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CASE SERIES

Three cases highlighting possible discrepancies in the interpretation of transgender DXA scores

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Key Clinical Message

For diagnosis of osteoporosis, a *T*-score of ≤−2.5 is recommended for all transgender and gender-diverse patients aged 50 years or older, regardless of hormonal status. This case series presents 3 transgender individuals younger than 50 years undergoing gender-affirming hormone therapy (GAHT) who had DXA scores suggestive of osteoporosis. We highlight possible discrepancies in DXA scan interpretations, especially in forearm bone mineral density measurements. We present the baseline (prior to beginning GAHT), 6-month, and 1-year follow-up DXA data along with pertinent labs to include 25-OH vitamin D, calcium, and alkaline phosphatase, for 2 transgender males (assigned female at birth) and 1 transgender female (assigned male at birth) undergoing GAHT who had low *Z*-scores and *T*-scores suggestive of osteoporosis. Multiple studies have analyzed the BMD data of individuals taking GAHT over time, which identify possible causes for low baseline *Z*-scores for transgender females, but less so for transgender males. Other than positional statements, guidelines remain unclear regarding diagnostic approaches to osteoporosis and low *Z*-scores in transgender individuals who are premenopausal or under 50 years of age. This case series addresses discrepancies in interpretation that may be encountered by clinicians with baseline and follow-up DXAs, especially involving the forearm, during the course of GAHT. This highlights the importance of establishing clearer guidelines for the diagnosis and treatment of osteoporosis and low BMD for chronological age in the transgender population.

KEYWORDS

BMD, DXA, osteoporosis, transgender

1 | INTRODUCTION

Osteoporosis has been a major area of research for the last several years, with various guidelines set forth by the World Health Organization (WHO).[1] The WHO defines osteoporosis as BMD measurements 2.5 standard deviations or more below young Caucasian female references. While this definition is necessary to establish

the prevalence of osteoporosis, it is recommended to not be used as the sole determinant for treatment decisions. Furthermore, these diagnostic criteria should not be applied to premenopausal women, men younger than 50 years, or children.[1]

When evaluating transgender individuals who are premenopausal or younger than 50 years old, there are currently no clear guidelines on whether DXA reference data should be interpreted based on birth-assigned sex or affirmed gender.[2–5] This can pose a clinical dilemma for physicians obtaining baseline and follow-up DXAs for individuals undergoing gender-affirming hormone therapy (GAHT), as it remains unclear at which point low BMD for chronological age or osteoporosis must begin pharmacological therapy based on reference *T*-scores and *Z*-scores. We report 3 cases of low BMD for chronological age in transgender individuals.

2 | METHODS

The laboratory studies were performed at a Tertiary Medical Center. The DXA was done by Hologic™ (Hologic, Inc., Marlborough, MA). Approved protocol consents were obtained.

3 | CASE REPORT

The three patients presented to the endocrinology clinic for baseline, 6-month, and 1-year follow-ups per protocol. Patient 1 was a 30-year-old transgender male (assigned female at birth) with a past medical history of anxiety, depression, and untreated asymptomatic Hashimoto's thyroiditis. Vitamin D deficiency was treated with ergocalciferol and his other medications were hydroxyzine, sertraline, and levonorgestrel intrauterine device. He was a nicotine user but quit prior to beginning gender-affirming hormone therapy (GAHT). The patient was placed on testosterone topical gel (Fortesta™) 2 pump actuations on each thigh daily, and he has tolerated this well. Physical examination was unremarkable. He has noticed increased facial hair, increased sweating, more noticeable heat intolerance as well as a new onset of snoring. Baseline laboratory studies were significant for 25-OH vitamin D deficiency and normal serum calcium (Table 1). At six-month follow-up, serum testosterone levels were in the male physiologic range (average levels 534 ng/dL) but estradiol levels remained elevated (average 132.5 pg/mL). At one-year follow-up, serum testosterone levels remained in the male range (average levels 368.4 ng/dL) and estradiol levels remained mildly elevated (average 59.3 pg/mL).

