undergoing CSHT for 1 year. Moreover, a systematic review and meta-analysis[26] **including** 392 transwomen revealed an increase in BMD at the lumbar spine, but not at femoral neck, after 12 and 24 months of estrogen therapy. The increased BMD observed in the first years of CSHT in those studies might have resulted from estrogen-mediated filling of the remodeling space, affecting the balance of osteoblast and osteoclast activity and suppressing bone turnover[8,27]. In the present study, bone mass remained stable over time, perhaps because most transwomen had already used CSHT, albeit at irregular doses and for irregular periods of time, before starting a standard treatment at our outpatient clinic.

Some studies with small sample sizes have shown a high prevalence of osteoporosis and osteopenia in transwomen after long-term CSHT. Wierckx et al[28] evaluated 50 transwomen after gender-affirming surgery and 10 years of regular estrogen therapy. In that group, the frequency of osteoporosis was 23.4% at the lumbar spine, 8.7% at femoral neck, 2.1% at the total hip, and 25.5% at the left radius. Another study[29] showed similar results after 15 years of CSHT. A retrospective analysis including 45 transwomen with mean age of 39.5 years reported that 75% were osteopenic. Also, T'Soen et al[4] evaluated 50 transwomen at least 3 years after the start of CSHT and 1 year after gender-affirming surgery. A prevalence of 26% of low bone mass at lumbar spine and 2% at the total hip was found, but no significant differences on hormone values were observed between subjects with a Z-score > or < -2.0. Taken together, data from these studies and the present work suggest that transgender women undergoing CSHT may be at risk for low bone mass, mainly after long-term hormone treatment.

Changes in body composition could exert a role in bone mass variation in transwomen during treatment. In this sense, the reduction of endogenous testosterone in transwomen could lead to loss of muscle and gain of fat mass, as reported by Lapauw et al[6]. Using DXA, those authors examined the body composition of 23 subjects treated with CSHT for 8 years. They found that total lean mass was 20% lower, and total fat mass was 30% higher, as compared to a male control group. Other studies showed similar results[21,25,28]. The main mechanisms underlying the adverse effect of muscle loss on bone status include decreased mechanical stimuli, since muscle mass has been shown to be an important factor in the acquisition of bone geometry in adulthood[17,30]. By promoting deprivation of the anabolic activity of testosterone, CSHT might cause an increase in fat mass and a decrease in muscle mass, leading to less bone surface strain and smaller bone size over time[6].

While in the present study we found a slight but significant decrease in ALM, a positive correlation between lumbar spine BMD and both ALM and fat mass was observed. These changes are expected as part of the female sexual transition, and may explain, at least in part, the impact of CSHT on BMD in transwomen. ALM and fat mass were independent predictors of lumbar spine BMD, explaining approximately 15% of the bone mass variation in this site. Regarding total femur BMD, age and fat mass were also independent predictors, explaining 20% of BMD variation at this site. These results are similar to those found by Ho-Pham et al[20], who observed that age and fat mass are positively associated with BMD in men and women. Considering the prevalence of 18% of low bone mass detected in our group of transwomen, the increase in fat mass observed may not be enough to prevent the bone loss that is possibly related to lower ALM. Another possible explanation for the high prevalence of low bone mass in our group of transwomen might be the presence of this condition prior to the start of CSHT[31], perhaps as a result of a low level of physical activity[32,33].

One strength of our study is the focus on a less well represented ethnic group, transgender women from southern Brazil. Also, all BMD and body composition data were measured using the same equipment and were analyzed by the same researcher (TMF), which increases the reliability of the results. Conversely, a limitation was the impossibility of recording the baseline BMD and body composition of participants before the start of CSHT, since most transwomen were already using some kind of CSHT when they entered the study protocol. Another limitation was the lack of data on physical activity, dietary calcium and vitamin D intake, and daily sun exposure. However, below a latitude of approximately 35° (which is the case of the city where the study was performed), UVB radiation is known to be sufficient for year-round vitamin D synthesis[34].

