Gender-affirming hormones: Bone density gains for some, losses for others?

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Bone health in transgender individuals undergoing gender-affirming hormone therapy (GAHT) has been a persistent clinical question, particularly given the window of adolescence for peak bone mass accrual, which is important for lifelong skeletal health. While some data exist, a clear picture across different age groups and sexes assigned at birth has remained elusive, leaving clinicians to navigate a complex relationship of hormonal effects on skeletal integrity. A new prospective study offers some clarity, demonstrating that GAHT can improve bone mineral density (BMD) in younger transgender individuals, though effects vary significantly by age and assigned sex.1

KEY TAKEAWAYS

- The Pivot: Gender-affirming hormone therapy improves bone density in younger transgender individuals, particularly those assigned male at birth, but can lead to modest loss in older individuals assigned female at birth.
- The Data: Lumbar spine BMD increased from 0.97 ± 0.16 to 1.02 ± 0.14 g/cm² ($p < 0.001$) in AMAB individuals after one year of GAHT.
- The Action: Early initiation of GAHT may offer skeletal benefits for AMAB individuals, while AFAB individuals, especially those over 20, warrant closer monitoring for femoral neck bone loss.

The skeletal effects of gender-affirming hormone therapy are not uniform, a point often overlooked in broader discussions of transgender healthcare. Individuals assigned male at birth (AMAB) frequently present with reduced bone mineral density even before starting GAHT, a baseline that complicates the interpretation of subsequent changes. For those assigned female at birth (AFAB), baseline BMD findings are more variable, suggesting different underlying skeletal dynamics. Understanding these pre-treatment differences is important for assessing the true impact of hormone therapy on bone health.1

This prospective observational study, conducted at the University Hospital of Padua between January 2020 and November 2024, enrolled 269 participants. The cohort included 162 transgender individuals undergoing GAHT and 107 age-matched cisgender controls. Researchers performed dual-energy X-ray absorptiometry (DXA) scans at baseline and again after one year of GAHT to precisely measure changes in bone mineral density. The study aimed to compare BMD changes in transgender individuals with their cisgender counterparts and to identify age-dependent responses to hormone therapy.1

The Age-Dependent Bone Response

After one year of gender-affirming hormone therapy, individuals assigned male at birth (AMAB) showed a significant increase in lumbar spine bone mineral density. Their BMD rose from 0.97 ± 0.16 to 1.02 ± 0.14 g/cm² ($p < 0.001$). This improvement was particularly pronounced in younger individuals, specifically those under 20 years of age. This finding highlights the potential for bone accrual during a developmental period when skeletal growth plates are still active and bone remodeling is highly responsive to hormonal shifts.1

But the picture was not uniformly positive across all groups. Individuals assigned female at birth (AFAB) experienced a modest but statistically significant reduction in femoral neck BMD. Their values decreased from 0.81 ± 0.12 to 0.79 ± 0.13 g/cm² ($p < 0.05$). This bone loss was most evident in the 20-30 year age group, suggesting that the impact of testosterone therapy on bone density in AFAB individuals may be site-specific and age-dependent. The mechanisms underlying this site-specific loss warrant further investigation, as they could involve differential responses of cortical versus trabecular bone to testosterone.1

Age-stratified analyses provided a clearer understanding of these divergent outcomes. Younger participants, generally those in their teens, consistently demonstrated greater improvements in bone mineral density. This suggests that the skeletal system, particularly during adolescence and early adulthood, retains a higher capacity for bone accrual in response to hormonal interventions. Conversely, participants over 20 years of age exhibited either stable or declining BMD values, indicating a reduced skeletal responsiveness to GAHT as individuals age. This pattern highlights the importance of timing in initiating hormone therapy, especially when considering long-term bone health outcomes.1

Linear regression analysis further solidified age as an independent predictor of BMD change. The analysis confirmed that older age was significantly associated with reduced skeletal responsiveness to GAHT, particularly at key femoral sites. This statistical confirmation reinforces the clinical observation that the window for optimal bone accrual during GAHT may close as individuals move past their early twenties. Clinicians should consider these age-related differences when counseling patients about the potential skeletal effects of hormone therapy.1

Mechanisms and Clinical Context

The differential effects observed between AMAB and AFAB individuals, and across age groups, likely stem from the complex relationship of sex hormones on bone metabolism. In AMAB individuals, estrogen therapy, often combined with anti-androgens, can promote bone formation and reduce bone resorption, especially when initiated during adolescence. This mirrors the natural process of bone accrual in cisgender females during puberty. The significant increase in lumbar spine BMD in younger AMAB individuals aligns with this understanding, suggesting that estrogen's anabolic effects are most potent during periods of active skeletal growth.1

