Original Article

Study of Effects of Gender-Affirming Hormone Therapy on Bone Mineral Density in Individuals with Gender Dysphoria

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Abstract

Introduction: Gender affirming hormone therapy (GAHT) is the mainstay treatment in transitioning individuals and has positive physical and psychological effects. Among the things to monitor in transgender patients on long-term hormones, bone health is an essential consideration. As the calcium intake in the Indian population is less, and many gender-incongruent individuals may not take adequate calcium in their diet, we needed data on the bone health of Indians with gender dysphoria as the information available globally may not apply to our population. **Materials and Methods:** The study was performed to assess bone mineral density in individuals with gender dysphoria who were on gender-affirming hormonal therapy for at least 6 months. It was a hospital-based cross-sectional study of bone mineral density measured at two sites – hip and spine in individuals with gender dysphoria on GAHT for at least six months. **Results:** A total of 30 individuals were included in this study. The mean age of individuals with Gender dysphoria was found to be 28.17 ± 6.15 years, and the age range was 19-42 years. Out of the 30 individuals, 14 were transgender males, and the remaining 16 were transgender females. Bone mineral density at the hip and spine in transgender males was 1.047 ± 0.124 g/cm^2 and 1.065 ± 0.115 g/cm^2, which was better compared to transgender females in whom the bone mineral density at hip and spine was 0.899 ± 0.873 g/cm^2 and 0.854 ± 0.099 g/cm^2 ($P = 0.001$ for hip; $P = 0.000$ for spine). The Z score at hip and spine were better in transgender males as compared to transgender females ($P < 0.001$ for hip; $P < 0.001$ for spine) when compared to genetic sex and at the spine ($P = 0.001$) when compared to affirmed sex. In this study, we observed that the transgender females who underwent orchidectomy had a lower mean Z score at spine compared to individuals who did not undergo the procedure. **Conclusions:** The current study results indicate that GAHT does have positive effects on bone health in transmen.

Keywords: Bone health, Dual-energy X-ray absorptiometry (DXA), gender dysphoria

Introduction

Gender dysphoria (GD) is the distress and unease experienced if gender identity and affirmed gender are not completely congruent.[1] Gender-affirming hormone therapy (GAHT) is the mainstay treatment in transitioning individuals and has positive physical and psychological effects. Among the things to monitor in transgender patients on long-term hormones, bone health is an essential consideration.[2] There are no well-defined guidelines for monitoring bone mineral density (BMD) in transgender individuals, especially in India, where most patients are not on regular follow-up, and the cost is a significant issue. There is no clear consensus regarding the indications for performing a baseline DXA in GD individuals and at what intervals measurements should be repeated. The consensus for control population gender, which is to be used for comparison, is also not there. As the calcium intake in the Indian population is less, and many gender-incongruent individuals may not take adequate calcium in their diet,[3,4] we needed data on the bone health of Indians with GD as the information available globally may not apply to our population. Our study attempts to address a few of the above issues. This study aims to congregate data on bone health in individuals with GD and may help the concerned authorities in making policy decisions about treatment costs and follow-up.

Access this article online

Quick Response Code:

Website: https://journals.lww.com/indjem/

DOI: 10.4103/ijem.ijem_265_23

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Submitted: 18-Jun-2023 **Published:** 11-Jan-2024
Accepted: 24-Sep-2023

How to cite this article: Bobba R, Kalra P, Dharmalingam M. Study of effects of gender-affirming hormone therapy on bone mineral density in individuals with gender dysphoria. Indian J Endocr Metab 2023;27:486-91.

The objective of this study

To study the BMD in individuals with GD who were on gender-affirming hormonal therapy for at least 6 months. The data were compared with genetic and affirmed sex normative data.

Materials and Methods

It was a hospital-based cross-sectional study of BMD measured at two sites – hip and spine in individuals with GD on GAHT for at least 6 months. The patients were included irrespective of the gender reassignment surgery (GRS) status. This study was performed on individuals with GD visiting the Department of Endocrinology of a tertiary care centre in South India from August 2018 to January 2020. BMD was conducted by HOLOGIC QDR 4500 X-RAY Bone Densitometer. The database used for comparison for the calculation of Z scores were of National Health and Nutrition Examination Survey (NHANES). Serum calcium by colorimetric assay (O-Cresolphthalein Method). The serum albumin was analysed by colorimetric assay with the Endpoint method (Bromocresol Green (BCG) method). Serum phosphorous was analysed by the Molybdate Ultraviolet (UV) method. The 25 hydroxy vitamin D was conducted by ECLIA. All blood samples were collected in the fasting state. Transwomen were treated with antiandrogen treatment consisting of oral spironolactone (50 to 150 mg daily) accompanied by oral oestrogen treatment consisting of oestradiol valerate (4 to 6 mg daily). Transmen were treated with either intramuscular testosterone esters (250 mg every 2 to 3 weeks) or testosterone undecanoate (1000 mg every 12 weeks).

