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TRANSGENDER HEALTH

Bone Mineral Density in Transgender Individuals After Gonadectomy and Long-Term Gender-Affirming Hormonal Treatment

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ABSTRACT

Introduction: Establishing the influence of long-term, gender-affirming hormonal treatment (HT) on bone mineral density (BMD) in transgender individuals is important to improve the therapeutic guidelines for these individuals.

Aim: To examine the effect of long-term HT and gonadectomy on BMD in transgender individuals.

Methods: 68 transwomen and 43 transmen treated with HT who had undergone gonadectomy participated in this study. Dual-energy x-ray absorptiometry (DXA) scans were performed to measure BMD at the lumbar spine and total hip. Laboratory values related to sex hormones were collected within 3 months of performing the DXA scan and analyzed.

Main Outcome Measure: BMD and levels of sex hormones in transwomen and transmen.

Results: In transwomen, the mean BMD values at the lumbar spine and total hip at the first DXA scan were, respectively, 0.99 ± 0.15 g/cm^2 (n = 68) and 0.94 ± 0.28 g/cm^2 (n = 65). In transmen, the mean BMD values at the lumbar spine and total hip at the first DXA scan were, respectively, 1.08 ± 0.16 g/cm^2 (n = 43) and 1.01 ± 0.18 g/cm^2 (n = 43). A significant decrease in total hip BMD was found in both transwomen and transmen after 15 years of HT compared with 10 years of HT ($P = .02$).

Conclusion: In both transwomen and transmen, a decrease was observed in total hip bone mineral density after 15 years of HT compared to the first 10 years of HT. **Dobrolińska M, van der Tuuk K, Vink P, et al. Bone Mineral Density in Transgender Individuals After Gonadectomy and Long-Term Gender-Affirming Hormonal Treatment. J Sex Med 2019; 16:1469–1477.**

Key Words: Cross-sex hormonal treatment; Gender dysphoria; Transgender

INTRODUCTION

Sex hormones play an important role in bone formation and bone resorption. In contrast to bone mineral density (BMD), differences in bone composition during puberty between boys and girls develop due to changing hormone levels.[1,2] In females, estrogens limit periosteal bone expansion and stimulate endocortical apposition. In males, the periosteal expansion is stimulated by both estrogens and testosterone.[3] Because of these differences in bone formation, men develop not only larger bones but also stronger bones, making them more resistant to bending forces.[3]

Later in adulthood, BMD is maintained; however, it begins to decrease with time. Osteoporosis is diagnosed when BMD is 2.5 standard deviations or more below normal values of the same birth sex. Individuals with osteoporosis are prone to fractures, such as vertebral fractures and femoral neck fractures.[4] In postmenopausal women, the prevalence of osteoporosis is increased.[5] The same risk applies to women who are prematurely in menopause due to, for example, ovariectomy or loss of ovarian hormone production due to radiation or chemotherapy. With adequate hormonal substitution, BMD is maintained or even increased in these women.[6]

In transgender individuals, hormonal treatment (HT) is implemented not only to achieve a change in appearance but also

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to maintain bone mineral density. Before gonadectomy, transwomen are treated with estrogen and antiandrogens, and after gonadectomy they are treated only with estrogen. Transmen are treated with testosterone before and after gonadectomy. Several studies have assessed the effect of HT on BMD. Differences in BMD between the transgender population and male and female controls before the start of hormonal therapy have been described.[7–9] A difference in lifestyle is reported as being one of the main factors causing these differences.

A meta-analysis of 13 short-term (12–24 months) cohort studies showed that in transmen HT is not associated with significant changes in BMD, which contrasts with the case for transwomen, in whom HT is associated with increased BMD at the lumbar spine.[10] During short-term treatment with HT (3 months to 2 years), a stable or even increased BMD has been described in transgender individuals.[9–11]

Studies assessing the effect of long-term treatment with HT (2–35 years) report various outcomes, with some reporting a stable or increased BMD[8,12,13] and some a decreased BMD.[14] The majority of these studies involved relatively small populations (range 10–84) and covered a relatively short follow-up period; exceptions include the studies by Broulik et al,[13] Van Caenegem et al,[15] and Sosa et al.[16] So far, only 6 studies have been published representing both transwomen and transmen,[8,9,11,17–19] as other studies represent either transwomen or transmen.[8,12,13,16–18,20–22]

Another concern is whether clinicians should use the sex assigned at birth or the affirmed gender for assessing osteoporosis. Although some researchers use the sex assigned at birth, under the assumption that BMD peaks at puberty and most individuals begin HT in adulthood, it is important to determine which reference values properly reflect the risk of osteoporosis.

