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Effect of Hormone Replacement Therapy on Bone Health and Density in Transgender Individuals

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EFFECT OF HORMONE REPLACEMENT THERAPY ON BONE HEALTH AND DENSITY IN TRANSGENDER INDIVIDUALS

by

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Abstract

Background: This article is an examination of the effects of hormone replacement therapy on bone health and density in transgender individuals. The use of gender affirming hormone therapy and surgery is on the rise nationally. This bears the question: what side effects may result from use? Hormones have previously been studied for their protective effects on bone health, but there is a distinct lack of research into the effects of long-term gender-affirming hormone therapy.

Objective: To answer the research question: What effect does gender-affirming hormone therapy have on bone density in adult and adolescent transgender individuals over at least a 12-month period.

Design: Scoping literature review utilizing sources from January 2011 to September 2022. The academic databases used in the collection of sources include PubMed and CINAHL Complete.

Participants/Setting: Studies selected must have participants that identify as transgender and currently be receiving, or have previously received, gender-affirming hormone therapy. Inclusion criteria for adolescent individuals was identical to adults, with the addition that they must be past Tanner Stage II in puberty.

Main Outcome Measure: It was hypothesized that the use of estrogen therapy in individuals would have a protective effect on bone mineral density and health, whereas testosterone therapy would have a deleterious effect when used on its own.

Results/Conclusion: The use of gender-affirming therapy in transgender individuals is recognized as safe for adults and adolescents. Estrogen therapy had a mostly protective effect on bone mineral density, which reduces fracture and osteoporosis risk. Testosterone therapy had less effect on bone mineral density. While there were some incidences of bone mineral density

growth, overall testosterone had a neutral effect on bone health. In adolescents, GnHR agonists were the primary treatment and resulted a in decrease of bone mineral density. This deleterious effect was lessened with the addition of sex hormones.

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INTRODUCTION

Background

Currently, 25 million people in the world self-identify as transgender.[1,2] The term transgender was coined in 1971 and refers to individuals whose gender identity is incongruent with the sex they are assigned at birth. While other terms, such as transsexual, cross-gender, cross-sexual, or transgendered exist, they are considered to be outdated and should be avoided unless specifically requested by the individual.

The incongruence between assigned sex and gender has resulted in gender dysphoria for transgender individuals, thus prompting the use of gender-affirming hormone therapy (GAHT) and gender-affirming surgery (GAS).[1] GAHT for transgender women (assigned male at birth, otherwise known as AMAB) generally includes estrogen, with the option of anti-androgen therapy, whereas GAHT for transgender men (assigned female at birth, AFAB) includes testosterone therapy.[1] GAHT and GAS have been defined as medically necessary by the World Professional Association for Transgender Health, as they have been shown to drastically improve psychosocial outcomes.[3,4]

Hormones

Hormones play key roles within the body; therefore, healthcare providers must be aware of common side effects that occur during GAHT. Estrogen is the main regulator of bone health in the body and maintains peak bone mineral density. Research has found that reducing the amount in the body during GAHT has been linked with a decline in bone mineral density.[3] Estradiol assists in skeletal development.[5] The effect of testosterone on bone health is harder to pinpoint. Testosterone has been shown to increase muscle mass while simultaneously decreasing body fat.[1] This can increase the mechanical load placed directly on the bone, consequently causing increased bone mass.[6] However, this also can increase the risk of mechanical strain or fracture.[6]

Male-to-female (MtF) patients utilize estrogen and anti-androgens, including spironolactone and gonadotropin-releasing hormone agonists (GnRH).[5] Spironolactone inhibits androgen receptors, which reduces facial hair and male alopecia while adding to estrogen intake.[5] GnRH agents work alongside spironolactone to restrain luteinizing hormone secretion, which results in gonadal suppression and testosterone inhibition.[5] Female-to-male (FtM) patients utilize GnRH agonists, as well as 5-alpha reductase inhibitors, medroxyprogesterone, and selective serotonin receptor inhibitors (SSRIs).[5]

