

Bone Health in Transgender Individuals: A Narrative Review on the Impact of Gender-Affirming Hormone Therapy

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Abstract

Bone health is a critical aspect of transgender and gender-diverse (TGD) care, as sex steroids are central for bone accrual during puberty and skeletal maintenance in adulthood. This life-course narrative review synthesizes evidence by age group, sex assigned at birth, and hormone regimen, evaluating bone mineral density (BMD), fracture risk, and monitoring practices while considering study quality and limitations. Puberty suppression with GnRH agonists in adolescents reduces lumbar spine Z-scores by 0.5–1.0 SD within two years. After gender-affirming hormone therapy (GAHT), bone indices generally recover, with lumbar spine Z-scores increasing by approximately 0.3–0.5 SD within 24–36 months; however, catch-up remains incomplete in adolescent transgender women when estradiol levels are subphysiologic. In adults, adequate GAHT preserves or increases site-specific BMD, whereas hypogonadism after gonadectomy, poor adherence, or adverse lifestyle factors may accelerate bone loss. In older adults, fracture incidence in transgender women is higher than in cisgender men (4.4 vs 2.3 per 1,000 person-years; HR 1.9, 95% CI 1.3–2.7) but comparable to that of cisgender women (HR 1.05, 95% CI 0.75–1.49). In contrast, fracture rates in transgender men are lower than or similar to those observed in cisgender men. Maintaining physiologic estradiol levels (100–200 pg/mL) in transgender women and testosterone levels (400–700 ng/dL) in transgender men is essential for bone protection. Recommended management includes risk-based dual-energy X-ray absorptiometry (DXA) monitoring, consideration of bone turnover marker (BTM) monitoring in selected individuals, vitamin D and calcium optimization, weight-bearing exercise, lifestyle counseling, and fall prevention. Despite encouraging BMD outcomes, data on long-term fracture risk, skeletal microarchitecture, and diverse hormone regimens remain limited, underscoring the need for large-scale longitudinal research.

Keywords: transgender; bone mineral density; gender-affirming hormone therapy

Transgender and gender-diverse (TGD) individuals are those whose gender identity does not align with the sex assigned at birth.^{1–3} Many individuals experience gender dysphoria, a form of psychological distress that arises from this incongruence.^{2,3} Gender-affirming interventions, including puberty suppression and gender-affirming hormone therapy (GAHT), are essential components of care. They help alleviate this distress and support individuals in achieving consistency between physical appearance and gender identity.^{4,5}

Sex steroids, particularly estrogen and testosterone, are vital for bone metabolism. They regulate bone formation, resorption, and overall skeletal maintenance throughout life.^{6,7} During puberty, the surge of these hormones drives rapid skeletal growth and mineral accrual until peak bone mass (PBM) is reached in early adulthood. Achieving optimal PBM is important, as it largely determines long-term bone strength and the future risk of osteoporosis and fragility fractures.^{8,9}

In transgender individuals, bone health is affected by multiple unique factors, particularly the use of puberty suppression and GAHT, which play critical roles in skeletal development and maintenance. Gonadotropin-releasing hormone agonists (GnRHa) are commonly used to delay puberty and prevent the development of undesired secondary sex characteristics. However, prolonged suppression of

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endogenous sex steroids during this critical period may temporarily reduce bone mineral accrual and compromise microarchitecture.^{10,11}

Initiating GAHT, whether following or in conjunction with GnRHa, typically results in the recovery or preservation of bone mass, although outcomes vary with hormone regimen, dosage, and treatment duration.^{12,13} In transgender women, estrogen combined with an anti-androgen has been shown to increase lumbar-spine bone mineral density (BMD), while transgender men receiving testosterone typically experience improvements in both trabecular and cortical bone parameters.^{12,14} However, inadequate dosing, poor adherence, or prolonged hypogonadal states after gonadectomy may lead to bone loss over time.¹⁵

Although evidence is expanding, many questions remain unanswered. Long-term data on fracture risk and the impact of extended GnRHa use on PBM are still limited¹⁶⁻¹⁸. Some studies suggest that lower BMD Z-scores during puberty suppression might reflect delayed bone accrual rather than a permanent deficit.^{16,19} Further longitudinal research is needed to clarify these outcomes.²⁰

This narrative review synthesizes current knowledge on bone health in TGD populations across life stages. It first outlines normal bone physiology and the role of sex hormones, then examines how hormonal interventions affect bone outcomes in children, adolescents, adults, and older individuals. It also highlights research gaps and clinical considerations to guide future studies and optimize long-term skeletal care.

Literature Search Strategy

A literature search was conducted using major biomedical databases, including PubMed, ScienceDirect, and Google Scholar. Additional relevant articles were identified through manual searches of the reference lists of selected studies. The search focused primarily on publications from 2015 to 2025; earlier landmark studies and clinical guidelines were included when relevant. The search focused primarily on publications from 2015 to 2025; earlier landmark studies and clinical guidelines were included when relevant. Studies were included if they were published in peer-reviewed journals, conducted in human subjects, and addressed topics related to bone health in transgender individuals. The search strategy employed combinations of the following keywords: “transgender,” “gender-diverse,” “gender-affirming hormone therapy,” “bone mineral density,” “bone health,” “bone turnover markers,” “osteoporosis,” “GnRH agonist,” “puberty suppression,” and “fracture risk.” Boolean operators such as AND, OR, and NOT were used to refine the search according to the objectives of this review. Only English-language publications were considered. Titles and abstracts were initially screened for relevance, followed by full-text review of eligible articles. Studies were excluded if they were duplicate publications, lacked clear methodological descriptions, had inaccessible full texts, or consisted solely of editorials or commentaries without original research data. The selected studies were subsequently analyzed

and synthesized to provide a comprehensive overview of bone health across the lifespan in TGD individuals.

