Osteoporosis and Bone Health in Transgender Persons

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KEYWORDS

• Osteoporosis • Bone density • Transgender • Hormone therapy
• Gender affirmation • Dual-energy x-ray absorptiometry

KEY POINTS

- Gender-affirming hormone therapy in transgender people has been shown to maintain or improve bone density with unknown effect on fracture risk.
- Screening for osteoporosis should be based on clinical risk factors, including time off sex steroid hormone therapy after gonadal removal.
- Children and adolescents may be at risk for decreasing bone density while on pubertal blockade without sex steroid hormone replacement.
- Transgender people with the highest fracture risk should receive osteoporosis therapy based on guidelines for the general population.

INTRODUCTION

Transgender children and adults receive gender-affirming hormone therapy to improve gender dysphoria and to better align their physical and emotional characteristics with their affirmed gender.[1] Gender-affirming hormone therapy includes the sex steroid hormones in transgender men and women and medications to lower testosterone such as spironolactone in transgender women.[2] Gonadotropin-releasing hormone (GnRH) agonists can also be used to delay puberty in youth and lowers

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testosterone in transgender women. Both these therapies can impact bone health, which has been a concern in transgender populations.

The most recent US population studies estimate that approximately 0.6% of adults, or 1.4 million Americans, identify as transgender.[3] There are no current estimates of the prevalence of osteoporosis or low bone mass in transgender individuals in the United States. Furthermore, there is a paucity of data regarding fracture rates in these patients.

Both sex steroids—estrogen and testosterone—have been shown to be important factors in bone formation during puberty and bone turnover during adulthood.[4] During puberty, males attain a larger, but not denser, bone mass than females owing to greater periosteal apposition from testosterone stimulation.[5] There is no difference in peak volumetric bone mineral density (BMD) or the amount of bone within the periosteal envelope (quantified by grams per cubic centimeter) between the sexes.[5] Estrogen plays an important role in the acquisition of healthy bone in males.[6] Males with inactivating mutations in the estrogen receptor and aromatase genes have low bone mass despite normal or high levels of testosterone.[7–9] Both men and women in hypogonadal states have higher rates of osteoporosis, and treatment with hormone supplementation has been shown to improve bone density.[10–14]

This review focuses on the clinical aspects of the screening and diagnosis of osteoporosis and the treatment of low bone mass in transgender males and females. Topics regarding bone mass in children and adolescents are also covered.

DIAGNOSIS AND SCREENING

Diagnosis of Osteoporosis in Trans Persons

There are no studies that have evaluated whether clinicians should use birth assigned sex or affirmed gender for the determination of the T-score or the Z-score. The T-score is a value calculated by comparing bone density in postmenopausal women or men over the age of 50 to the bone density of a healthy gender matched adult at the time of peak bone mass.[15] A T-score value of −2.5 or less is considered osteoporosis; a T-score between −1.0 and −2.5 is considered low bone mass (osteopenia).[15] The Z-score is used for patients under the age of 50 and is a value calculated by comparing an individual's bone density to age-, sex-, and ethnicity-matched controls.[15]

The International Society for Clinical Densitometry recommends use of a "Caucasian (non-race adjusted) female reference for cisgender men and women of all ethnic groups."[16] This recommendation is primarily based on the availability of fracture data by bone density measurement. Thus, using the Caucasian female reference range would better reflect fracture risk in both transgender women and men. Finally, the presence of fragility fractures or the occurrence of hip or vertebral fracture in the absence of major trauma independent of BMD would constitute a diagnosis of osteoporosis.[17]

Screening in Trans Women

The recommended screening modality for osteoporosis is dual energy x-ray absorptiometry of the lumbar spine, total hip, and femoral neck.[18] There are few studies that examine the prevalence of osteoporosis and low bone density in transgender women based on dual energy x-ray absorptiometry. A study from Belgium found that, in hormone treatment–naive transgender women, the prevalence of osteoporosis and low bone density in the lumbar spine was 16% and 32%, respectively (based on the male reference range).[19] The authors postulated that the high prevalence of osteoporosis and low bone density in young transgender women was due to a less active lifestyle as determined by a physical activity questionnaire.[19]