There are several routes available for the administration of GAHT, depending on the type of therapy and needs of the patient. In MtF patients, estradiol can be given orally, subcutaneously, or transdermally.[4] Adjunctive agents, such as spironolactone, cyproterone, or progesterone, are generally given orally.[4] In FtM patients, testosterone can be given as an injection, either subcutaneously or intramuscularly, or as a transdermal patch.[4] The route of administration is selected on the basis of several factors, such as availability, tolerability, location, and affordability.[4]

Definition of Terms Associated with Transgender Individuals

Term	Definition
Transgender	Gender identity does not match sex assigned at birth.
Transgender woman (trans woman, MtF)	Sex assigned at birth is male but individual identity is female.
Transgender man (trans man, FtM)	Sex assigned at birth is female but individual identity is male.
Gender-affirming hormone therapy (GAHT)	Hormone therapy used to reduce gender dysphoria by adapting body and features to be congruent with gender identity.
Gender-affirming surgery (GAS)	Surgery to adapt body and features to be congruent with gender identity. Many still use the phrase sex-assignment surgery, but this term is considered outdated and should be avoided.
Assigned (male/female) at birth	Refers to the sex assigned at birth and differs from gender identity. Sex assignment is generally restricted to that of male or female, and is generally denoted by the terms AFAB (assigned female at birth) or AMAB (assigned male at birth).

Estrogen[7]	Steroid hormone that promotes development and maintenance of female body characteristics. Also helps regulate bone health and peak mineral density.
Testosterone[8]	Steroid hormone responsible for inducing and maintaining male secondary sex characteristics.
Androgen[9]	Sex hormone that helps start puberty and body development. Testosterone is the most common androgen.
Spironolactone[10]	Androgen blocker with suppressive effect on testosterone synthesis.
Gonadotropin-releasing hormone (GnRH)[11]	Hormone that regulates pubertal onset, sexual development, and ovulatory cycles (in females).

Table 1: Terminology

Thesis Question

Currently, there is a large gap in existing data regarding best practices in transgender health. This can be attributed to several factors: lack of training and education for providers, discrimination, and lack of insurance coverage for gender-affirming care.[1] Due to this, studies looking at the effect of GAHT are limited and employ small sample groups. This review aims to clarify existing data and determine what effect GAHT has on bone density in adult and adolescent transgender individuals over at least a 12-month period.

Methods

Search Procedures

Literature for this scoping review was sourced through a comprehensive electronic search between September 2021 and September 2022. The databases PubMed and CINAHL Complete were utilized as sources. The search itself was conducted using the key words: "transgender, gender-affirming hormone therapy, bone mineral density, bone health" and "hormones, testosterone, and estrogen". Other terms for transgender persons such as "transgendered person/s" OR "transsexual person/s" OR "cross-sex person/s" were included to encompass more literature.

Due to the lack of existing data in this field, the inclusion criteria were wide. Participants included individuals who identified as transgender, were currently receiving gender-affirming hormone therapy or had in the past, and adults or adolescents past Tanner Stage II. A publication range between January 2011 and May 2022 was chosen to ensure more relevant data. Exclusion criteria included individuals who were transgender but not receiving any method of hormone therapy, cisgender participants, articles not in English, or publications prior to January 2011. Previous gender-affirming surgery was not an exclusion criterion.

To reduce the risk of bias, a PRISMA protocol was followed.[12] Results from each keyword search were recorded, then screened for repeat studies, which were consequently removed. After duplicates were removed, the author reviewed each article to screen for exclusion criteria, as outlined above. The author then reviewed all articles for content, in order to decide what was applicable to the thesis topic. This process was repeated by a second individual to confirm which articles were relevant, thus ensuring that no literature was missed. The flowchart below outlines the process.