Bone Biology & Sex Hormones

Childhood and adolescence represent critical periods of bone accrual, with the greatest gains achieved in the final decade of growth.⁴⁻⁶ In adulthood, skeletal strength is largely determined by PBM, which predicts osteoporosis and fracture risk.^{7,8} Failure to achieve PBM predisposes individuals to fragility fractures later in life.⁹

Men generally achieve higher PBM than women, with values approximately 5–15% greater depending on skeletal site. For example, population data indicate femoral-neck PBM of about 0.93 ± 0.14 g/cm² in men versus 0.86 ± 0.12 g/cm² in women, underscoring sex-specific differences in bone geometry.¹⁰ Maximizing bone accrual during adolescence is therefore crucial for preventing osteoporosis in later life.¹¹ Hip bone geometry, including subperiosteal width and endocortical diameter, corresponds with affirmed gender identity only when puberty suppression begins early; otherwise, geometric patterns follow sex assigned at birth.¹²

Sex steroids are essential for bone accrual in adolescence and skeletal maintenance in adulthood. They govern sexual dimorphism of bone mass and regulate remodeling and BMD throughout life.^{13,14}

Estrogen

Estrogen is pivotal for bone homeostasis. In cisgender women, periosteal apposition and rapid longitudinal growth during puberty are stimulated through the GH-IGF-1 axis, with IGF-1 enhancing osteoblast activity. In adulthood, estrogen maintains bone mass by inhibiting osteoclasts and stimulating osteoblasts.^{15,16} A key mechanism involves the RANKL–RANK–OPG pathway, whereby estrogen downregulates RANKL and upregulates OPG, reducing osteoclast differentiation and bone resorption. Estrogen deficiency after menopause increases RANKL expression and accelerates bone loss. This imbalance enhances osteoclast differentiation and bone resorption, leading to deterioration of trabecular bone microarchitecture.¹⁷

In men, aromatization of testosterone to estrogen is critical for bone maintenance; men with aromatase deficiency exhibit low bone mass.¹⁸ Estrogen promotes osteoblastogenesis while suppressing marrow adipogenesis, decreases bone turnover, and preserves trabecular microarchitecture. Estradiol is key for trabecular integrity, while androgens complement geometry-shaping effects.¹⁹

Testosterone

Testosterone directly stimulates bone formation and indirectly via aromatization to estradiol. It increases muscle mass, enhances mechanical loading, and promotes periosteal

apposition, yielding greater cortical thickness.²⁰ Testosterone deficiency in men is associated with 10–15% lower BMD, whereas replacement increases lumbar-spine BMD by 7–8% within two years.²¹

Testosterone contributes to skeletal integrity, as evidenced in women with androgen insensitivity syndrome, who frequently exhibit reduced BMD. Androgens facilitate subperiosteal expansion and cortical thickening, thereby enhancing bone geometry and strength^{22,23}, while aromatization adds anabolic and antiresorptive effects.²⁴ In TGD individuals, bone health reflects both hormonal and lifestyle influences. Testosterone supports periosteal apposition, muscle-driven loading, and estradiol-mediated skeletal protection. Similar mechanisms may occur in transgender individuals when hormone levels remain subphysiologic during or after GAHT.

Baseline Modifiable Risks

Bone health in TGD individuals depends on both lifestyle and treatment-related factors in addition to sex steroids. Nutritional status plays a key role: low calcium intake is associated with reduced BMD, and vitamin D deficiency is common and linked to impaired bone accrual.^{4,17} Serum 25(OH)D concentrations below 20 ng/mL (< 50 nmol/L) are correlated with suboptimal bone mass.¹⁷ Adequate calcium and vitamin D supplementation is therefore recommended. Although effects on BMD remain inconsistent, some studies suggest greater benefit among transgender women.^{4, 10}

Vitamin D deficiency is highly prevalent worldwide, with serum 25(OH)D concentrations below 20 ng/mL (< 50 nmol/L) observed in approximately 30–80% of the global population and 40–60% across Southeast Asia. Among TGD youth, insufficiency is even more pronounced: studies report vitamin D levels below 50 nmol/L in 74% of adolescent transgender men and 78% of adolescent transgender women prior to puberty suppression.^{4,10,17,25} Suboptimal vitamin D status, often resulting from limited sunlight exposure, indoor lifestyle, or low dietary intake, has been associated with impaired bone accrual during adolescence and early adulthood. These findings highlight the importance of routine assessment and correction of vitamin D levels before or during GAHT initiation.^{4,17}

Physical inactivity is another major determinant of low BMD, particularly in transgender women who are generally less physically active than their transgender men peers. Sedentary behavior and reduced weight-bearing activity are common in both transgender and cisgender populations and are strongly associated with diminished bone mass accrual.^{4,10,17} Conversely, structured weight-bearing and resistance training programs have been shown to produce modest but clinically meaningful increases in spine and hip BMD, typically in the range of 1–3% over 6–12 months when performed regularly.^{26,27} Insufficient physical activity during adolescence and young adulthood therefore represents a critical yet modifiable barrier to achieving optimal skeletal strength prior to hormonal intervention.^{4,10,17}

During adolescence, achieving ≥ 60 minutes per day of physical activity, incorporating moderate-to-vigorous and impact components, contributes substantially to PBM accrual.^{17,19} In TGD populations, lower baseline physical activity, particularly among transgender women, has been associated with reduced lean mass and lower BMD prior to GAHT. Low activity is also a recognized risk factor for low Z-scores in TGD youth, especially when combined with low BMI and vitamin D deficiency.^{4,17,28,29} In addition, substance use including alcohol, cannabis, amphetamines, and opioids is more prevalent among transgender women and may further compromise bone health.^{4,10} Therefore, individualized, gender-affirming exercise prescriptions emphasizing progressive resistance, safe impact, and balance training are strongly encouraged to maintain skeletal health. Such differences in physical activity and other lifestyle behaviors may partly account for the lower BMD Z-scores observed in transgender women compared with transgender men.⁷ In addition, body mass index (BMI) is an important determinant of bone status: lower BMI is associated with reduced BMD, whereas higher BMI correlates positively with hip and femoral-neck Z-scores in both adolescent transgender men and adolescent transgender women.^{20,28} Therefore, an individualized exercise program that takes gender identity into account, emphasizing resistance training, safe levels of impact exercise, and balance training, should be strongly recommended to help maintain optimal bone health.