Since the late 1970s, the University Medical Center of Groningen (UMCG) in the Netherlands has offered a treatment program for transgender individuals according to the professional standards of the World Professional Association of Transgender Health (WPATH).[23] When individuals have been diagnosed with gender dysphoria, the real-life test begins, combined with HT. When the real-life test has been completed with success, individuals can apply for gonadectomy. After that, life-long continuation of HT is necessary to maintain the secondary sex characteristics of the desired gender and to protect against excessive bone loss. Because it is uncertain what effect HT has on BMD, BMD is assessed every 5 years in transgender individuals treated at the UMCG. The aim of our study was to provide additional information on the effect of gonadectomy and long-term HT on BMD in individuals diagnosed with gender dysphoria, both transmen and transwomen. The outcome of this study may contribute to improved therapeutic guidelines for individuals with gender dysphoria in the future.

MATERIALS AND METHODS

Study Population

All individuals diagnosed with gender dysphoria[20,24] between 1979 and 2014 in the UMCG were identified and selected for this study. This study was proposed to the UMCG Medical Ethical Committee, but, due to the retrospective design of the study, further application was not warranted, as the Medical Research Involving Human Subjects Act was not relevant. Every individual was treated following the WPATH standards of care. The research group consisted of 68 transwomen and 43 transmen. Individuals were included if they were treated with HT and had undergone gonadectomy, and if at least 1 dual-energy x-ray absorptiometry (DXA) scan had been performed. A flowchart of inclusion criteria is shown in Figure 1. Exclusion criteria were defined as having comorbidity regarding sex hormones, androgen insensitivity syndrome, sex chromosome anomalies, preexisting bone conditions, or long-term treatment with corticosteroids. Demographic variables were collected from patient medical records. Treatment of transwomen from the beginning of HT therapy consisted of oral or subcutaneous estradiol. Prior to gonadectomy, the estrogen therapy was combined with antiandrogens. In transmen, the cross-sectional hormone therapy consisted of intramuscular or transdermal treatment with testosterone. In both transwomen and transmen, HT after gonadectomy was continued, with the exception of antiandrogens in transwomen.

DXA Scans

BMD was measured at the lumbar spine and total hip by DXA using the Hologic Discovery A (Hologic Inc.; Bedford, MA). BMD is expressed as g/cm^2. Standard reference databases were used to calculate T- and Z-scores.[21,22] Data for the lumbar spine were taken from a study on healthy American men and women,[21] and total hip data were obtained from the National Health and Nutrition Examination Survey III study.[22] In our study, T- and Z-scores were defined for both male and female genders in both transwomen and transmen. Osteoporosis was defined as having a T-score ≤ -2.5 SD compared to normal values for young adults.[4] Low bone density for age was defined as a Z-score below -2.0 SD compared to normal values for young adults. The first measurements of BMD took place within 5 years after gonadectomy, and measurement of BMD was repeated every 5 years thereafter. In 25 transwomen and 19 transmen, more than 1 DXA scan was performed.

Laboratory Analysis

Laboratory values considering sex hormones were included if blood samples were drawn within 3 months before or 3 months after performing a DXA scan. Laboratory values collected beyond this time range were not included, as these were not considered to be representative for the hormone status at the time the DXA scan was performed. Laboratory findings that were analyzed included