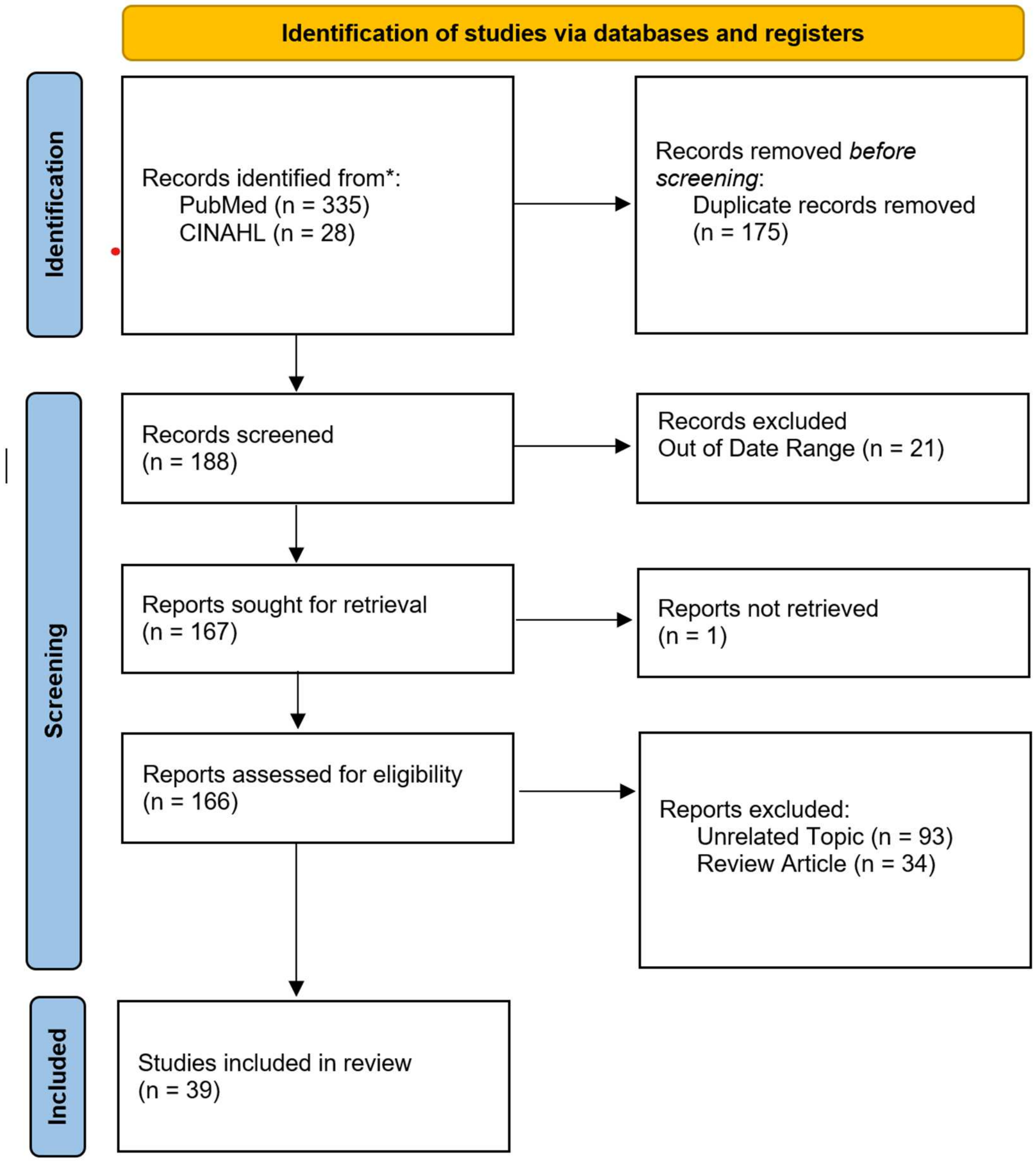

Figure 1: PRISMA Inclusion Flowchart

SUMMARY OF LITERATURE

Adolescent Gender-Affirming Hormone Therapy

Participants were recruited for several studies regarding the effect of GAHT and gonadotropin-releasing hormone (GnRH) agonists on the bone mineral density (BMD) of transgender adults and adolescents.[13] These studies specifically targeted the adolescent transgender population. One study found that trans girls presented with lower baselines of BMD from the start.[13] GnRH agonists were given to participants once they reached puberty, which was measured via Tanner's stages. Participants were required to be at least Tanner stage II and no later than Tanner stage V.[13] GnRH agonists were given for 2-4 years, after which GAHT was added to the therapy regimen. In trans girls, there was a slight increase in BMD in the lumbar area following treatment and no significant increase in trans boys.[13]