Inclusion criteria

All the individuals with GD who were more than 18 years old and diagnosed by the Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) and who gave their consent were included in the study. The study was approved by the institutional ethics review board.

Exclusion criteria

GD individuals with chronic kidney disease – Stage 4 or 5, chronic liver disease, on Highly Active Anti Retroviral Therapy (HAART), on chronic steroid therapy, have been excluded. GD individuals with primary hyperparathyroidism, uncontrolled thyroid disease and any known secondary causes of osteoporosis were not included in our study.

Statistical methods

All the quantitative variables like BMD were expressed as mean and standard deviation. All the BMD values were computed into T and Z scores. Differences in the mean value were tested for statistical significance by Student's *t*-test or Mann–Whitney test. Differences in the proportions were tested for statistical significance by applying the Chi-square test/Fischer's exact test.

Ethical Clearance Statement

Ethical committee name, approval number, approved date The study was approved by ethics committee of M S Ramiah Medical College, Bengaluru vide letter number MEU-SS/EC/02/2018 dated 10/1/2018.

A written informed consent was obtained for participation in the study and use of the patient data for research and educational purposes.

The procedures followed the guidelines laid down in the Declaration of Helsinki (2013).

Results

A total of 30 individuals were included in this study. The mean age of individuals with GD was found to be

Table 1: Demographic characteristics of the cohort

Variable	Mean or Frequency
Sex	
Transgender males (F->M)	14 (46.7%)
Transgender females (M->F)	16 (53.3%)
Age (years)	
Transgender males	26.79±5.70
Transgender females	29.38±6.45
BMI (kg/m^2)	
Transgender males	25.27±5.44
Transgender females	25.16±6.08
Education	
No formal schooling	1 (3.3%)
Up to 12 class	14 (46.7%)
Graduates	13 (43.3%)
Postgraduates	2 (6.7%)
Occupation	
Formal gainful employment	19 (63.3%)
Begging	4 (13.3%)
Sex worker	2 (6.7%)
Student/homemaker	5 (16.7%)
Religion	
Hindu	22 (73.3%)
Christian	6 (20%)
Muslim	2 (6.7%)
Gender Reassignment Surgery	
Orchidectomy	12 (40%)
No GRS	18 (60%)
Family Support	
Transgender males	9 (64.3%)
Transgender females	7 (43.8%)
Hormone Therapy	
Inj Testosterone undecanoate 1000 mg	5 (35.7%)
Inj Testosterone enanthate 250 mg	9 (64.3%)
Tab. oestradiol valerate 4 mg	11 (68.75%)
Tab. oestradiol valerate 6 mg	5 (31.25%)
Duration of Hormone Therapy	
Transgender males	
>1 year	5 (35.7%)
<1 year	9 (64.3%)
Transgender females	
>1 year	6 (37.5%)
<1 year	10 (62.5%)

GRS=Gender Reassignment Surgery, Transgender male=refers to individuals affirmed female at birth but who identify and live as men, transgender female=refers to individuals affirmed male at birth but who identify and live as women

28.17 ± 6.15 years, and the age range was 19-42 years. Out of the 30 individuals, 14 were transgender males, and the remaining 16 were transgender females. The baseline characteristics are displayed in Table 1.

BMD at the hip and spine in transgender males was 1.047 ± 0.124 g/cm^2 and 1.065 ± 0.115 g/cm^2. It was better compared to transgender females in whom the BMD at the hip and spine was 0.899 ± 0.873 g/cm^2 and 0.854 ± 0.099 g/cm^2 (P = 0.001 for hip; P = 0.000 for spine).

The mean BMI of transgender males in our study population was 25.27 ± 5.44 kg/m^2, and of transgender, females was 25.16 ± 6.08 kg/m^2.

Mean corrected calcium was 9.13 ± 0.32 mg/dl, phosphorous was 3.83 ± 0.48 mg/dl and Vit D levels were 23.32 ± 6.86 ng/ml.