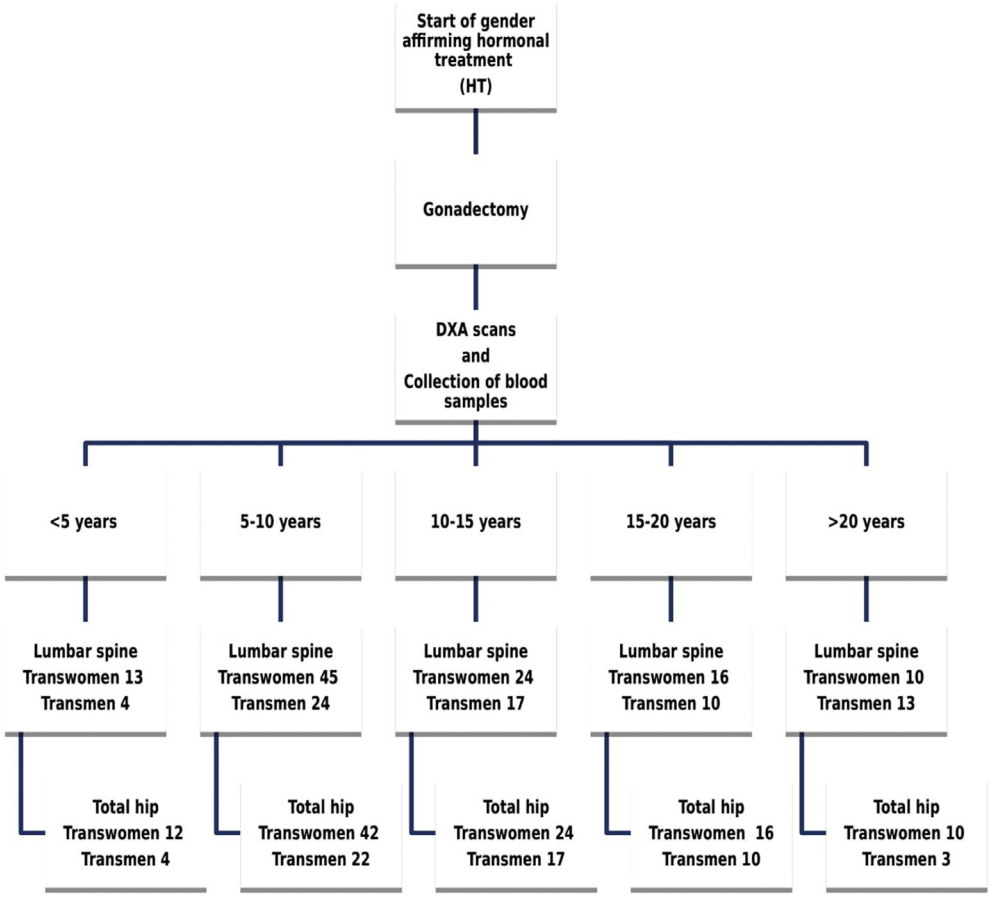

Figure 1. Flowchart of inclusion of the study population showing the reported number of transwomen and transmen with dual x-ray absorptiometry scans and hormone measurements at that time. Figure 1 is available in color online at www.jsm.jsexmed.org.

estradiol (E2), testosterone (T), luteinizing hormone (LH), and follicle-stimulating hormone (FSH). E2 values were determined using radioimmunoassay (in-house; PerkinElmer Inc., Waltham, MA; Roche Holding AG, Basel, Switzerland), and LH and FSH values were determined using luminescence immunoassay (PerkinElmer; Amersham Corp., Arlington Heights, IL). The PerkinElmer AutoDELFIA was substituted for the Amersham Amerlite. The formula used to translate the LH values of the Amerlite to the AutoDELFIA was 1,473 × Amerlite + 0.537 (in U/L); for FSH values, the formula was 1,246 × Amerlite − 0.261 (in U/L). Serum values of T were determined using in-house radioimmunoassay.

Statistics

When a normal distribution was present, variables were expressed as mean ± SD. When the assumptions for a normal distribution were not met, the median (1st, 3rd quartile) was used. *P* values were considered significant at <.05. All tests were 2 sided. For the normally distributed group comparison, the 1-way analysis of variance or Student's T-test was used. Non-normally distributed data were compared using the Mann-Whitney test. Correlations were calculated with linear regression and Pearson's correlation coefficient. For analyzing longitudinal data, a generalized estimating equation (GEE) was used.[25] The GEE is known to achieve higher statistical power with repeated measurements and with missing data than the repeated measures analysis of variance.[4,26] In our GEE model, gender, age at the time of the DXA scan, scan location (lumbar spine, total hip), and time from the beginning of HT and gonadectomy were included. BMD was a dependent variable. Time was analyzed as a categorical variable with a time point set every 5 years. All calculations were made using SPSS 23 (IBM; Armonk, NY).

RESULTS

We selected 116 transgender individuals with 1 or more DXA scans. After 5 subjects were excluded because they did not meet the requirements, 111 transgender individuals were included and analyzed for this study. A total of 176 DXA scans were analyzed in this group. Transwomen were significantly older than transmen at the time of the first DXA scan during the first 15 years of HT (44 ± 11 years vs 39 ± 10 years) ($P < .001$).