A second study in adolescents confirmed the above results in trans girls. Participants in this study were treated initially with GnRH (1-2 years) and then treated with gender affirming hormones, estrogen or testosterone.[3] As in the above study, trans girls showed no change in BMD on GnRH and slight increase in BMD with onset of estrogen.[3] Trans boys showed an increase in lumbar BMD; however, when GnRH was the only gender affirming treatment, BMD in trans boys decreased significantly, but stabilized with addition of testosterone.[3] Similarly, bone turnover also decreased in trans boys when only using GnRH agonists, only to stabilize with the addition of GAHT.[14] Another study found that initiation of GAHT in trans boys (Tanner Stage IV-V) resulted in increased LBM and grip strength.[15]

These studies were contradicted by Klink et. al in a study done with 34 transgender adolescents.[16] BMD decreased in both trans girls and trans boys, showing that GAHT given during puberty may increase risk of BMD loss. This finding was echoed in another study comprised of 51 trans girls (Tanner Stage IV-V) and 119 trans boys (Tanner stage IV-V).[17] After treatment with GnRH agonists, there was a significant drop in BMD at the lumbar spine and total hip in trans girls, which were found to be already low at baseline.[17] Trans boys showed similar drops in BMD. Stoffers et. al also noted that BMD z-scores decreased during GnRH agonist therapy[18], while another study noted that bone mass accrual was inhibited and BMD decreased in trans girls using GAHT.[15] This result may highlight the importance of using estrogen or testosterone therapy in conjunction with GnRH agonists in the adolescent populations, as the addition of sex steroids can help mitigate osteoporosis risk and maintain existing bone density.

Adult Testosterone Therapy

Increases in BMD were determined by dual energy x-ray absorptiometry (DXA scan)[1,2,3,14,19,20,21,22,23] and grip strength.[3,21] Grip strength has been shown to be a predictor of bone mass across gender- as grip strength increases, so does BMD.[24] Other studies utilized markers such as type 1 procollagen (PINP), which measures rates of bone formation and resorption[4,5], and other biochemical indices.

Studies showed that increased testosterone generally led to improved or maintained BMD. One study showed a particular BMD growth in the lumbar spine and hip[25], while another found an increase in BMD in the femoral neck.[19] Both studies show preservation of BMD during testosterone therapy, although more research may be needed to determine why certain locations are affected more than others. Scharff et. al noted an increased grip strength in FtM participants after one year of GAHT, which was associated with growth of lean body mass.[20] Grip strength and lean body mass were also improved as well in a study done by Van Caenegem et. al.[26] When using type I procollagen (PINP) as the measurement in long-term GAHT, there was also a slight increase in PINP bone formation rates.[5]

One side effect reported from the use of testosterone was a slight decrease in hand grip strength in participants of one study, which was hypothesized to be due to an induced anabolic effect on the muscle.[5] Andrade et. al found similar results in their study, noting that trans men undergoing testosterone therapy have lower grip strength than age matched cisgender men. The authors also noted a lower total body and femoral neck BMD in trans men, despite having the same testosterone levels as cis men.[27] Similarly, another study found that bone resorption increased in transgender men, causing lower BMD in the lumbar area[28] as well as the radius and tibia.[26]

Other studies found that there was no change in the bone morphology of trans men during GAHT, as the bone microarchitecture remained stable with no changes in BMD.[29] Fighera et. al found that long-term GAHT had a neutral effect on BMD in trans men.[19] The formulation of the testosterone therapy did not seem to have an effect on bone health or BMD.[30]