For AFAB individuals, testosterone therapy aims to induce virilization. While testosterone is generally considered bone-protective, its effects on bone density can be complex and may vary by skeletal site and baseline hormonal milieu. The modest reduction in femoral neck BMD observed in AFAB individuals, particularly in the 20-30 year age group, could be due to several factors. These might include a transient increase in bone turnover, a shift in bone remodeling balance, or even a relative estrogen deficiency if testosterone therapy effectively suppresses endogenous estrogen production without fully compensating for its bone-protective effects. The mechanisms of bone density changes are not always straightforward.1

The study's findings also resonate with broader endocrinological principles regarding peak bone mass. Peak bone mass is typically achieved in the late teens to early twenties, after which bone density tends to stabilize or gradually decline.

Interventions that influence bone metabolism during this period, which is important for lifelong skeletal health, can have lasting effects on an individual's lifetime risk of osteoporosis and fractures. The greater BMD improvements seen in younger participants suggest that GAHT, when initiated early, can positively influence this trajectory, particularly for AMAB individuals who may start with lower baseline BMD.1

This research adds to a growing body of evidence on the long-term health outcomes of gender-affirming care. While the focus here is on bone density, the broader context of hormone therapy involves numerous physiological changes. Clinicians managing transgender patients must consider a holistic approach, integrating skeletal health monitoring into routine care. This includes regular DXA scans, especially for AFAB individuals in the 20-30 year age group, and potentially calcium and vitamin D supplementation, as recommended in general endocrinology practice. For a comprehensive overview of endocrine management, the Oxford Handbook of Endocrinology and Diabetes can be a useful reference.

Caveats and Future Directions

The observational nature of this study is an important caveat. While prospective, it lacks the randomization of a controlled trial, meaning unmeasured confounders could influence the results. The study also had a relatively short follow-up period of one year. Bone remodeling is a slow process, and longer-term data are needed to fully understand the sustained effects of GAHT on bone mineral density and, specifically, on fracture risk. A one-year snapshot, while informative, cannot definitively predict lifelong skeletal health.1

The study's population size, with 162 transgender individuals, provides a reasonable sample for initial observations, but larger, multicenter studies would offer greater statistical power and generalizability. The cisgender control group, while age-matched, did not undergo the same hormonal interventions, making direct comparisons of hormonal effects challenging. Future research could benefit from comparing different GAHT regimens or dosages, as well as exploring the impact of puberty blockers prior to hormone initiation.1

Another area for further exploration is the specific type and duration of hormone therapy. The study broadly refers to GAHT, but the precise regimens (e.g., specific estrogen formulations, testosterone esters, anti-androgens) and their dosages can vary widely. These nuances could influence bone outcomes and were not detailed in the abstract. Understanding these specific therapeutic variables will be essential for refining clinical guidelines. The study did not report on lifestyle factors such as diet, physical activity, or smoking, all of which are known determinants of bone health and could interact with hormone therapy effects.1

The study also did not address the impact of pre-existing conditions or other medications that might affect bone metabolism. Many transgender individuals may have comorbidities or be on other medications that could influence their bone health trajectory. Accounting for these factors in future studies would provide a more complete picture of the risks and benefits of GAHT. The question of whether these bone density changes translate into clinically meaningful differences in fracture rates remains unanswered by this study. That is the next endpoint for investigation.1

> **CLINICAL IMPLICATIONS**
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> This study provides a much-needed data point for clinicians managing transgender patients, particularly regarding bone health. The clear age-dependent response means that a one-size-fits-all approach to

> monitoring bone density is insufficient. For younger AMAB individuals, early initiation of GAHT appears to be genuinely beneficial for bone accrual, a finding that should inform discussions around the timing of therapy. But the modest bone loss in the femoral neck for AFAB individuals, especially those in their twenties, cannot be ignored. This group requires closer surveillance, potentially with earlier or more frequent DXA scans than currently standard. It highlights the need for individualized care plans that consider both assigned sex at birth and age at initiation.
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> The short follow-up period is the obvious limitation. One year of data is a start, but it does not tell us about long-term fracture risk or sustained bone density changes over decades. Clinicians must continue to counsel patients that while initial bone density changes are observed, the full picture of lifelong skeletal health with GAHT is still emerging.

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