Patient 2 was a 24-year-old transgender male (assigned female at birth) with a past medical history of vasovagal syncope. He infrequently consumed alcoholic beverages and denied tobacco use. He was changed from testosterone topical gel (Fortesta™) 3 pump actuations to intramuscular testosterone 50 mg IM weekly due to skin irritation. Physical examination was unremarkable. He was satisfied with the physical changes he has been experiencing including a deeper voice, hair growth on face, chin, thighs, and lower abdomen, increased strength, muscular growth, and absence of menses. Baseline laboratory studies were significant for 25-OH vitamin D deficiency and normal serum calcium (Table 1). At 6-month follow-up, mid-cycle testosterone levels were normal (average 714 ng/dL), and estradiol levels (average 45.6 pg/mL) were at goal. At one-year follow-up, testosterone levels remained in the male physiologic range (average 410.9 ng/dL), and estradiol levels (average 44 pg/mL) were at goal.

Patient 3 was a 29-year-old transgender female (assigned male at birth) with no significant past medical history. She reported a maternal and paternal history of cardiovascular disease. She consumed one alcoholic beverage per night and denied tobacco use. The patient tolerated estradiol transdermal patch (0.2 mg twice weekly) and oral spironolactone 50 mg daily. She was satisfied with the physical changes she has been experiencing, to include fat redistribution, breast development, and slowed body hair growth. Baseline laboratory studies were significant for 25-OH vitamin D deficiency and normal serum calcium (Table 1). At 6-month follow-up, her serum testosterone and estradiol levels were 13.9 ng/dL and 89.6 pg/mL, respectively. At one-year follow-up, she remained at goal for serum testosterone (average 13.9 ng/dL) and estradiol (average 152.6 pg/mL).

All three patients reported no personal or family history of osteoporosis and no history of fractures. Patient 1 had his daily cholecalciferol 1000 international units (IU) changed to weekly ergocalciferol 50,000 IU due to continued low vitamin D levels during the 6-month follow-up and patients 2 and 3 had been taking daily cholecalciferol 1000 IU.

Baseline DXA data was significant for patient 3 (transgender female) having a lumbar spine *T*-score of −2.5 (male reference) and *Z*-score of −2.1 compared to female reference (Table 1). 6-month DXA data showed normal-range scores for patient 3 but patients 1 and 2 (transgender male) both had ⅓ forearm *T*-scores at or below −2.5 and *Z*-scores below −2 compared to male reference (Figure 1A–C). 1-year DXA data showed normal-range scores for patients 2 and 3 but patient 1 had a ⅓ forearm *T*-score at or below −2.5 and a *Z*-score below −2 compared to reference males. The patients

TABLE 1 Baseline demographic characteristics, DXA findings, and lab results of the 3 patients.

Characteristics	Patient 1	Patient 2	Patient 3
Age, years	30	24	29
Identity	Transgender male	Transgender male	Transgender female
BMI, kg/m^2	24	25	25
BMD, g/cm^2			
AP spine	0.955	1.157	0.821
Femoral neck	0.83	0.848	0.695
Total hip	1.05	1.031	0.809
⅓ forearm	0.71	0.702	0.742
T-score, male reference			
AP spine	−1.2	0.6	−2.5
Femoral neck	−0.7	−0.6	−1.7
Total hip	0.1	0.0	−1.5
⅓ forearm	−2.0	−2.0	−1.4
T-score, female reference			
AP spine	−0.8	1.0	−2.1
Femoral neck	−0.2	0.0	−1.4
Total hip	0.9	0.7	−1.1
⅓ forearm	0.3	0.1	0.8
Z-score, male reference			
AP spine	−1.2	0.6	−2.5
Femoral neck	−0.6	−0.6	−1.6
Total hip	0.2	0.0	−1.4
⅓ forearm	−1.9	−1.9	−1.3
Z-score, female reference			
AP spine	−0.8	1.1	−2.0
Femoral neck	−0.1	0.0	−1.3
Total hip	0.9	0.7	−1.1
⅓ forearm	0.4	0.2	0.9
Calcium, mg/dL (Reference: 8.6–10.2 mg/dL)	9.5	9.4	9.7
Alkaline phosphatase, U/L (Reference: 35–104 U/L)	67	68	62
Vitamin D 25-hydroxy, ng/mL (Reference: 29–100 ng/mL)	19.1	21.3	28.5

had normal-range *T*-scores and *Z*-scores compared to reference females at baseline, 6-month, and 1-year follow-ups. Body mass index (BMI) and laboratory study findings for serum calcium, alkaline phosphatase, and 25-OH vitamin D were included in Table 1. The remaining comprehensive metabolic panel and complete blood count labs were normal for all 3 patients at baseline, 6-month, and 1-year follow-ups.