Other medical contributors include chronic corticosteroid use, which induces secondary osteoporosis. Gonadectomy per se is not a risk factor if adequate GAHT is maintained; bone loss reflects insufficient hormone replacement rather than surgery.⁴

Life-Course Effects of Interventions

1. Children and Adolescents (<18 years)

GnRHa therapy is a reversible intervention used to delay puberty and allow adolescents more time to explore gender identity before irreversible secondary sex characteristics develop.^{8,21,24} It suppresses gonadotropin secretion and slows bone mass accrual, leading to BMD Z-score declines of approximately 0.5 to 1.0 SD within two years of treatment.^{8,21} Importantly, this decline in Z-scores does not necessarily represent true bone loss, but rather reflects a relative delay in bone accrual compared with age-matched peers during a critical period of skeletal growth.

GnRHa therapy also reduces bone turnover markers such as procollagen type I N-terminal propeptide (PINP), a marker of bone formation, and C-terminal telopeptide of type I collagen (CTX), a marker of bone resorption, indicating decreased bone formation and resorption.^{8,21} Estrogen deficiency during suppression promotes adipogenesis over osteoblastogenesis, increasing bone-marrow adipose tissue (BMAT) and impairing bone formation.^{4,18}

TGD youth frequently exhibit low BMD even before treatment, with lumbar-spine Z-scores ≤ -2 in 20–30% of adolescent transgender women and 10–15% of adolescent transgender men. Key risk factors include low BMI, reduced physical activity, vitamin D deficiency, and factors disproportionately affecting adolescent transgender women.^{8,17,21} The Endocrine Society recommends starting GnRHa at Tanner stage 2–3 and introducing GAHT around age 16.²⁴ The duration of GnRHa treatment generally ranges from 1 to 3 years. During this period, the absolute BMD tends to remain stable; however, the Z-score reflecting age- and sex-adjusted reference values continues to decline progressively, indicating a relative lag in bone accrual compared with age-matched peers.^{8,21} Long-term effects on PBM and fracture risk remain uncertain.^{4, 18–20} A recent systematic review confirmed consistent declines in BMD Z-scores during GnRHa treatment.³²

Catch-up After GAHT Initiation

Catch-up in bone mass commonly occurs following the initiation of GAHT. In adolescents who have undergone puberty suppression with GnRHa, the re-introduction of sex steroids via GAHT stimulates renewed bone mineral accrual. Prospective studies demonstrate significant increases in bone mineral apparent density (BMAD) within 24–36 months after GAHT initiation, with lumbar-spine Z-scores rising by approximately 0.3–0.5 SD.^{6,8,21} Among adolescent transgender men youth, BMD typically returns to baseline levels, whereas in adolescent transgender women, recovery may remain incomplete when estradiol concentrations are subphysiologic.^{4,6,8} Long-term data up to 12 years show near-normal mean Z-scores, though small lumbar-spine deficits can persist in adolescent transgender women.²¹ In transgender men, early testosterone exposure has been shown to stimulate bone formation and turnover marker responses during GAHT initiation.³³ Early initiation of GnRHa at Tanner stages 2–3 has been associated with hip geometry aligning more closely with the affirmed gender.^{8,32,34}

GAHT is typically introduced gradually around age 16, following psychological evaluation and, when applicable, prior puberty suppression.^{24,32} 17 β -estradiol, administered orally, transdermally, or parenterally, is recommended as the standard estrogen preparation for feminizing hormone therapy in both adolescents and adults.^{9,24} A low-dose regimen is initiated and titrated gradually to mimic physiologic pubertal development and to minimize premature epiphyseal closure.^{17,21,34} The therapeutic goal is to maintain serum estradiol concentrations within the physiologic female range (100–200 pg/mL) while suppressing serum testosterone below 50 ng/dL. Ethinyl estradiol and conjugated estrogens are contraindicated due to their increased risk of thromboembolic and hepatic complications.^{9,24}

Anti-androgen therapy may be started concurrently with or prior to estradiol to enhance testosterone suppression and promote optimal skeletal response.^{9,10} Common agents include

cyproterone acetate (25–50 mg/day) and spironolactone (50–200 mg/day). Cyproterone acetate exerts potent anti-gonadotropic effects but may impair bone accrual when used as monotherapy and carries risks of hepatotoxicity, hyperprolactinemia, and meningioma with long-term exposure.^{9,10,23} Spironolactone has a milder anti-androgenic effect and requires potassium monitoring due to possible hyperkalemia.^{10, 24} Individuals taking spironolactone require potassium checks every 3 months in the first year and annually thereafter.¹⁰ DXA screening for osteoporosis is advised after ≥ 10 years of GAHT or beginning at age 50 (or 60 if no additional risk factors are present).^{4,10,29} 5- α -reductase inhibitors (finasteride, dutasteride) are not recommended as first-line anti-androgens because they do not sufficiently reduce serum testosterone and provide only partial androgen blockade.⁹