Hormone therapy is associated with increases in BMD in trans women. A recent metaanalysis demonstrated a statistically significant increase in BMD in transgender women at 12 and 24 months in the lumbar spine compared with baseline across 9 studies.[20] The clinical significance of this change in BMD on fracture risk is unknown; however, estrogen has been shown to increase bone density and decrease fracture risk in postmenopausal cisgender women.[21] There has been no observed difference in fracture rates between trans women compared with control men.[22,23]

The Endocrine Society Practice Guidelines[2] recommend that clinicians obtain BMD for screening purposes in trans women when risk factors for low bone density exist, such as smoking, low body weight, chronic corticosteroid use, heavy alcohol use,[24] and particularly in patients who stop hormone therapy after undergoing gonadectomy. Various risk factors to consider are presented in **Fig. 1**.

Screening in Trans Men

There are a handful of studies that provide data on bone density in transgender men before the start of hormone therapy. In 1 study, the bone density at lumbar, femoral neck and total hip (reported in grams per square centimeter) of 16 trans men compared with control women was similar.[25] In another study, a slightly higher bone density was seen in the femoral neck in trans men compared with control cisgender females (1.02 vs 0.95 g/cm^2, respectively; $P = .02$).[26]

During treatment, a recent metaanalysis found no statistically significant changes in BMD at 12 and 24 months after the initiation of treatment compared with baseline values in testosterone-treated trans men.[20] One study included in the metaanalysis did find a positive effect of testosterone treatment of bone density with an increase in mean BMD of 7.8% at the femoral neck over a 2-year period.[27] There are few

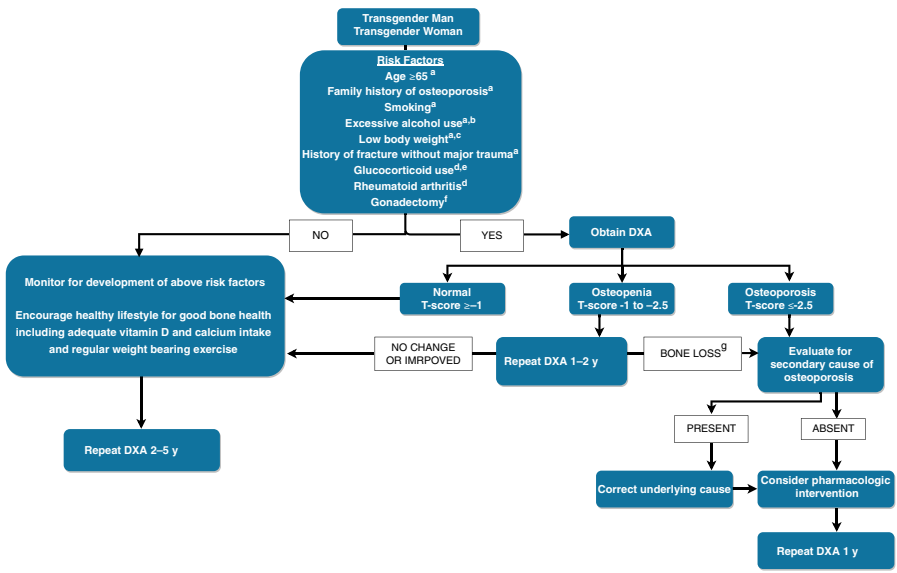

Fig. 1. Suggested approach to screening and the treatment of adult transgender patients. [a] American Association of Clinical Endocrinology/American College of Endocrinology Guidelines.[39] [b] Three or more drinks per day. [c] Weighing less than 127 lbs or a body mass index (BMI) of less than 20 kg/m. [d] Risk factors included in the FRAX tool[40]. [e] Prednisolone 5 mg/d or more for 3 months or more, current or past. [f] Endocrine Society Clinical Practice Guidelines.[2] [g] Bone loss greater than least significant change.

data regarding fracture rates in transgender men. In a 1-year prospective study, 53 trans men receiving testosterone therapy over a 1-year period had no observed osteoporotic fractures.[28] Adequate levels of testosterone therapy are needed to maintain bone density, and luteinizing hormone levels in the normal range have been shown to be a useful marker in determining sufficient levels of testosterone therapy to prevent bone loss (ie, an inverse relationship between BMD and serum luteinizing hormone levels).[29]

Screening for osteoporosis in trans men is appropriate in patients who stop or are intermittently compliant with testosterone therapy, especially in those who have undergone a gonadectomy.[2] In 1 study done in Singapore, postgonadectomy trans men both on regular testosterone treatment and those off testosterone treatment or intermittently compliant with treatment were found to have a lower BMD as compared with values in trans men without gonadectomy.[30] In concordance with the Endocrine Society Clinical Practice guidelines,[2] screening for osteoporosis is appropriate when risks for bone loss are present and potentially in those patients who have increased luteinizing hormone values. Other features to consider are presented in **Fig. 1**.