In transgender males, the mean Z score for hip and spine was 0.91 ± 1.03 and 0.38 ± 0.90 compared to their genetic sex and 0.09 ± 0.86 and -0.85 ± 0.91 compared to their affirmed sex.

In transgender females, the mean Z score for hip and spine was -0.85 ± 0.57 and -2.13 ± 0.90 compared to their genetic sex and -0.31 ± 0.71 and -1.65 ± 0.94 compared to their affirmed sex.

In transgender males, there was no difference in Z scores of hip and spine between individuals on Inj testosterone undecanoate 1000 mg 3 monthly (N = 5) (0.30 ± 0.73 and 1.14 ± 0.91 at hip compared with affirmed and genetic sex and -0.10 ± 0.85 and 0.30 ± 0.78 at spine compared with affirmed and genetic gender) and those on Inj testosterone enanthate 250 mg once in two to three weeks (N = 9) (-0.06 ± 0.94 and 0.75 ± 1.12 at hip compared with affirmed and genetic sex and -0.28 ± 1.19 and 0.21 ± 1.21 at spine compared with affirmed and genetic sex; P = 0.48 (compared with affirmed gender) and P = 0.51 (compared with natal sex) for hip: P = 0.77 (compared with affirmed gender) and P = 0.89 (compared with natal sex) for spine).

In transgender females, there was no statistical significance difference in Z scores between individuals on tablet oestradiol valerate 4 mg (N = 11) (-0.37 ± 0.81 and -0.86 ± 0.64 at hip compared with affirmed and genetic sex and-1.80 + 1.07 and -2.25 ± 1.04 at spine compared with affirmed and genetic sex) and those who were on 6 mg oestradiol valerate (N = 5) (-0.20 ± 0.49 and -0.84 ± 0.47 at hip compared with affirmed and genetic sex and -1.34 ± 0.48 and -1.86 ± 0.46 at spine compared with affirmed and genetic sex; P = 0.67 (compared with affirmed gender) and P = 0.94 (compared with natal sex) for hip; P = 0.38 (compared with affirmed gender) and P = 0.44 (compared with natal sex) for spine.

In transgender females who underwent orchidectomy (N = 12), mean Z scores at the hip and spine were -0.45 ± 0.66 and -1.96 ± 0.78 when compared to affirmed gender and -0.97 ± 0.54 and -2.4 ± 0.77 when compared to genetic sex. In transfemales who did not undergo orchidectomy (n = 4), the mean Z scores at hip and spine were 0.08 ± 0.78 and -0.75 ± 0.84 when compared to affirmed gender and -0.53 ± 0.62 and -1.30 ± 0.80 when compared to genetic sex. The transfemales who did not undergo orchidectomy had better bone health at spine (P = 0.02 when compared with affirmed gender and P = 0.03 when compared with genetic sex), while the bone health at the hip was not different (P = 0.21 when compared with affirmed gender and P = 0.19 when compared with genetic sex) [Table 2].

Table 2: Comparison of Z scores and bone health parameters between transwomen and transmen

	Transmen (F->M) (n=14)	Transwomen (M->F) (n=16)	P
Genetic Sex:			
Z score hip	0.91±1.03	-0.85±0.57	0.000
Z score spine	0.38±0.90	-2.13±0.90	0.000
Affirmed sex:			
Z score hip	0.09±0.86	-0.31±0.71	0.190
Z score spine	-0.85±0.91	-1.65±0.94	0.001
Vitamin D levels (ng/ml)	26.62±6.47	20.43±5.90	0.041
Corrected calcium (mg/dl)	9.08±0.28	9.18±0.36	0.386
Phosphorous (mg/dl)	3.62±0.53	4.0±0.38	0.036

Acne was the most common side effect in transgender males on testosterone therapy, occurring in 64.3% of individuals. In transgender females on oestrogen, weight gain was reported by 31% of individuals.

Most transgender males were on hormonal therapy for more than a year compared to transfemales, in whom the majority were on hormonal therapy for less than a year.

Discussion

This is the first study from India to measure the BMD of transgender individuals. Our study was a pilot study trying to monitor the bone health of transgender individuals visiting the transgender clinic at our hospital.

Our study assessed BMD using both female and male databases for all transgender individuals. We have compared their affirmed gender BMD with both their affirmed and natal gender control data.

Our study population was relatively younger, with a mean age of 28.17 ± 6.15 years and an age range of 19-42 years.