In adolescent transgender men, testosterone therapy supports cortical bone expansion and improves BMD when serum testosterone is maintained within the physiologic male range.^{6,10,12,33} Adequate hormone replacement following gonadectomy is crucial to prevent bone deterioration.^{10,13} Proandrogenic progestins, such as lynestrenol, were previously used in Europe for ovulation suppression or hormonal regulation in women, and occasionally in transgender individuals. Previous studies have shown that lynestrenol does not significantly reduce bone mass, and some evidence suggests that it may even produce a slight increase in BMD.^{10,13} However, these agents are no longer recommended in current clinical practice and have been replaced by standard testosterone formulations, which provide more consistent virilization and superior metabolic stability.^{9,24}

Restoration of physiologic sex-steroid levels through GAHT is the key determinant of the catch-up in bone mineralization observed after puberty suppression. Adequate estrogen or testosterone replacement, together with lifestyle factors such as sufficient calcium and vitamin D intake, weight-bearing exercise, and avoidance of smoking or alcohol excess, supports attainment and maintenance of PBM in TGD youth.^{15,17,19,23}

Assessment in Youth: DXA and Baseline Labs

Baseline DXA is recommended before GnRHa initiation, with follow-up every 1–2 years and again at GAHT initiation.^{4,8,21} The International Society for Clinical Densitometry (ISCD) advises sex-assigned-at-birth reference data for youth and gender-identity-concordant data for adults. Lumbar spine and TBLH are preferred DXA sites.^{4,29,35}

Regular monitoring of serum 25-hydroxyvitamin D (25OHD) is recommended throughout puberty suppression and subsequent hormone therapy, as vitamin D plays a crucial role in bone mineral accrual during adolescence. Vitamin D deficiency is common among TGD youth, particularly in transgender girls due to limited sunlight exposure and suboptimal dietary intake. Baseline assessment and at least annual monitoring of 25OHD levels are advised. Maintaining adequate

vitamin D status (≥ 50 nmol/L or 20 ng/mL) is essential to support optimal bone mineralization and maximize the skeletal benefits of hormone therapy.^{17,18,24}

2. Adults (18–49 years)

Early adulthood is critical for achieving and maintaining PBM, which determines long-term skeletal health.^{4,10} Most transgender individuals initiate GAHT after puberty; thus, baseline bone geometry typically reflects sex assigned at birth. GAHT preserves or increases BMD when hormone levels are maintained within physiologic ranges.^{6,10,23}

For transgender women, serum estradiol should be maintained at 100–200 pg/mL and testosterone suppressed < 50 ng/dL.^{10,24} For transgender men, testosterone levels should remain 400–700 ng/dL, allowing aromatization to estradiol for trabecular bone support.^{6,10} BMD monitoring every 1–2 years is advised until PBM is achieved (typically ages 25–30) and periodically thereafter.^{4,29}

Short-term studies show lumbar-spine BMD increases 2–5% in transgender women and 5–7% in transgender men within 1–2 years of GAHT.^{6,12} In contrast, total BMD tends to remain unchanged over 10 years, though small improvements appear with longer follow-up (~15 years).¹³ Microarchitectural analyses show lower total and cortical vBMD and greater cortical porosity in transgender women compared with cisgender men.⁷ Long-term follow-up and systematic reviews confirm persistent trabecular deficits after GnRHa therapy and emphasize adequate estradiol therapy.^{8,21,32}

Factors Contributing to Bone Loss After GAHT

Hypogonadism from inadequate GAHT, particularly after orchiectomy or oophorectomy, is a major risk factor for bone loss.^{10,24} In transgender women, estradiol levels below physiologic thresholds (< 50 pg/mL) associate with bone deterioration, whereas maintenance within the female range preserves skeletal integrity. Pre-GAHT anti-androgen monotherapy has also been linked to reduced BMD. In transgender men, insufficient testosterone replacement after oophorectomy similarly predisposes to skeletal imbalance.^{4,6,10}

Baseline findings from the COMET cohort have clarified skeletal characteristics before hormone initiation. Transgender women exhibited lower areal BMD at the lumbar spine and total hip, reduced lean mass, and higher fat mass, whereas transgender men demonstrated higher lean mass and BMD comparable to cisgender women. These disparities likely reflect combined lifestyle, nutritional, and endocrine influences.²⁸

Interindividual variation in androgen sensitivity further modulates skeletal responses. Within COMET, longer androgen-receptor (AR) CAG-repeat length correlated with lower lumbar-spine BMD and adverse cortical indices in transgender men, suggesting genetic variation in AR signaling contributes to bone outcomes.³¹

Other factors may influence bone health in transgender individuals receiving GAHT. The use of aromatase inhibitors, such as letrozole in combination with testosterone after oophorectomy, may attenuate BMD gains compared with testosterone monotherapy.^{4,6} Caution is warranted when initiating or continuing GAHT in individuals with chronic kidney disease, unstable coronary artery disease, polycythemia, or a history of venous thromboembolism, as these comorbidities may increase the risk of adverse metabolic or vascular outcomes.^{10,24}

In adulthood, lifestyle factors remain crucial for preserving bone mass and mitigating age-related bone loss, particularly among individuals receiving long-term GAHT. Common risk factors in adults include inadequate vitamin D and calcium intake, low body mass index, smoking, alcohol consumption, and substance use, all of which can suppress bone formation and enhance bone resorption.^{4,17,18}

Regular participation in weight-bearing and resistance exercises is essential to maintain bone strength during adulthood in both transgender women and transgender men. Transgender women generally engage in less physical activity compared with transgender men and cisgender counterparts, which may partly explain their lower BMD. Encouraging regular physical activity and maintaining physiologic hormone levels are therefore key strategies for preventing low bone mass and preserving skeletal health in the long term.^{4,10}