4 | DISCUSSION

It is reported that osteoporosis or low bone mass (osteopenia) occurs in approximately 53 million adults in the United States of America. Guidelines for indications of bone mineral density testing have been published by several organizations, and these vary according to the populations addressed and several confounding factors. The 2020

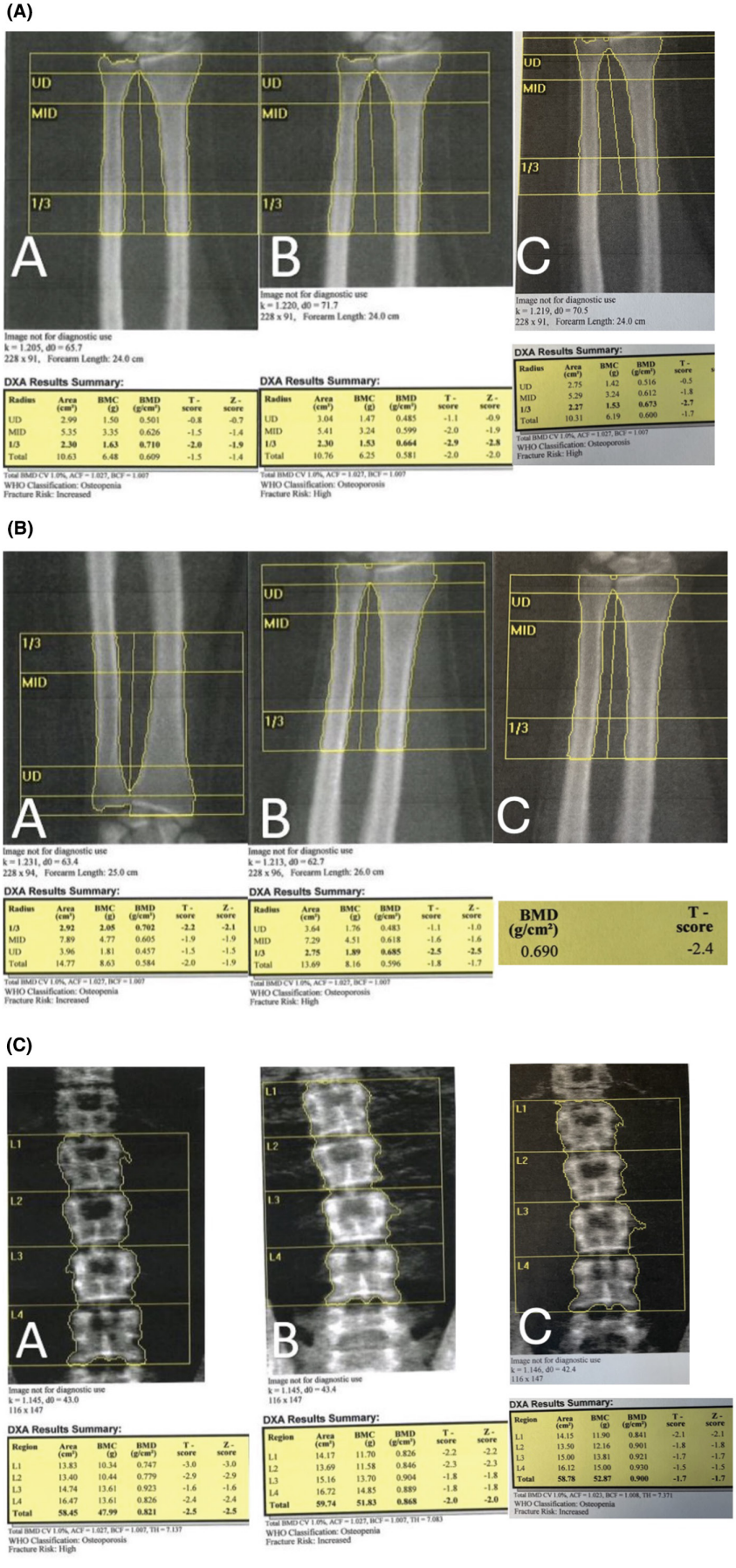

FIGURE 1 (A) Forearm BMD of patient 1. (B) Forearm BMD of patient 2. (C) Lumbar spine BMD of patient 3.