Most transgender individuals in India have their first clinical visit in their late third and fourth decade after attaining financial self-sufficiency, unlike in Western countries where individuals have their first visit during puberty or peripuberty.[5]

BMD at the spine in transgender males and transgender females in our study was 1.06 ± 0.11 g/cm^2 and 0.85 ± 0.09 g/cm^2, respectively. In comparison to the research conducted by Van Kesteren *et al.*,[6] which showed a spine BMD of 1.08 ± 0.13 g/cm^2 in transfemales after one year of oestrogen

therapy and 1.14 ± 0.15 g/cm^2 in transmales after one year of testosterone therapy. In our study, most transfemales had undergone orchidectomy and were on oestrogen therapy for only a short duration. This might have led to their low BMD at the spine compared to the above study. Transgender males in our study had intact ovaries, which might have led to better BMD compared to transfemales.

A study conducted by Mueller *et al*.[7] showed that sex steroids, testosterone and oestradiol were essential to maintain bone health in men and women, and bone health was significantly affected in both hypogonadal men and women. A similar inference was seen in our study: transgender females who underwent orchidectomy had lower mean Z scores at the spine compared to individuals who had not undergone orchidectomy, but Z scores at the hip were not different.

A cross-sectional study by Van Caenegem E *et al*.,[8] which evaluated BMD in 50 transgender males with a mean age of 37 ± 8 years and on cross-sex hormonal therapy for about ten years, found that individuals had spine BMD 1.03 ± 0.10 g/cm^2 and hip BMD of 0.96 ± 0.12 g/cm^2.

In our study, evaluating BMD in 14 transgender males with a mean age of 26.79 ± 5.70 years, we found that bone mineral density at the hip and spine in transgender males was 1.047 ± 0.124 g/cm^2 and 1.065 ± 0.115 g/cm^2. The young age of the individuals and the presence of ovaries might have led to better BMD in our cohort compared to the above study.

The study by Fighera TM *et al*.,[9] from southern Brazil, evaluated 142 transwomen (mean age: 33.7 ± 10.3 years; BMI: 25.4 ± 4.6) during the first three months of regular oestrogen treatment and found that BMD was similar in trans and reference women, and lower at all sites in transwomen vs. men. In our study, transwomen had a lower BMD at both spine and hip compared to their genetic database (male) vs. affirmed (female) sex.

The study by Petr Dan Broulik *et al*.,[10] which explored the influence of long-term androgen supplementation (18 years) on bone metabolism in transmen, showed that 35 transmen (aged 47 ± 4) who were treated with testosterone esters and testosterone undecanoate showed BMD at the hip was higher, but it was not different at the spine.

Most of our transmen had maintained their BMD at both hip and spine, which may be due to their younger age and the presence of ovaries despite the short duration of therapy.

Oestrogen causes an increased incidence of thromboembolism given its known mechanism for promoting prothrombotic factors and given evidence from clinical trials of cisgender women on oestrogen therapy. However, other factors increase the risk of thromboembolism in transgender women, including the formulation of oestrogen, the route of administration, the postoperative state (especially following gender-affirming surgery), and age.

The earliest reports found a 45-fold increase in the expected incidence of venous thrombosis and/or pulmonary embolism in Dutch transgender women taking primarily ethinyl oestradiol and cyproterone acetate.[11]

A more recent review of 10 cohort studies based in Europe and Canada found a low incidence of thromboembolism in transgender women on oral oestradiol in the range of 2-4 mg daily or transdermal oestradiol 0.1 to 0.2 mg/day.[12] The guidelines recommend the use of oestrogen compounds that can be measured in blood and against synthetic or conjugated oestrogens, which make monitoring blood levels difficult and are associated with more side effects.[1,13]

None of the transgender females were on transdermal oestrogen in the present study due to its sparse-availability in India. All of our transgender females were on oral estradiol valerate as it was readily available, cheap, and had an excellent safety profile.

