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Mini Review

Bone Health in Transgender Individuals

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Abstract

Bone health in transgender individuals is crucial yet frequently neglected, requiring attention from treating physicians. Before starting gender-affirming hormone treatment (GAHT), transwomen typically exhibit lower bone mineral density (BMD) compared to cisgender men, likely due to hormone-independent factors. BMD significantly increases within the first year of GAHT, then gradually declines, though it remains above baseline levels. In transmen, BMD before and after GAHT closely aligns with that of cisgender women. It is essential to adhere to the International Society for Clinical Densitometry guidelines when ordering, performing, or interpreting a BMD scan for gender-diverse patients. While the risk of fragility fractures varies between transmen and transwomen, the fracture sites and characteristics mirror those seen in the cisgender population.

Keywords: Transgender; Bone Health; GAHT; BMD

Introduction

"Transgender" is an umbrella term for individuals whose gender identity and/or expression differs from what is typically associated with the sex they were assigned at birth [1]. In the United States, approximately 1.3 million adults and 300,000 youths aged 13 to 17 identify as transgender [2]. Although recent prevalence data for India are lacking, the overall prevalence appears to be increasing. Gender Affirming Hormone Therapy (GAHT) is administered to align individuals' physical features with their identified gender, thereby alleviating gender dysphoria [3]. GAHT includes the administration of testosterone to promote masculinization in transgender men and estrogen therapy, alone or with anti-androgens, to promote feminization in transgender women. Gonadotropin-releasing hormone (GnRH) agonists are used to suppress pubertal changes in youth and in some adults to suppress gonadal hormone secretion. In adults, GAHT is often accompanied by surgeries to align secondary sexual characteristics with the identified sex. Besides modifying secondary sexual characteristics, GAHT also has systemic effects on bone health, raising concerns about osteoporosis or low bone mass and fracture in the transgender population. This review aims to describe the impact of GAHT on bone health, osteoporosis, and fracture risk within this group.

Bone pathophysiology: an overview

During puberty, estradiol stimulates periosteal bone apposition, and in men, testosterone, through aromatization to estrogen, has an anabolic effect on bone [4]. Additionally, testosterone promotes muscle growth, which, through mechanical loading, stimulates bone growth [5].

In young individuals with gender dysphoria, the use of GnRH agonists to block puberty prevents the development of unwanted secondary sexual characteristics associated with the sex assigned at birth. Puberty suspension with GnRH agonists is typically indicated as early as Tanner stage 2 of pubertal development, while hormone therapy with gonadal steroids generally begins around the ages of 16 to 18. The accrual of bone mass during puberty is a crucial determinant of peak bone mass. Treatment with GnRH agonists results in decreased areal and volumetric bone mineral density (BMD), preventing the attainment of peak bone mass compared to cisgender controls [6].

The initiation of GAHT can partially reverse the bone loss associated with pubertal suppression but may not be sufficient to restore BMD to levels seen in age-matched cisgender individuals who

undergo spontaneous puberty. This disparity potentially places transgender individuals at a higher risk of fractures later in life [7].

GAHT in adult transwomen and transmen

For transwomen, the typical regimen for GAHT involves estrogen in combination with antiandrogens like spironolactone or cyproterone acetate (CA), and/or the addition of a GnRH agonist if the testes are not removed. Spironolactone, an antagonist of aldosterone with moderate antiandrogen activity, does not significantly reduce testosterone concentrations to female reference ranges but promotes feminization due to its antiandrogen and potential estrogenic activities [8]. CA exerts its antiandrogen effects by suppressing testosterone production and competitively blocking the androgen receptor [9]. Estradiol in transwomen can be administered through various routes—oral, transdermal, and parenteral. However, there is limited data regarding the effectiveness of different estradiol formulations on bone health in transwomen [10].

For transmen, the standard GAHT consists of testosterone therapy. Options include testosterone cypionate, enanthate, or undecanoate; testosterone gel at 1.62%; and transdermal testosterone patches. The impact of different administration routes on bone health remains unclear. A study comparing transdermal with short- and long-acting testosterone formulations found no difference in bone mineral density (BMD) after one year of therapy [11].

Regarding bone turnover markers, levels of the N-terminal propeptide of type I procollagen increase among both trans men and trans women following the initiation of GAHT, while levels of C-telopeptide of type I collagen have shown inconsistent results [12]. Further studies are required to understand the clinical relevance of these bone turnover markers.