NONPHARMACOLOGIC THERAPY IN TRANSGENDER PERSONS FOR BONE HEALTH

Vitamin D, calcium, and weight-bearing activity should be encouraged for all transgender persons to ensure optimal bone health. Studies[19,31] examining vitamin D status in transgender adults have demonstrated mean serum 25-hydroxyvitamin D concentrations below the optimal level of 30 ng/mL (75 nmol/L) as suggested by the Endocrine Society[32] and American Association of Clinical Endocrinologists.[33] Van Caenegem and colleagues[19] reported that the low vitamin D status in transgender women could be due to decreased physical activity. Indeed, Jones and colleagues[34] reported that transgender persons engage in less physical activity than cisgender people, which may limit sunlight exposure and weight-bearing activities. Furthermore, lower dietary intake of vitamin D[35] and increased adiposity,[36] as reported in transgender women, is associated with lower vitamin D status.

All transgender persons should be encouraged to ingest at least 1000 mg of calcium and 800 to 1000 IU of vitamin D from the diet and engage in regular weight-bearing activity.[33] Those with risk factors for vitamin D deficiency, such as a body mass index of greater than 27 or inadequate dietary intake of vitamin D, should have a serum 25-hydroxyvitamin D measurement. Individuals with serum 25-hydroxyvitamin D concentrations of less than 30 ng/mL should attempt correction of the level to greater than 30 ng/mL with vitamin D supplements and/or increased intake of vitamin D–containing foods. 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.

BONE MASS IN CHILDREN AND ADOLESCENTS

Very few studies have examined the impact of gender-affirming hormone therapy in transgender children. The largest study examined 34 transgender children who were treated with GnRH agonists at the earliest stages of puberty for approximately 1 to 2 years followed by gender-affirming hormone therapy for 5 years.[37] They reported no change in absolute BMD (aBMD) of the spine in trans girls during GnRH therapy and slight increase in aBMD after the initiation of gender-affirming hormone therapy. In trans boys, the investigators reported significant decreases in aBMD of the spine at the start of GnRH therapy and stabilization of aBMD of the spine after

the initiation of gender-affirming hormone therapy. However, in both groups of trans boys and trans girls, the Z-scores of the spine were less than 0. This small study raises concerns regarding prolonged GnRH therapy on bone health without sex steroid hormone replacement in transgender children and adults. Further studies should investigate the timing and duration of GnRH therapy that may impact bone health in postpubertal children and adults.

TREATMENT OF OSTEOPOROSIS IN TRANSGENDER PERSONS

Most of the studies that have been conducted in transgender populations have been of individuals under the age of 50. According to World Health Organization criteria, osteoporosis cannot be diagnosed using T-scores alone in individuals less than the age of 50.[38] There are no published reports examining the safety and efficacy of pharmacologic agents such as bisphosphonates in the treatment of osteoporosis in transgender populations. Therefore, in the absence of any transgender-specific data, pharmacologic therapy should be based on criteria put forth by guidelines by international societies in cisgender populations.[17]

SUMMARY

There has been a recent increasing interest in both the short- and long-term effects of sex steroid hormones on bone health in transgender persons. Based on the available data, hormone therapy seems to maintain or improve bone density in transgender adults in short-term follow-up. For transgender children and adolescents, there is concern that GnRH agonist use before the initiation of sex steroid hormones may put patients at risk for decreasing bone density. Both pharmacologic and nonpharmacologic treatments for transgender persons follow the same guidelines as in cisgender persons. See **Fig. 1** for a suggested approach to the screening and treatment of adult transgender patients.

More studies are needed to assess the long-term effects of hormone therapy on bone density and the clinical impact of these changes on fracture rates. As the population of transgender persons on hormone therapy ages, this consideration will become especially important. Further studies are also required to assess the timing and duration of GnRH agonists in transgender youth and the associated effects on bone density.

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