Most of our population were on estradiol valerate dose of 4 to 6 mg. Oestrogen is a crucial regulator of bone health, and oestrogen deficiency plays an essential role in the rapid decline in BMD. Oestrogen affects bone formation and resorption as it inhibits sclerostin, decreases osteoblast and osteocyte apoptosis, suppresses RANK-L and induces apoptosis in osteoclasts.[14]

In transmen, although oestrogen secretion from the ovaries is decreased in testosterone therapy, aromatisation from testosterone to oestradiol still occurs and is considered the critical sex steroid affecting bone homeostasis. Androgens stimulate osteoblast precursors by triggering interleukin-1b.[15] Androgens also reduce osteoclast formation and survival through indirect mechanisms involving the mesenchymal cells. Testosterone further helps with bone health preservation by increasing muscle mass.[16]

In our study, both transmen and tranwomen had a better BMD at the hip compared to the spine; this can be attributed to site-specific actions of sex hormones, which are different in men than in women. Oestrogen maintains cortical bone (80% of the bone mass) in both men and women. In women, oestrogen is the main hormone that maintains the cancellous bone, with small additional actions from testosterone. In contrast, in men, testosterone is the major hormone in the cancellous bone, with minor contributions from oestrogen.[17,18]

Chantal M Wiepjes *et al*.[19] found that transwomen had a low mean spine Z score before the start of GAHT, whereas this was not found in transmen.

A low bone density in transwomen before the start of GAHT was also described by Van Caenegem and colleagues.[20] They found that transwomen had lower 25(OH)D concentrations and lower muscle mass than control men, possibly due to fewer activities because of social isolation.

In our study, too, transgender females had lower vitamin D levels than transmen, which might have contributed to low BMD at the spine and hip compared to transgender males; these results were as per earlier studies.

GD individuals who undergo GRS have substantial periods of hypogonadism (>1 year) and might experience bone loss or failure of bone accrual during that time. These individuals should be considered for baseline measurement of BMD, and follow-up measurements are appropriate until this hypogonadism continues.

In our study, the Z score and BMD were calculated using both the natal sex and affirmed sex database, though the 2019 ISCD Official Position reference data (mean and standard deviation) of the gender conforming with the individual's gender identity should be used.[21] As all the individuals started hormonal treatment after puberty and, therefore, had already reached the age of peak bone mass that belongs to the sex affirmed at birth.

Although bone mass and size are strongly affected by gonadal sex steroids during puberty, changes in sex steroids over the lifespan can lead to changes in the skeleton regardless of bone accrual during adolescence. Therefore, it may be reasonable that transgender individuals who take hormone therapy should have their DXA for BMD compared to healthy control individuals of the same gender identity as their affirmed gender.

Our study found that transmen had better Z score at both hip and spine when calculated using their genetic sex database compared to their affirmed sex. Whereas in transwomen, their Z score at the hip and spine were better when computed using affirmed sex databases than their genetic sex though it was lower in both ways. The transwomen have a bone loss when their testosterone levels decline secondary to surgery or medications. However, their bone loss continues, and they were found to have lower Z scores compared to their natal gender. Thus levels of testosterone seemed to have a higher impact on bone health in both transfemales and transmales.

To date, there have been no studies from India evaluating the impact of GAHT on BMD. The current study is aimed to update the available evidence regarding the effect of GAHT on BMD in transgender men and women.

The potential study limitations of our study include a relatively small number of participants, many participants had less than 1 year duration of gender-affirming hormone therapy, and a lack of information regarding weight-bearing exercise, all of which can influence BMD. Due to financial constraints, monitoring of serum oestradiol and PTH levels could not be performed.

The current study results indicate that hormone therapy positively affects bone health in transmales, and transgender males had better bone health than transfemales.

Conclusion

Indian population has lower calcium intake compared to their Western counterparts, which adversely affects their bone health.

Hence, vitamin D, calcium and weight-bearing activity should be encouraged for all transgender persons to ensure optimal bone health. Other considerations to improve bone health include limiting alcohol intake, tobacco cessation, adequate sex steroid hormone intake and maintaining or achieving a normal body mass index.

There were apprehensions about the long-term effects of hormonal therapy on bone health as initial studies revealed that transwomen on long-term hormonal therapy had lower BMD compared with control men, and it was feared that hormonal therapy in transmen might decrease oestradiol concentrations and negatively affect bone health.

The current study results indicate that GAHT does have positive effects on bone health in transmen. This could be attributed to the beneficial effect of oestrogen on bone metabolism in GD individuals as none of them had done oophorectomy.

This study also observed that the transgender females who underwent orchidectomy had a lower mean T score and Z score hip and spine compared to individuals who did not undergo the procedure. The transfemales have poorer bone health as compared to transmales.

Financial support and sponsorship

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. We thank Ramaiah Memorial Hospital President Dr Naresh Shetty for allowing free DXA scans for our subjects.

Conflicts of interest

There are no conflicts of interest.

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