3. Older Adults (≥ 50 years)

Among older transgender adults, emerging cohort data suggest sex-specific fracture patterns and reinforce the importance of age-aligned screening and therapy. In adults aged ≥ 50 years, bone health warrants particular attention since sex steroids remain critical for bone remodeling. However, longitudinal evidence beyond 10 years of GAHT, especially in relation to fracture risk, remains limited.^{4,10,13}

In general, the continuation of GAHT into midlife and older age is recommended to prevent hypogonadism and mitigate age-related bone loss. Treatment should be maintained as long as there are no absolute contraindications, such as hormone-sensitive cancers, venous thromboembolism, severe hepatic impairment, or uncontrolled cardiovascular disease. Withdrawal of sex-steroid therapy can result in rapid declines in BMD, reduced muscle mass, and increased fracture risk. Treatment should therefore be individualized based on comorbidities, functional status, and overall goals of care.^{5,10,24}

In transgender women, maintenance of estrogen therapy remains essential for skeletal health, particularly after orchiectomy. A switch from oral to transdermal 17β -estradiol is advised to minimize cardiovascular and thromboembolic risk. Lower target estradiol concentrations (approximately 50–100 pg/mL) may be appropriate in older adults, with regular monitoring of cardiovascular status and liver function.^{5,10,24}

In transgender men, physiological testosterone replacement continues to be important for maintaining bone mass and muscle integrity. Dose adjustment or a change to transdermal formulations may be considered to reduce hematologic and metabolic risks. Monitoring of serum testosterone, hematocrit, and lipid profile every 6–12 months is recommended, as polycythemia and dyslipidemia can occur with long-term therapy.^{10,12,24}

Overall, long-term GAHT should not be routinely discontinued with aging. Instead, therapy should be tailored to maintain physiological hormone levels using the lowest effective dose and the safest route of administration. Regular reassessment of hormone status, BMD, and cardiometabolic parameters is essential to preserve the benefits of GAHT while minimizing risks in older TGD adults.^{5,10,24,29}

Fracture Incidence & Microarchitecture

Large-scale nationwide data demonstrate that transgender women aged ≥ 50 years have a higher fracture risk than age-matched cisgender men, with a hazard ratio (HR) of 1.9 (95% CI 1.3–2.7). The absolute incidence was 4.4 per 1000 person-years in transgender women compared with 2.3 per 1000 in cisgender men, while fracture rates in transgender men were lower than or similar to those of cisgender men, and the risk in transgender women was comparable to that of cisgender women (HR 1.05, 95% CI 0.75–1.49).¹³ This increased fracture risk in transgender women may not be explained solely by differences in BMD and may also reflect lower muscle mass, reduced physical activity, and higher fall risk. Fracture patterns in older transgender women closely mirror those of cisgender women, consisting predominantly of fragility fractures at the hip, spine, distal forearm, and humerus, rather than the traumatic fracture patterns more typical of cisgender men.^{4,10} These findings are partly explained by reduced baseline BMD before GAHT initiation.^{4,10}

Moreover, high-resolution peripheral quantitative computed tomography (HR-pQCT) studies have demonstrated microarchitectural impairments in transgender women, characterized by lower volumetric bone mineral density (vBMD), increased cortical porosity, and reduced trabecular bone volume. These alterations may reflect both pre-treatment skeletal differences and periods of subphysiologic estradiol exposure.^{7,28}

Conversely, transgender men appear less susceptible to fractures than both cisgender men (OR 0.57, 95% CI 0.35–0.94) and cisgender women (OR 0.79, 95% CI 0.48–1.30).¹³ This relative protection may reflect normal pre-GAHT BMD and the long-term anabolic effects of testosterone, which enhance muscle mass and mechanical loading.^{4,10,12} In transgender men aged ≥ 50 years, bone turnover markers decline within 12 months of testosterone therapy, while lumbar spine BMD increases significantly, likely mediated by aromatization to estradiol that suppresses bone resorption.^{12,24}

Screening & Management

Bone health monitoring in transgender youth should be adapted to treatment stage. In children and adolescents receiving GnRHa, baseline DXA should be obtained prior to treatment and repeated every 1–2 years during therapy.^{8, 21} Interpretation of Z-scores is best performed using sex-assigned-at-birth reference data.^{29,35} Bone turnover markers such as P1NP and CTX may also provide adjunctive information on skeletal remodeling. For adolescents starting GAHT, DXA should be repeated at initiation and then annually until PBM is reached, typically between ages 25–30.^{4,10,17}

Despite these insights, high-quality long-term studies of fracture outcomes in older TGD adults remain limited.^{10,13} Screening and diagnostic strategies should mirror those in cisgender populations but be contextualized to gender identity. BMD assessment by DXA in adults aged ≥ 50 years should include clearly defined measurement sites: the lumbar spine, total hip, and femoral neck, as these regions are most sensitive to age-related bone loss and are directly associated with fracture risk. In adults younger than 50 years, DXA examinations are typically performed based on individual risk factors. Therefore, specific scan sites are not mandatory but should be selected according to the clinical context and the purpose of longitudinal follow-up.^{29,35}

In adults aged ≥ 50 years, the evaluation of BMD using the T-score remains the international standard for the diagnosis of osteoporosis. For both cisgender men and women, as well as transgender individuals, T-scores are derived from the Caucasian young-adult female reference database, as endorsed by the World Health Organization (WHO) and the International Society for Clinical Densitometry (ISCD). This database serves as the global reference for diagnosing osteoporosis and assessing fracture risk across populations. Osteoporosis is diagnosed when T-scores ≤ -2.5 or when there is a history of fragility fracture at the hip or spine, whereas osteopenia is defined as a T-score between -1.0 and -2.5 .^{29,30,35}