Adult Estrogen Therapy

Studies in trans women differed on whether or not estrogen therapy helps maintain bone mineralization. Vlot et. al found that after one year of receiving GAHT, the increased estrogen reduced osteoclast activity, inhibiting bone resorption, which resulted in improved BMD.[31] Another study had similar findings of increased BMD due to inhibition of bone resorption in trans women, but noted that both the type and dose of estrogen affected how much BMD increased.[28] Estrogen was also found to help decrease bone turnover, which is inversely related to BMD.[31] Estrogen therapy may also have a positive effect on both trabecular bone score, which is an indicator of bone microarchitecture, as well as osteoporosis risk.[32] Participants in another study saw increased BMD in the lumbar spine and were shown to have decreased risk for osteoporosis while receiving estrogen therapy.[4,21,31,32,33]

A study by Chrisostomo et. al found that total femur and femoral neck BMD increased alongside spine BMD. While an increase was shown in this study from before GAHT to after, it is important to note that BMD was still lower in the transgender cohort than in the cisgender cohort.[22] Several studies have also noted higher incidence of low bone mass at baseline in transgender women.[19,22,29,34,35,36] This can mean that although estrogen therapy improves BMD individually, trans women may be more at risk for osteoporosis and fractures than their cisgender counterparts.

Similar to Chrisostomo et. al, other studies found that estrogen had a positive effect on BMD, showing a slight increase in BMD at the lumbar spine after 12 months,[19] and an increase in BMD at the femoral neck, radius, lumbar spine, and total body.[35] These results were further confirmed by Gava et. al, whose study also showed an increase in BMD at the lumbar spine and total body after three years of GAHT.[37]

In contrast to the previous studies, Dobrolińska et. al determined that trans women with a previous gonadectomy who were undergoing estrogen GAHT, had a decrease in BMD at the total hip and lumbar spine.[38] They also noted that the decrease in BMD was more significant after 15 years of GAHT than at 10 years.[38] Bretherton et. al found that bone microarchitecture deteriorated during estradiol therapy specifically.[29] Deterioration of bone microarchitecture is characteristic of osteoporosis, as well as an indicator of bone fragility. Stevenson & Tangpricha concluded that trans women utilizing GAHT were at higher risk for osteoporosis.[2] While this could be due to estrogen GAHT, participants in this study were also given cyproterone acetate (a testosterone decreasing agent) as a precursor to estrogen GAHT. In studies that used cyproterone in cisgender men, BMD was significantly decreased.[23] These men also had higher risk of fractures, which coincides with osteoporosis risks. This may highlight the importance of simultaneous GAHT with adjuvant treatments.

Results and Practice Considerations

Studies consistently found a relationship between GAHT and bone mineral density. In adolescents, bone mineral density significantly decreased when treatment solely consisted of GnRH agonists. The addition of sex hormones (estrogen or testosterone) saw stabilization of bone mineral density levels. This is important to consider when developing appropriate treatment strategies for transgender youth. In trans men, results showed fewer significant changes in bone mineral density. Most studies attributed this to the protective role of small levels of estradiol in the body. Some studies found a slight increase in BMD and grip strength, however; most studies noted that testosterone therapy had a neutral effect on bone health. Bone mineral density was consistently found to be increased in trans women with initiation of estrogen hormone therapy, despite generally being low prior to the start of treatment. Most increases in BMD were located in the lumbar spine. This increase in BMD helps to reduce fracture and osteoporosis risk in transwomen as well.

Limitations

Limitations to this review primarily include the lack of overall research in the field. There are limited studies regarding the effect of hormones and GAHT on bone health in transgender individuals. While research surrounding transgender health is growing, obstacles such as healthcare bias and discrimination, lack of access, and financial barriers impede it. Many studies in this review also utilize small sample sizes, which may impact the validity of the findings.

Strengths

Strengths of this review are in the protocol followed to ensure lack of bias. This review followed a structured scoping approach to collecting the literature, as outlined and defined by PRISMA. This lends increased credibility and validity to the process and increases the strength of the evidence.