Transwomen

General Characteristics

68 transwomen were included in the study. At the start of HT and at the moment of gonadectomy, the mean ages were 36 ± 12 years

Table 1. Demographic variables and laboratory values in transgender individuals*

	Transwomen	Transmen
Number of individuals	68	43
Age at start of HT (yr)	36 ± 12	30 ± 8
Age at first DXA scan (yr)	44 ± 11	39 ± 10
Age at gonadectomy (yr)	38 ± 12	32 ± 9
Time (mo)		
Interval of HT to gonadectomy	22.5 (16.0, 30.5)	20.0 (16.0, 24.0)
Interval of HT to first DXA	83.5 (66.5, 111.5)	87.0 (73.0, 150.0)
Interval of gonadectomy to first DXA	60.0 (41.0, 87.5)	62.0 (49.0, 129.0)
Anthropometrics		
Start of HT		
Weight (kg)	72.8 ± 12.2 (n = 52)	70.2 ± 17.0 (n = 31)
BMI (kg/m^2)	22.9 ± 3.0 (n = 51)	24.4 ± 5.6 (n = 28)
Height (cm)	179.0 ± 7.9 (n = 60)	170.0 ± 7.5 (n = 32)
First DXA		
Weight (kg)	80.6 ± 24.2 (n = 35)	75.6 ± 14.2 (n = 18)
Body mass index (kg/m^2)	24.9 ± 6.7 (n = 35)	27.2 ± 5.1 (n = 17)

Serum markers measured within 3 months of DXA scan

	Transwomen			Transmen		
Hormone	Value	Number of individuals	Reference value for women	Value	Number of individuals	Reference value for men
Estradiol (nmol/L)	0.20 (0.06–0.28)	47	0.1–1.27	0.09 (0.03–0.12)	17	0.05–0.22
Testosterone (nmol/L)	2.00 (1.50–2.15)	15	1.0–3.5	27.00 (16.75–29.50)	23	16–40
LH (U/L)	11.50 (4.46–21.72)	72	—	18.30 (6.65–28.50)	43	—
FSH (U/L)	17.70 (5.79–48.52)	64	—	34.60 (13.70–58.67)	40	—

DXA = dual-energy x-ray absorptiometry; FSH = follicle-stimulating hormone; HT = hormonal treatment; LH = luteinizing hormone.
*Variables are displayed as mean ± SD when a normal distribution was present or as median (1st, 3rd quartile) when there was not a normal distribution present. For each variable, the number of individuals involved (n) is given. Reference values for the male gender hormones are given in the last column.

and 38 ± 12 years, respectively. The remaining clinical characteristics are reported in Table 1. The mean age at the first DXA scan was 44 ± 11 years. Median times from the beginning of HT and gonadectomy to the first DXA scan were 83.5 (66.5, 111.5) months and 60.0 (41.1, 87.5) months, respectively. The median time between HT and gonadectomy was 22.5 (16.0, 30.5) months.

DXA Scans

We analyzed BMD based on 108 DXA scans of the lumbar spine and 102 DXA scans of the total hip; 37% of transwomen underwent more than 1 scan. Bone density parameters measured during the first scan are displayed in Table 2. Changes in BMD every 5 years are displayed in Figure 2A. Mean BMD values at the lumbar spine and total hip at the first DXA scan were, respectively, 0.99 ± 0.15 g/cm^2 (n = 68) and 0.94 ± 0.28 g/cm^2 (n = 65). A significant decrease in total hip BMD was demonstrated after 15 years of HT (0.89 ± 0.15 g/cm^2) compared to 10 years of HT (0.98 ± 0.27 g/cm^2) (−0.12; 95% CI, −0.23, −0.02; P = .02). There was also a significant decrease in total hip BMD 15 years after gonadectomy (0.92 ± 0.14 g/cm^2) compared to the first 5 years (1.03 ± 0.36 g/cm^2) (−0.17; 95% CI, −0.33, −0.01; P = .03).

We found a significant difference in T-scores and Z-scores between the female reference and male reference (Figure 3A). The female T-score (−0.02 ± 1.21) was significantly higher than the male T-score (−0.65 ± 1.00) in total hip (P < .001). Also, female Z-scores were significantly higher than Z-scores for males for both lumbar spine (0.10 ± 1.34 vs −0.59 ± 1.28; P < .001) and total hip (0.35 ± 1.27 vs −0.42 ± 1.05; P < .001). Based on male reference values, 18% of transwomen had osteoporosis, but when compared to female reference values only 5% had osteoporosis.