osteoporosis guidelines from the American Association of Clinical Endocrinology define osteoporosis as a *T*-score of −2.5 or lower in the lumbar spine (anteroposterior), femoral neck, total hip, or 1/3 radius (33% radius), even in the absence of a prevalent fracture.[6] In our 3 patients, no significant changes were noted in the hip and spine; however, there was a significant change in diagnosis using the forearm BMD. It currently has unclear clinical implications.

Although ISCD recommendations suggest measuring forearm BMD in very obese patients, hyperparathyroidism, and in situations where hip and or spine cannot be measured, several investigators have measured forearm BMD in the transgender population. The International Society of Clinical Densitometry (ISCD) released position statements in 2019 regarding the approach of calculating BMD data for transgender and non-gender-conforming individuals.[7,8] The ISCD classifies calculating *Z*-scores by matching the individual's gender identity (affirmed gender) as having a good quality of evidence for transgender females, and fair quality of evidence for transgender males. The ICSD also provides a good quality of evidence for using Caucasian female *T*-scores <2.5 as a reference for osteoporosis in both transgender males and females 50 years of age or greater, regardless of GAHT use.[9] No recommendations are currently made by the ISCD for transgender patients who are younger than 50 years. These positional statements provide some direction, but it remains unclear what interventions should be taken for our patient's low *Z* and *T*-scores. *Z*-scores representing low BMD for chronological age could warrant further ancillary studies to identify a possible cause in our patients, even though their only risk factor is or was low serum vitamin D level.

Considering the results of the 10-year study by Wiepjes et al,[7] it is plausible to establish guidelines that require a set amount of time from the initiation of GAHT prior to starting a work-up for secondary causes of low BMD for chronological age. It is unclear in our patients whether the noted decrease in bone mineral density is transient since we have only performed serial BMD measurements in short 6-month intervals. ISCD recommends osteoporosis diagnosis if the *T*-score is −2.5 or less in the lumbar spine, total hip, or femoral neck. In certain circumstances, the forearm (33% radius) can be used.[10] If applying these criteria to our patients, patients 1 and 2 were not in the osteopenic range whereas, in patient 3, lumbar spine, femoral neck, and total hip were in the osteopenic range. When evaluated by male reference *Z*-scores, LS and upper 1/3 forearm showed osteopenia in patient 1, osteopenia in the forearm of patient 2, osteoporosis in LS, and osteopenia at all the other sites in patient 3.

It is important to discuss the effects of GAHT on BMD when evaluating osteoporosis risks in transgender individuals. Caenegem et al reported *T*-scores <−2.5 in 16% of transgender females.[11] Van Kesteren et al demonstrated that serum LH levels in transgender males were inversely related to bone density, suggesting that decreased sex hormone levels are associated with bone loss, and thus suggesting that maintaining normal-range LH levels is important to preserve bone mass. Multiple studies demonstrate that estrogen preserves BMD in transgender females who continue estrogen and antiandrogen therapies.[12–14] Adequate treatment with testosterone is important to maintain bone mass in transgender males.[15] Testosterone's protective effect may be mediated through peripheral conversion to estradiol via aromatase, both systemically and locally in the bone.[16]

Transgender males undergoing GAHT typically only require testosterone therapy for the maintenance of bone mass and optimized gonadal suppression. Transgender females often need estrogen in conjunction with an antiandrogen such as spironolactone or a gonadotropin-releasing hormone (GnRH) agonist. The use of GnRH agonists has been linked to BMD decreases when used alone, but in combination with estrogen studies have shown no significant negative effects on short-term bone health.[17] Limited data exist regarding long-term GnRH use in conjunction with estrogens. Similarly, limited data is available for long-term use of other GAHT agents.[12,16–18]