In conclusion, the prevalence of low bone mass for age was fairly high in this sample of transwomen from southern Brazil (18%). Lumbar spine BMD was lower than in reference men, but similar to that of reference women. These findings may reflect the lower ALM secondary to CSHT-suppressed levels of testosterone. Further long term studies are needed in order to determine the clinical relevance and the progressive nature of CSHT-related bone loss. Until then, monitoring of bone mass by DXA should be considered at any time in individuals who are not compliant with hormone therapy or who develop risks for bone loss. In low-risk individuals, screening can be performed at age 60 years. Intervals between DXA testing should be individualized according to clinical status. Non-pharmacological lifestyle-related strategies for preventing bone loss may benefit transgender women receiving long-term CSHT.

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Table 1. Baseline hormonal features and body composition of transwomen and reference cis women and men

Variable	Transwomen (n=142)	Cis women (n=17)	Men (n=22)	p
Age	33.70 (10.29)	33.29 (5.26)	30.77 (5.89)	0.408
BMI	25.37 (4.62)	26.58 (5.16)	26.32 (3.91)	0.434
TT (nmol/L)	1.17 (0.38-16.01)[a]	0.79 (0.38-1.07)[b]	16.39 (11.54-18.61)[c]	**<0.001**
SHBG (nmol/L)	63.55 (40.37-99.17)[a]	49.55 (32.27-70.87)[a,b]	27.20 (20.82-36.22)[b]	**<0.001**
FAI	2.27 (0.50-36.51)[a]	1.48 (1.08-2.53)[a]	56.88 (49.86-66.76)[b]	**<0.001**
Estradiol (pmol/L)	166.11 (69.09-267.98)[a]	232.74 (154.73-379.58)[a]	70.48 (52.86-104.26)[b]	**<0.001**
ALM	22.32 (3.95)[a]	22.01 (10.10)[a]	27.43 (10.88)[b]	**0.003**
Total fat mass (kg)	20.78 (10.07)[a]	27.42 (10.87)[b]	22.01 (10.10)[a,b]	**0.040**
L1-L4 BMD (g/cm²)	1.150 (0.160)[a]	1.210 (0.110)[a,b]	1.250 (0.130)[b]	**0.022**
L1-L4 Z-score	-0.3 (1.3)	0.2 (0.9)	0.2 (1.1)	**0.025**
Femoral neck BMD (g/cm²)	1.010 (0.170)[a]	1.020 (0.100)[a,b]	1.130 (0.110)[b]	**0.004**
Femoral neck Z-score	-0.2 (1.3)[a]	0.1 (0.8)[a,b]	0.5 (0.8)[b]	**0.027**
Total femur BMD (g/cm²)	1.010 (0.150)[a]	0.990 (0.080)[a]	1.140 (0.110)[b]	**0.001**
Total femur Z-score	-0.4(1.0)[a]	0.0 (0.6)[a,b]	0.3 (0.8)[b]	**0.003**
% Low bone mass (n)	18.3 (26)[a]	0 (0)[b]	0 (0)[b]	**0.001**

Values are expressed as means ± SD or medians and 25–75 inter-quartile range (one-way ANOVA - *post hoc* Tukey test) or percentage (absolute number) (χ^2 test); different superscript letters in each row indicate which groups differ statistically for the specific variable.

BMI: body mass index, TT: total testosterone, SHBG: sex hormone binding globulin, FAI: free androgen index, ALM: appendicular lean mass, BMD: bone mineral density.

Table 2. Multiple linear regression analysis of lumbar spine/total femur BMD *vs.* age, estradiol, total fat mass and appendicular lean mass