Although osteoporosis diagnosis in this age group is based solely on the T-score, many DXA laboratories also report the Z-score to assess whether bone mass is appropriate for age and sex, and to identify potential secondary osteoporosis or hormonal disorders that may affect bone metabolism. In general, a Z-score below -2.0 indicates bone mass significantly lower than the expected range for age and warrants further evaluation. However, Z-scores are not used for diagnostic purposes in adults but provide valuable supportive clinical information.^{30,35}

The ISCD (2023) further recommends documenting both sexes assigned at birth and gender identity in DXA reports to ensure physiologically accurate interpretation, particularly for Z-scores, in the context of the individual's hormonal status. For transgender individuals receiving GAHT for ≥ 1 year, Z-scores should be compared with gender-identity-concordant reference data, as bone metabolism and structure have largely adapted to the affirmed hormonal milieu. Conversely, those

who have received GAHT for < 1 year should continue to be compared with sex-assigned-at-birth reference data to ensure accuracy and continuity in longitudinal follow-up.^{29,35}

In adults younger than 50 years, BMD should be assessed using the Z-score rather than the T-score, as individuals in this age group may not yet have reached the plateau of PBM. Using the T-score in this population may overestimate the degree of low bone mass. A Z-score ≤ -2.0 indicates bone mass below the expected range for age and should prompt investigation for underlying causes. However, this criterion is not diagnostic for osteoporosis, unless low-trauma or fragility fractures are present. For transgender adults, the ISCD (2023) recommends using sex-assigned-at-birth reference data when GAHT has been administered for less than 1 year, and switching to gender-identity-concordant reference data once GAHT has been continued for ≥ 1 year, to ensure that the evaluation accurately reflects the individual's hormonal and skeletal physiology.^{29,30,35}

The 10-year fracture risk can be estimated using the FRAX tool, which incorporates clinical risk factors such as age, sex, parental fracture history, smoking, alcohol use, glucocorticoid exposure, and comorbidities, and may be further refined with the Trabecular Bone Score (TBS), which reflects trabecular bone microarchitecture and provides additional information beyond BMD. According to Osteoporosis Canada, a 10-year probability of major osteoporotic fracture (MOF) $\geq 20\%$ is considered high and warrants pharmacologic therapy, while moderate-risk cases (10–19%) may be managed based on individual clinical factors.³⁰ Clinical assessment should also consider GAHT adherence, gonadectomy history, and additional risk factors including smoking, low body weight, glucocorticoid therapy, and alcohol excess.^{4,10} Sex steroid replacement remains essential after gonadectomy to prevent iatrogenic hypogonadism and bone loss.^{4,10,24}

Prevention and management principles in older transgender generally align with those applied to cisgender populations, but they must be individualized according to GAHT status and personal risk profiles. Fall prevention and regular weight-bearing or resistance exercise are recommended throughout the lifespan to preserve bone and muscle mass, while targeted counseling is important for transgender women, who tend to engage less in physical activity. Ensuring optimal nutrition through sufficient vitamin D and calcium intake, adequate sunlight exposure, and supplementation when indicated is essential, particularly for individuals with malnutrition, low body mass index, or eating disorders.^{4,10,17}

Pharmacologic therapy mirrors cisgender practice, as no TGD-specific drug data are available. Bisphosphonates and other antiresorptives are effective in reducing fracture risk and may be considered in transgender women when estradiol replacement is inadequate or contraindicated. Treatment decisions should integrate FRAX/CAROC risk estimates and T-scores, with initiation typically warranted at $\geq 20\%$ 10-year fracture risk, T-score ≤ -2.5 , age ≥ 70 years, or presence of hip/vertebral fracture or multiple fragility fractures.^{29,30} Hormone

levels should be monitored closely to ensure GAHT adequacy in skeletal protection, particularly post-gonadectomy, and comorbidities or concomitant medications (e.g., long-term glucocorticoids) must be taken into account.^{4,10,24}

Potential of Bone Turnover Monitoring

Beyond conventional DXA-based assessment, biochemical bone turnover markers (BTMs) provide valuable insights into the dynamic skeletal effects of GAHT and GnRHa. Recent evidence from Thai transgender men supports the association between testosterone therapy and dynamic changes in bone formation and resorption markers, aligning with international observations.^{12,33}

Serial measurement of BTMs, particularly serum P1NP and CTX, offers a dynamic evaluation of skeletal metabolism that complements DXA.^{4,29} Because GAHT and GnRHa induce rapid hormonal shifts, BTMs can detect alterations in bone remodeling within 3–6 months, well before measurable BMD changes occur.^{10,24}

Incorporating BTMs into clinical monitoring may help identify suboptimal hormone dosing, poor adherence, or early hypogonadism following gonadectomy, allowing timely therapeutic adjustments. Although reference ranges have not yet been validated specifically for transgender populations, available data indicate that trends in P1NP and CTX reliably reflect treatment-related changes in bone turnover and may predict subsequent BMD outcomes and fracture risk. Future research should establish population-specific reference intervals, assess cost-effectiveness, and determine whether BTM-guided interventions can optimize long-term skeletal health in TGD individuals.^{24,29,33}

Discussion

Bone health in TGD individuals is primarily determined by adequate and sustained exposure to sex steroids, the timing of hormonal interventions, and modifiable lifestyle factors. Puberty suppression with GnRHa predictably decreases bone accrual during adolescence.^{8,21} Subsequent initiation of GAHT allows for partial or near-complete recovery of BMD, particularly at the lumbar spine and hip.^{6,10} However, recovery may remain incomplete in some transgender women particularly when estradiol levels are subphysiologic.^{4,8} These findings emphasize the need for maintaining sufficient and continuous sex-steroid replacement to achieve PBM and preserve skeletal health.