Laboratory Values

All means of laboratory values were in the normal range of female reference values. Table 1 shows the laboratory values for transwomen. A significant inverse correlation was found among LH, FSH, and BMD at both the lumbar spine and total hip: LH and BMD lumbar spine r = −0.38 (P = .004); LH and BMD total hip r = −0.44 (P = .019); FSH and BMD lumbar spine r = −0.6 (P < .001); and FSH and BMD total hip r = −0.51 (P = .002).

Table 2. Bone density parameters of transgender individuals with DXA*

First DXA scan		
Parameter	Transwomen	Transmen
BMD lumbar spine (g/cm^2)	0.99 ± 0.15 (n = 68)	1.08 ± 0.16 (n = 43)
T-score, male	−0.87 ± 1.33 (n = 68)	0.06 ± 1.48 (n = 43)
T-score, female	−0.49 ± 1.32 (n = 68)	0.21 ± 1.51 (n = 43)
Z-score, male	−0.59 ± 1.28 (n = 68)	0.27 ± 1.57 (n = 43)
Z-score, female	0.10 ±1.34 (n = 68)	0.48 ± 1.64 (n = 43)
BMD total hip (g/cm^2)	0.94 ± 0.28 (n = 65)	1.01 ± 0.18 (n = 43)
T-score, male	−0.65 ± 1.00 (n = 65)	−0.10 ± 0.99 (n = 43)
T-score, female	−0.02 ± 1.21 (n = 65)	0.08 ± 1.13 (n = 43)
Z-score, male	−0.42 ± 1.05 (n = 65)	0.10 ± 1.07 (n = 43)
Z-score, female	0.35 ± 1.27 (n = 65)	0.32 ± 1.18 (n = 43)
Osteoporosis based on male scores (%)	18 (n = 11 out of 61)	33 (n = 13 out of 39)
Osteoporosis based on female scores (%)	5 (n = 3 out of 63)	4 (n = 2 out of 36)
Low bone density based on male scores (%)	5 (n = 3 out of 63)	20 (n = 8 out of 39)
Low bone density based on female scores (%)	5 (n = 3 out of 63)	0 (n = 0 out of 39)

BMD = bone mineral density; DXA = dual-energy x-ray absorptiometry.
*Variables are displayed as mean ± SD when a normal distribution was present. In case of an abnormal distribution, the median (1st, 3rd quartile) is given. For each variable, the number of individuals (n) in whom the variable was measured is given. T- and Z-scores and the percentage of osteoporosis were calculated with both male and female reference values. Osteoporosis is defined as having a T-score ≤ −2.5 SD.

Transmen

General Characteristics

43 transmen were included in this study. The mean ages at the beginning of HT and at gonadectomy were, respectively, 30 ± 8 years and 32 ± 9 years. The remaining clinical characteristics are reported in Table 1. The mean age at the first DXA scan was 39 ± 10 years. The median times from the beginning of HT and gonadectomy to the first DXA scan were, respectively, 87.0 (73.0, 150.0) months and 62.0 (49.0, 129.0) months. The median time between HT and gonadectomy was 20.0 (16.0, 24.0) months.

DXA Scans

We analyzed BMD based on 68 DXA scans of the lumbar spine and 66 DXA scans of the total hip. In 42% of transmen, more than 1 DXA scan was performed. Bone density parameters measured during the first scan are displayed in Table 2. The changes in BMD every 5 years are displayed in Figure 2B. Mean BMD values at the lumbar spine and total hip at the first DXA scan were, respectively, 1.08 ± 0.16 g/cm^2 (n = 43) and 1.01 ± 0.18 g/cm^2 (n = 43). BMD in the total hip was found to be the highest (1.04 ± 0.12 g/cm^2) between 10 and 15 years of HT. A significant decrease in total hip BMD was found after 15 years of HT (0.95 ± 0.14 g/cm^2) compared to the first 10 years of HT (1.02 ± 0.18 g/cm^2) (−0.12; 95% CI, −0.23, −0.02; $P = .02$). There was also a significant decrease in total hip BMD 15 years after gonadectomy (0.98 ± 0.21 g/cm^2) compared to the first 5 years (1.05 ± 0.23 g/cm^2) (−0.17; 95% CI, −0.33, −0.01; $P = .03$). Figure 3B shows the means of the T-scores and Z-scores based on male reference values; 33% of transmen had osteoporosis, but when compared to female reference values only 4% had osteoporosis.