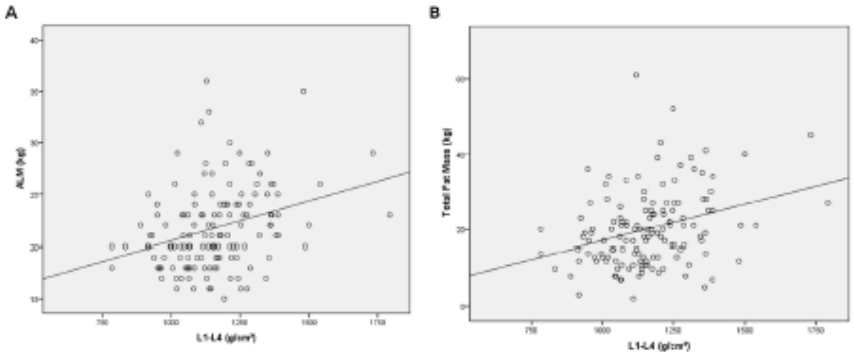
	B (95%CI)	p	R^2	Adjusted R^2
L1-L4 BMD vs.				
Age (years)	-0.002 (-0.005; 0.001)	0.165	0.177	0.149
Estradiol (pmol/L)	0.000 (0.000; 0.000)	0.369		
Total fat mass (kg)	0.005 (0.000; 0.000)	**0.001**		
Appendicular lean mass (kg)	0.009 (0.001; 0.016)	**0.022**		
Total femur BMD vs.				
Age (years)	-0.004 (-0.007; -0.002)	**0.001**	0.233	0.206
Estradiol (pmol/L)	0.083 (0.000; 0.000)	0.356		
Total fat mass (kg)	0.006 (0.000; 0.000)	**0.000**		
Appendicular lean mass (kg)	0.001 (-0.007; 0.009)	0.774		

Table 3. Hormone features and body composition at baseline and after 31 months of follow-up in 46 transwomen

	Baseline	31 months	p
Age (years)	33.70 (10.29)		
BMI	25.66 (4.16)	26.22 (3.96)	0.082
TT (nmol/L)	1.17 (0.48-15.87)	0.86 (0.31-13.31)	0.526
SHBG (nmol/L)	66.4 (39.5 - 95.5)	57.0 (33.5 - 73.6)	0.772
FAI	1.61 (0.51 - 22.3)	5.58 (0.41 - 43.6)	0.407
Estradiol (pmol/L)	209.25 (94.71-358.66)	128.12 (35.61-213.65)	0.082
ALM (kg)	22.3 (3.7)	21.5 (3.3)	**0.004**
Total fat mass (kg)	22.1 (8.7)	24.8 (9.4)	**0.003**
L1-L4 BMD	1.200 (0.190)	1.190 (0.180)	0.106
L1-L4 Z-score	-0.0 (1.5)	-0.2 (1.4)	0.118
Femoral neck BMD	1.030 (0.160)	1.030 (0.170)	0.409
Femoral neck Z-score	-0.1 (1.2)	-0.1 (1.2)	0.938
Total femur BMD	1.040 (0.160)	1.030 (0.160)	0.536
Total femur Z-score	-0.2 (1.0)	-0.3 (1.0)	0.711

Values are expressed as means ± SD or medians and 25–75 interquartile range (paired-sample t-test).

BMI: body mass index, TT: total testosterone, SHBG: sex hormone binding globulin, FAI: free androgen index, ALM: appendicular lean mass, BMD: bone mineral density.



CONSIDERAÇÕES FINAIS

Em nosso estudo com mulheres trans, a DMO e massa magra apendicular foi similar entre mulheres trans e controles femininos, e menor comparando mulheres trans com controles masculinos. Foi observada elevada prevalência de baixa massa óssea quando comparado aos controles homens e mulheres. A maior parte das mulheres trans incluídas apresentava história de uso irregular de terapia estrogênica por longo período, com diferentes tipos e doses de estrogênio. Durante o seguimento por 31 meses, em que um tratamento padronizado foi estabelecido, não houve mudança significativa na DMO, sugerindo que outros fatores podem interferir na avaliação da massa óssea nesta população.

Com base nos achados da revisão sistemática e meta-análise, não foi observada diferença na DMO da coluna lombar e fêmur em homens trans durante a terapia androgênica. Em mulheres trans, não houve diferença significativa no fêmur, mas foi observado discreto aumento da DMO na coluna lombar. Contudo, as evidências são de baixa e moderada qualidade, e estudos com maior tempo de acompanhamento, TH regular e com ajuste para variáveis que podem influenciar a massa óssea são necessários.