In adults, GAHT generally maintains or improves BMD. Transgender women typically show stable or slightly increased BMD, whereas transgender men exhibit consistent gains at both cortical and trabecular sites.^{6,12} The anabolic effects of testosterone, partly through aromatization to estradiol, contribute to bone preservation.^{12,15} In contrast, discontinuation or inconsistent hormone use, especially after gonadectomy, can result in iatrogenic hypogonadism and accelerated bone loss.^{4,10} Aromatase-inhibitor therapy after oophorectomy may further reduce BMD compared with testosterone monotherapy.^{4,6}

Current international guidelines, including the Endocrine Society (2017), WPATH SOC8 (2022), and the Royal Thai College of Obstetricians and Gynaecologists (2023), recommend maintaining physiologic hormone targets and performing risk-based bone monitoring.^{23,24} The key recommendations for bone health monitoring across different age groups and treatment stages are summarized in Table 1. Recent position statements from the International Society for Clinical Densitometry (ISCD, 2023) and the Canadian Association of Radiologists (CAR, 2024) provide updated, complementary guidance on the selection of reference databases and interpretation of DXA results in TGD populations. For individuals younger than 50 years, both organizations recommend using Z-scores instead of T-scores, as PBM may not yet be achieved. According to ISCD, Z-scores should be referenced to sex assigned at birth if GAHT has been administered for less than one year and may shift to gender-identity-concordant reference data once GAHT has been stable for one year or longer. In contrast, CAR advises using age- and sex-matched normative data, without consideration of gender identity, to maintain consistency in national reporting standards.^{30,35}

For adults, ISCD recommends that when GAHT has been stable for at least one year, BMD interpretation should align with the affirmed gender. If hormonal exposure is intermittent, unclear, or inconsistent, dual reporting using both male and female reference data is acceptable to support individualized clinical interpretation.^{30,35} Meanwhile, CAR recommends that for adults aged 50 years and older, T-scores used for diagnostic and fracture-risk assessment be based on the White (Caucasian) female reference database for all sexes and gender identities, consistent with WHO diagnostic thresholds and national fracture-risk categorization.³⁰

Although the CAR guideline does not explicitly use the term *dual reporting*, it acknowledges that when the appropriate reference sex cannot be determined, DXA data may be analyzed and reported using both male and female databases, allowing clinicians to interpret findings according to each patient's hormonal and clinical profile. Together, these harmonized recommendations highlight an individualized yet standardized framework for BMD evaluation in TGD populations and are summarized in Table 2.

Table 1: Monitoring Recommendations for Bone Health in Transgender and Gender-Diverse Individuals.^{4,8,10,17,21,23,24,30,32}

Age Group / Setting	DXA / Imaging	Labs & Hormone Targets	Other Monitoring
Children & Adolescents on GnRHa	Baseline DXA before treatment; repeat every 1–2 years during GnRHa	–	Consider BTMs (P1NP, CTX) for skeletal activity and ensure adequate calcium/vitamin D intake
Adolescents starting GAHT	DXA at GAHT initiation, then annually until PBM achieved	Estradiol/testosterone titrated to affirmed gender targets	Monitor growth, pubertal progression, and nutritional status; reassess BMD if hormone levels remain below physiologic targets for ≥ 6 months
Adults <50 years	DXA individualized by risk; consider after 10 years of GAHT	Transgender women: estradiol 100–200 pg/mL, testosterone <50 ng/dL Transgender men: testosterone 400–700 ng/dL	Spironolactone: check potassium every 3 mo during first year, then annually. Ensure adequate vitamin D and calcium intake
Adults ≥ 50 years	T-score at spine, hip and femoral neck.	Transgender women: Estradiol 50–100 pg/mL Transgender men: testosterone 400–600 ng/dL	Screen for comorbidities (CV risk, glucocorticoid use, low BMI, etc.); FRAX for 10-yr fracture risk
Osteoporosis Diagnosis & Treatment	T-score ≤ –2.5, or hip/vertebral fragility fracture; osteopenia: T-score –1.0 to –2.5	–	Start antiresorptive/anabolic therapy if FRAX ≥ 20% or T-score ≤ –2.5 at ≥ 70 yrs

Table 2: DXA Interpretation and Reference Database by Age Group (Adapted from ISCD 2023 and CAR 2024).^{30,35}

Age Group / Population	Measurement Used	Reference Database (ISCD 2023)	Other Monitoring	Interpretation Note
Children & Adolescents (< 20 years)	Z-score	Sex assigned at birth	Not specified (follow ISCD)	Use sex assigned at birth due to growth differences; Interpret findings according to growth stage, pubertal status, and duration of hormonal treatment.
Young Adults (20–49 years)	Z-score	Gender identity if on GAHT ≥ 1 year; otherwise, sex assigned at birth. Dual reporting is acceptable if uncertain.	Z-score based on age- and biologic sex-matched norms. Dual reporting is acceptable if uncertain.	Align reference with gender identity when hormone exposure stable. Dual reporting when uncertain.
Older Adults (≥ 50 years)	T-score (with Z-score for supportive interpretation)	Gender identity if on GAHT ≥ 1 year; otherwise, dual reporting	Caucasian female reference for all adults, regardless of sex or gender identity.	ISCD allows gender-based or dual interpretation; CAR standardizes fracture risk using Caucasian female reference
Nonbinary Individuals (any age)	Z-score (<50 years) or T-score (≥50 years)	Sex assigned at birth or dual reporting if applicable.	Caucasian female reference recommended for adults ≥ 50 years.	No dedicated database: dual reporting improves interpretive clarity.