Bone health in Transwomen

Before the initiation of GAHT or orchiectomy, transgender women typically exhibit lower muscle mass, smaller bone size, and lower BMD compared to cisgender men [9,12]. Regarding bone structure, transwomen often have lower total and cortical volumetric BMD, reduced cortical thickness, increased cortical porosity, decreased trabecular volume, and fewer trabeculae, resulting in compromised bone microarchitecture [13]. The observed lower BMD and bone size in transwomen, compared to cisgender males before GAHT initiation, suggest the presence of hormone-independent factors [14]. Various studies have indicated that transwomen have a high prevalence of low vitamin D levels, eating disorders, lower engagement in sports and physical activities compared to age-matched cisgender males, and a higher prevalence of substance abuse, including alcohol, cannabis, amphetamines, and opiates [15].

After the initiation of GAHT, BMD typically increases significantly within the first year of therapy, followed by a gradual decline, although remaining above baseline levels [10,16]. Some studies have reported BMD losses in transwomen, which have been attributed to factors such as inadequate hormone dosing, poor adherence to therapy, or continued lower levels of physical activity [12].

Following gonadectomy, estrogen therapy becomes the primary treatment modality. The reduction in BMD after gonadectomy is more likely due to poor compliance or underdosing of GAHT rather than a direct effect of the surgery itself. Some authors have observed an inverse correlation between BMD and luteinizing hormone (LH) levels, leading to the use of LH monitoring in GAHT management [17,18]. However, this approach is not universally supported by other studies [19,20].

Bone health in transmen

BMD in transmen before GAHT is similar to that of cisgender women [10]. Areal BMD, trabecular and cortical BMD and Cortical bone size in transmen are similar to cisgender female [21]. Participation in sports and physical activity correlates with increase muscle mass and strength and peak bone mass [22,23]. Prevalence of fracture is similar to control population [24]. After initiation of GAHT BMD matches with the control population and studies have found that after 10 years of GAHT lumbar spine absolute BMD is similar to baseline measurements and lumbar spine Zscore to be increased [25]. In transmen who underwent gonadectomy but continues to have GAHT maintain their BMD to that of control [26]. Also volumetric BMD using QCT have shown increase in VBMD and cortical thickness on GAHT [13]. Thus transmen on GAHT is not at risk of osteoporosis irrespective of gonadectomy.

Screening for osteoporosis

The recommended screening modality for osteoporosis is dual-energy X-ray absorptiometry (DXA) of the lumbar spine, total hip, and femoral neck.

Baseline BMD assessment is indicated [27]:

- If the patient is not willing to undergo Gender Affirming Hormone Therapy (GAHT) after gonadectomy.
- Prior to GAHT if the patient has undergone gonadectomy or has any conditions that decrease gonadal steroid levels, such as hyperparathyroidism or glucocorticoid use.

Follow-up BMD assessment is indicated [27]:

- If the patient is on inadequate dosage or non-compliant with gonadal steroid therapy.
- If on GnRH agonist therapy.
- If planning to discontinue GAHT.
- If other preexisting conditions persist.

Studies suggest using female data instead of male data for calculating Z scores in transgender women, as their BMD is closer to that of cisgender females [25,28]. However, data for transgender men is conflicting. Some studies have shown that the mean BMD in transgender men is higher than cisgender females and closer to cisgender males, using male databases for BMD calculations [29]. Others have used cisgender female databases for calculating Z scores in transgender men [25,30,31].

Fracture risk

The risk of fragility fractures differs between transmen and transwomen, but the site and characteristics of fractures are similar to those in the cisgender population [32]. Transmen typically have a low prevalence of osteopenia before and during GAHT and do not exhibit an increased risk of fracture compared to cisgender individuals [33,34].

In contrast, the prevalence of low bone mass in transwomen is around 22% before initiating GAHT and increases to 26% after long-term therapy [20,25,35]. Additionally, the prevalence of osteoporosis, based on male reference standards, is approximately 20% in transwomen after more than ten years of GAHT [17,18,36].

A study by Wiepjes., *et al*. found that transwomen younger than 50 years of age, taking GAHT for an average of 8 years, had an increased fracture risk compared to age-matched cisgender women but not when compared to cisgender men. However, transwomen older than 50 years, taking GAHT for an average of 19 years, had a similar fracture risk compared to age-matched cisgender women and a higher fracture risk compared to cisgender men [37].

The Fracture Risk Assessment (FRAX) Tool is commonly used to assess fracture risk but lacks specification for transgender and gender non-conforming (TGNC) patients. It does not account for gender identity, history of gonadectomy, or use of GAHT, making it less applicable in assessing fracture risk for transgender individuals [24].

In an Italian study [38], an adapted version of FRAX score, called DeFRA was used. The use of this DeFRA score was created with the purpose of overcoming some of the limitations of FRAX and to improve fracture risk prediction.

Conclusion

Medical care for transgender individuals is indeed an area that has historically been neglected, and GAHT can impact various systems, including bone health. However, with proper compliance, bone health can be preserved in adult transgender individuals receiving GAHT. Despite this, data on fracture risk in this population remains sparse.

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