Laboratory Values

Table 1 reveals the laboratory values for transmen. Median values of estradiol and testosterone were in the normal range for the male gender. LH and FSH values were increased compared to male reference values. A significant inverse correlation was found between FSH and BMD at both locations: FSH and BMD lumbar spine $r = -0.56$ ($P = .005$); FSH and BMD total hip $r = -0.44$ ($P = .032$); and LH and BMD total hip $r = -0.45$ ($P = .025$).

DISCUSSION

This study explored the long-term effects of HT and gonadectomy on BMD in individuals with gender dysphoria. We found that both duration of treatment with HT, as well as the time passed since gonadectomy, caused a decrease in total hip BMD in transwomen and transmen after 15 years. Another noticeable finding in this study is the significant difference in both T-scores and Z-scores comparing female and male reference scores. This finding also influences the prevalence of osteoporosis. We noticed more findings of osteoporosis in transwomen when male reference values were used. According to the hormone levels, a significant inverse correlation was found for LH and FSH with BMD.

The study of Van Caenegem et al[27] implemented short-term HT (BMD measured at 12 and 24 months) and showed increased BMD in transwomen, and Wiepjes et al[28] demonstrated increased lumbar spine BMD in transmen. Based on a

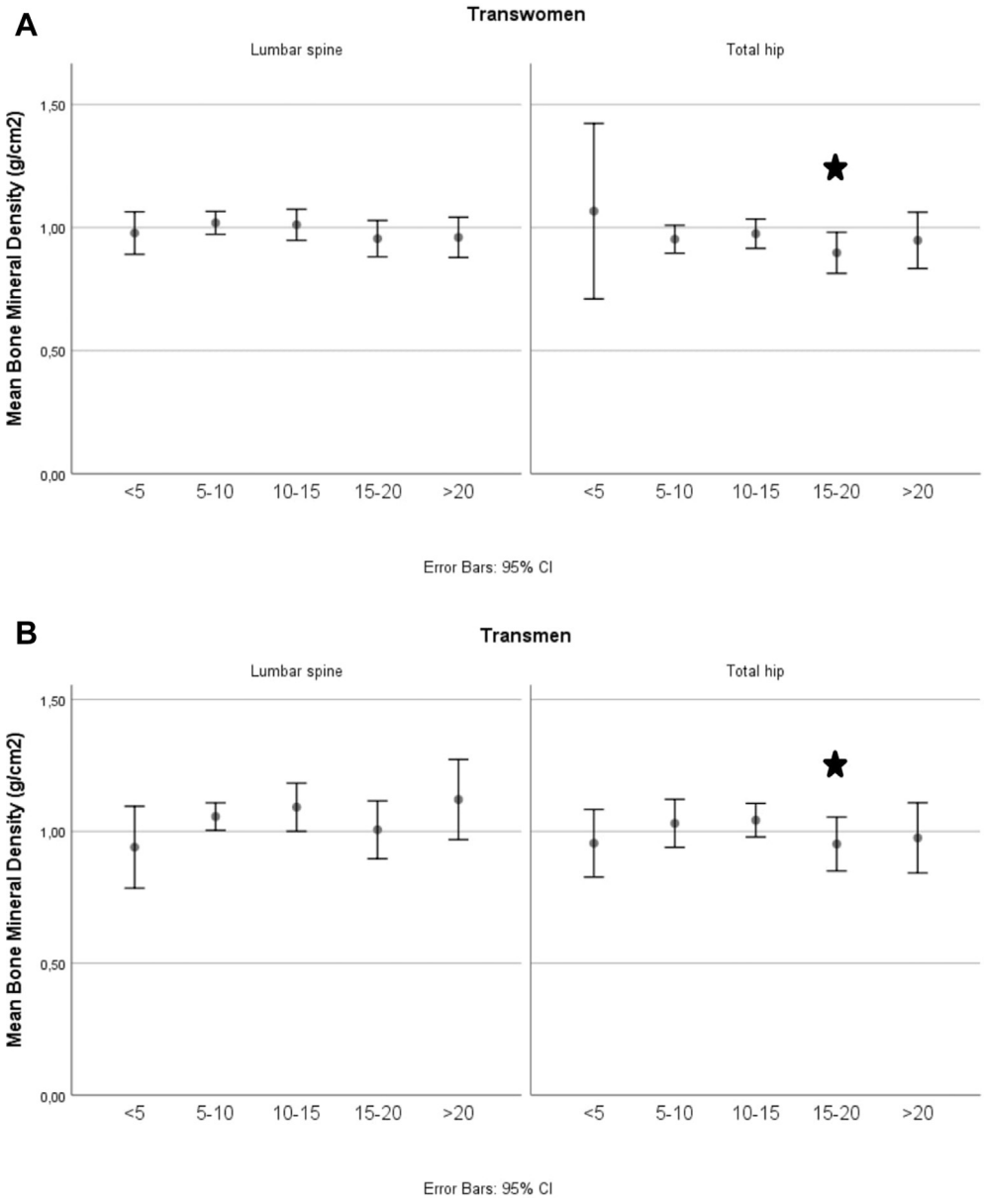

Figure 2. Bone mineral density parameters of transgender individuals and frequency of dual x-ray absorptiometry scans. Variables are displayed as mean ± standard error. Asterisks indicate $P < .05$.