Transdermal 17 β -estradiol is preferred for older transgender women due to its lower cardiovascular and thromboembolic risk,^{5,24} while testosterone replacement should be continued in transgender men, with dosage and route tailored to maintain physiologic serum levels and minimize metabolic complications.^{10,16} Lifestyle and nutritional factors remain fundamental to skeletal protection. Risk factors for low BMD include vitamin D deficiency, inadequate calcium intake, low BMI, and physical inactivity.^{4,17} Transgender women are generally less physically active than transgender men, which may contribute to their relatively lower BMD.^{17,18} Regular weight-bearing and resistance exercise, smoking cessation, and sufficient vitamin D and calcium intake are universally recommended.^{4,10} Nutritional and lifestyle optimization is critical across the lifespan. Adequate intake of calcium and vitamin D through diet, sunlight exposure, or supplementation is recommended, as deficiencies are strongly linked to low BMD.^{4,10,17} Regular weight-bearing and resistance exercise should be promoted to support bone mass, with particular emphasis for transgender women, who often report lower levels of physical activity. Multidisciplinary involvement plays a pivotal role in optimizing bone health management. Counseling by dietitians and physiotherapists supports nutritional and physical activity goals.^{4,10} Referral to endocrinologists or bone specialists is appropriate for osteoporosis evaluation and pharmacologic treatment, including antiresorptive and anabolic therapies.^{29,30} Fertility preservation counseling should be provided prior to initiating GnRHa therapy for puberty suppression.^{24,33}

Among aging transgender adults, fracture patterns in transgender women resemble those of cisgender women, while transgender men appear relatively protected, likely due to the anabolic effects of testosterone.^{10,13} Continued GAHT beyond midlife is generally advised unless contraindicated, as withdrawal of sex steroids can rapidly induce bone loss.^{5,24} Hormone dose adjustment and regular laboratory monitoring, including hematocrit and lipid profile, are essential to ensure treatment safety.

Although the overall evidence supports the bone-preserving effects of adequate GAHT, several limitations persist. Most studies are observational and short-term, primarily from Western cohorts, with variability in DXA protocols and hormone assays.^{10,12,13} Fracture outcomes remain understudied, and the long-term skeletal effects of puberty suppression followed by GAHT are still unclear.^{8,21,29} The limited inclusion of older adults, nonbinary individuals, and ethnically diverse participants reduces generalizability. These limitations underscore the need for large, longitudinal, and multicenter studies to define lifetime fracture risk and optimize monitoring strategies across populations.

Knowledge Gaps and Future Directions

Despite significant progress, major knowledge gaps remain in understanding long-term skeletal outcomes among TGD populations. Most available studies focus on binary transgender

adults, leaving uncertainty about bone effects in nonbinary individuals who use flexible or partial hormone regimens.^{4,17} Many nonbinary adults maintain subphysiologic hormone levels, increasing the risk of iatrogenic hypogonadism and bone loss after gonadectomy.^{4,24} The International Society for Clinical Densitometry (ISCD) recommends referencing Z-scores to sex assigned at birth in nonbinary individuals, emphasizing the complexity of bone assessment in this group.^{30,35}

Long-term data beyond 10 years of GAHT remain scarce.^{10,13} The effects of early puberty suppression on PBM and later fracture risk are still uncertain.^{8,21} Methodological heterogeneity, small sample sizes, and limited inclusion of older and ethnically diverse participants further constrain interpretation.^{12,26} Future research should integrate clinical, hormonal, nutritional, and psychosocial determinants of bone health, with standardized DXA protocols and hormone monitoring.^{4,17}

Advanced imaging tools such as high-resolution peripheral quantitative computed tomography (HR-pQCT) may improve understanding of bone microarchitecture and strength beyond conventional DXA.^{28,32} Establishing longitudinal registries and age-stratified cohorts would enhance the evidence base and guide individualized interventions. Ongoing research into the ethical, psychosocial, and multidisciplinary aspects of lifelong hormone therapy, particularly in adolescents and nonbinary populations, is equally essential.³⁴

Conclusion

Across the life course, bone health in TGD individuals is shaped by the interplay of sex-steroid exposure, timing of medical interventions, and lifestyle factors. Puberty suppression with GnRHa reduces bone accrual during adolescence, but subsequent GAHT improves bone indices and partially restores BMD. In recovery may remain incomplete when estradiol exposure is inadequate, while in transgender men, testosterone therapy enhances bone formation through both androgenic and estrogenic mechanisms.

Adequate and continuous GAHT — estradiol for transgender women and testosterone for transgender men — preserves or enhances BMD during adulthood, whereas gonadectomy without hormone replacement accelerates bone loss. In later life, fracture patterns in transgender women parallel those of cisgender women, reinforcing the need for age-specific screening and osteoporosis prevention, while long-term testosterone use in transgender men appears bone-protective.

A comprehensive clinical approach should combine risk-based DXA monitoring, maintenance of physiologic hormone levels, and universal lifestyle strategies, including sufficient vitamin D and calcium intake, regular resistance and weight-bearing exercise, avoidance of smoking and excessive alcohol, and fall-prevention practices. These findings highlight the importance of individualized bone health monitoring and

maintaining physiologic sex-steroid levels throughout the lifespan to preserve skeletal integrity in transgender individuals. Although current evidence is reassuring, further long-term studies are required to clarify fracture outcomes, bone microarchitecture, and the impact of diverse hormone regimens. Expanding these data through large, longitudinal, and demographically diverse cohorts will be essential to optimize skeletal health across all TGD populations.

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Conflicts of Interest

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