Previous studies have reported BMD data in transgender populations before and after initiation of GAHT. Wiepjes et al analyzed BMD data of over 1200 transgender individuals over a 10-year period after starting GAHT and found that transgender females had lower mean lumbar spine *Z*-scores compared to reference males, while transgender males had a normal mean lumbar spine value.[7] The study additionally found that *Z*-scores increased for both transgender groups following 10 years of GAHT. Van et al evaluated over 40 transgender females and similarly found that baseline forearm, femoral hip, and lumbar spine BMD were significantly lower compared to reference males.[8,19] Several studies noted lower baseline lumbar spine *Z*-scores and 25-OH vitamin D levels in transgender females compared to transgender males, which was attributed to decreased physical activity and increased isolation compared to reference males.[7,8,11,18] These studies provided possible causes of patient 3's initial low T and *Z*-scores that improved following 6 months of GAHT. However, they did not provide guidance to interpret the significant BMD decline for patients 1 and 2 at 6-month follow-up.

Lapauw et al[20] measured BMD in transgender female subjects and showed that BMD of the lumbar spine, total hip, and distal radius were lower as compared to controls ($p < 0.010$). Furthermore, Wiepjes et al[18] showed a trend toward a higher fracture risk among younger transgender

female persons compared with age-matched control females (2.4% vs 1.6%, OR 1.49 CI 0.96–2.32) but did not reach statistical significance. Fracture among transgender male persons was not statistically different than the risk for age-matched referenced females (OR 0.79, CI 0.48–1.30) and was lower than that for age-matched reference males (OR 0.57, CI 0.35–0.94).[18]

The significant decrease in BMD in our patients after 6 months of GAHT questions whether osteoporosis screening via DXA should be initiated earlier than the age of 65 or menopause in transgender patients on GAHT. While Wiepjes et al[7] may have identified improved BMD over a 10-year period of GAHT, osteoporosis risks beyond that period are unclear. Earlier identification with subsequent management could positively improve morbidity and mortality in this population in the future. Nonpharmacologic approaches for the management of our patient's low-range *Z*-scores include weight-bearing exercises, decreased alcohol use, and the cessation of tobacco use.[21] Additional counseling on appropriate vitamin D and calcium intake is indicated, with supplementation of vitamin D and calcium when the levels are low. Our patient's age, premenopausal status, lack of fracture history, and isolated forearm *T*-scores at or below −2.5 on the 6-month DXA did not mandate initiation of pharmacological treatment with medications such as bisphosphonates based on current guidelines.[21,22] These guidelines are for the general population, as there have been no studies investigating the risks and benefits of pharmacological treatment of osteoporosis in the transgender population, especially in patients younger than 50 years old.[2]

Recent studies estimate that 0.6% of the United States population is transgender.[2] However, significant data on fracture risks and the prevalence of osteoporosis in transgender individuals is not known. With transgender individuals making up a significant percentage of our population, it would be beneficial to establish clear guidelines for the diagnosis and treatment of their low BMD for chronological age and osteoporosis. The low BMD for chronological age of our patients was managed with nonpharmacologic interventions, and they have been doing well while on GAHT.

5 | CONCLUSION

In summary, we reported 3 cases with low-range *Z*-scores in transgender individuals identified during baseline, 6-month, and 1-year follow-up DXAs. We reported numerous limitations of current bone density guidelines, to include at what age to begin screening, whether to use *Z* or *T*-scores, and whether to include forearm bone mineral density measurement. The long-term effects that GAHT may have on bone health remain unclear, posing the question of whether earlier screening may be needed in this population. Furthermore, current literature and guidelines emphasize the utility of *T* and *Z*-scores of the lumbar spine and hip, but with little mention on forearm bone mineral density measurement. Further studies are needed to define the role of forearm BMD in these subjects. ISCD recommends using *T*-score in the lumbar spine, total hip, or femoral neck. These issues pose clinical dilemmas for many physicians evaluating and treating transgender individuals who may be amenable to new osteoporosis guidelines for the transgender population that are tailored to the risk factors brought on by GAHT.

AUTHOR CONTRIBUTIONS

Sebastian C. De La Torre: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; validation; visualization; writing – original draft. **Cassandra M. Godar:** Formal analysis; writing – review and editing. **Mohamed K. M. Shakir:** Investigation; writing – review and editing. **Thanh D. Hoang:** Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; supervision; validation; visualization; writing – review and editing.

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None to declare.

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Not applicable.

ETHICS STATEMENT

The manuscript has been reviewed and approved by the IRB and Public Affairs Office.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

DISCLAIMER

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