long time assessment, Broulik et al[13] showed that in transmen there was a significant increase in total hip after 18 years of testosterone therapy, which might suggest that hormonal therapy itself protects BMD. The study carried out by Wiepjes et al[28] found no change in lumbar spine BMD during the first 10 years of HT. Because transgender persons who have undergone gonadectomy may choose to stop HT, the decrease in BMD over time that we found might be due to a lack of compliance. Moreover, gonadectomy is itself a risk factor for the decrease of BMD, as it exposes transgender individuals to the adverse effects of chronic hormone deficiency.

The high prevalence of osteoporosis that we found corresponds to findings provided by Ruetsche et al.[18] In their study, 18% of transwomen had osteoporosis after a median time of treatment with HT of 12.5 years. Van Caenegem et al[7] also found a high prevalence of osteoporosis in transwomen. In our study, and the studies mentioned earlier, genotypic (male) reference values are used to determine if osteoporosis is present in transwomen; however, when phenotypical (female) reference values are used, the prevalence of osteoporosis is more comparable to the Dutch population.[29] Due to the significant differences between male and female T-scores and Z-scores, it is still necessary to take into account both reference values, and reference values specific for transgender individuals should be developed. Also, a long-term, prospective study on this subject should be performed with a large study population. The use of peripheral and high-resolution quantitative computed tomography imaging would be of interest in the assessment of BMD. Before

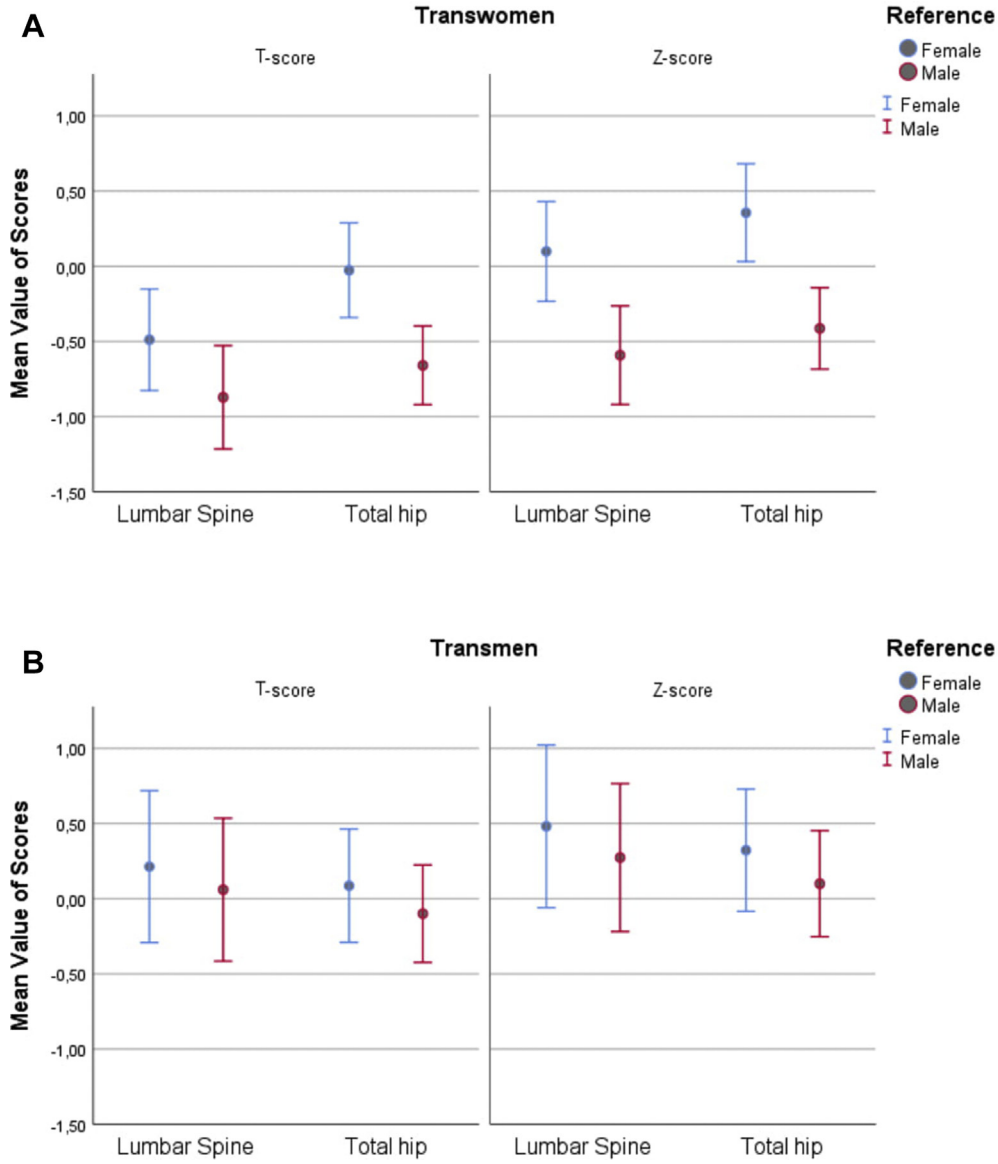

Figure 3. T- and Z-scores for transgender individuals measured in lumbar spine and total hip. Variables are displayed as mean ± standard error. Figure 3 is available in color online at www.jsm.jsexmed.org.

beginning HT, a baseline DXA scan should be performed so it is possible to detect changes in BMD caused by HT later. Given the low prevalence of gender dysphoria, cooperation among centers is necessary to carry out such a study.

We found a significant inverse correlation between LH and FSH values and BMD, a finding that has also been described in previous studies.[17,18] Testosterone and estrogens inhibit the secretion of gonadotropins (LH and FSH).[30,31] When low testosterone or estrogen levels are present, LH and FSH values rise. The decrease in BMD that was found with increasing LH and FSH values can probably be explained by an underdose of HT or poor compliance. We found higher LH and FSH values in transmen than in transwomen which could be explained by the fact that transmen had intramuscular testosterone administration, resulting in an initial peak in testosterone levels after which testosterone levels gradually decreased to values below normal values for men. In contrast to LH and FSH, no significant correlation was found between estradiol (in transwomen) and testosterone (in transmen) and BMD. LH and FSH levels provide a better benchmark for the quality of the HT substitution than estradiol and testosterone levels. For this reason, determination of LH and FSH values must be made with the DXA scans.

The fact that BMD began to decrease in total hip after 15 years of HT in both transwomen and transmen indicates that it may not be necessary to perform DXA scans every 5 years during the first 10 years of the therapy. This conclusion is supported by the results of Wiepjes et al,[28] who observed that regular BMD assessment without indication seems to be unnecessary. This finding also supports the recommendation of the Endocrine Society that BMD measurements should be conducted only when risk factors for osteoporosis exist.[32] It should be determined whether or not this recommendation applies to

individuals who have begun hormonal therapy after puberty and therefore had already reached the peak of bone mass. Individuals exposed to bone loss are specifically those who stop sex hormone therapy after gonadectomy.

The main limitation of this study was its retrospective design. Also, no control groups were included and no DXA scans were performed before the start of HT. Additionally, most transgender individuals included in the study received only 1 DXA scan. For this reason, differences found in BMD between transwomen and transmen cannot be attributed only to HT or gonadectomy, as these differences might have been present before the start of HT and before gonadectomy. Initial changes that might have occurred during the first years of HT and during the 5 years after gonadectomy are not documented. Additionally, information about the time and mode of hormone administration was not always consistent with the time of the DXA scan. Throughout the years, different measurement techniques were used in our laboratories. Because of this, old values were converted into new correct values.

CONCLUSIONS

In this study, we have provided further insight into the BMD of transgender individuals who have undergone gonadectomy and are on long-term HT. We observed a decrease in BMD in the total hip after 15 years of HT compared to the first 10 years of HT in both transwomen and transmen. There was also a significant decrease in total hip BMD 15 years after gonadectomy compared to the first 5 years. Additionally, in transwomen, female T-scores were significantly higher than male T-scores for the total hip. A high prevalence of osteoporosis was found in transmen and transwomen when male reference values were used. LH and FSH values proved to be good markers of compliance and dosage in this study.

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