Conclusion and Future Research

Research focused on transgender health is a growing topic of study. Future research will help to reduce sample size bias, which is recognized as a limitation of this review and area of research. In this review, the effects of GAHT on bone health were the primary factors looked at. However, there are other factors that play a role in bone health, such as age, weight, and diet. In particular, obesity has been recognized as playing a protective role in bone density and health. It would be interesting to explore this obesity paradox as it relates to the transgender population in future research. Other potential areas of research include the effect of diet on bone health, so that nutritional recommendations specific to transgender individuals receiving GAHT could be identified.

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Appendix

Study Reference #	Article Title	Authors	Year	Participants	Results	Conclusion
27	Bone mineral density, trabecular bone score and muscle strength in transgender men receiving testosterone therapy versus cisgender men	Andrade SRL, Mucida YM, Xavier JDC, Fernandes LN, Silva RO, Bandeira F.	2022	19 transgender men and 19 cisgender men	Estradiol levels are higher in trans men, but total muscle mass and hand grip strength are lower.	Despite similar testosterone levels, trans men undergoing testosterone therapy have lower muscle strength, mass, and total body/femoral neck BMD than cisgender men.
29	Bone Micro-architecture in Transgender Adults: A Cross-Sectional Study	Bretherton I, Ghasem-Zadeh A, Leemaqz SY, Seeman E, Wang X, McFarlane T, Spanos C, Grossmann M, Zajac JD, Cheung AS.	2022	41 transgender men, 71 cisgender female controls. 40 transgender women, 51 cis male controls.	Trans men had higher BMD than ciswomen, and no deficits in micro-architecture. Trans women had lower BMD than cis men and deteriorated bone microstructure.	Bone morphology is not compromised during testosterone therapy but is during estrogen therapy with estradiol. BMD was decreased in trans women compared to the control group.
22	Trans women and bone mineral density: a cross-sectional study in Brazilian population	Chrisostomo KR, Skare TL, Chrisostomo HR, Barbosa EJL, Nisihara R.	2020	31 trans women, 31 females, and 31 males	Low bone mass was found in 12.9% of trans women, 3.2% females, and 3.3% males. Trans women had lower spine and femur Z scores	Prior to GAHT, trans women are at increased risk for low bone mass. However, BMD and bone mass are preserved during estrogen therapy.
38	Bone Mineral	Dobrolińska	2019	68 trans	BMD at lumbar	There was a

	Density in Transgender Individuals After Gonadectomy and Long-Term Gender-Affirming Hormonal Treatment	M, van der Tuuk K, Vink P, van den Berg M, Schuringa A, Monroy-Gonzalez AG, García DV, Schultz WCMW, Slart RHJA.		women and 43 trans men who had undergone gonadectomy and were treated with GAHT.	spine and total hip for trans women: 0.99 ± 0.14 g/cm^2 and 0.94 ± 0.28 g/cm^2 Trans men: 1.08 ± 0.16 g/cm^2 and 1.01 ± 0.18 g/cm^2	decrease in total hip bone mineral density after 15 years of GAHT, compared to 10 years of GAHT, in both trans men and trans women.
19	Impact of cross-sex hormone therapy on bone mineral density and body composition in trans women	Fighera TM, da Silva E, Lindenau JD, Spritzer PM.	2018	142 trans women, with reference group of 22 men and 17 cis women	BMD was similar in trans and cis women. Low bone mass was found in 18% of trans women at baseline. LBM decreased over time in trans women, but BMD remained stable or increased.	Long-term GAHT had a neutral effect on BMD in trans men. BMD increased in lumbar spine in transgender women, despite being lower at baseline.
37	A comparison of 5-year administration of cyproterone acetate or leuprolide acetate in combination with estradiol in transwomen	Gava G, Mancini I, Alvisi S, Seracchioli R, Meriggiola MC.	2020	50 trans women receiving cyproterone acetate or leuprolide acetate	No change in OC, PTH, or BAP. Lumbar and total body BMD increased after 3 years.	Lumbar and total body BMD increased after 3 years.
16	Bone mass in young adulthood following gonadotropin-releasing hormone analog treatment and cross-sex hormone treatment in adolescents	Klink D, Caris M, Heijboer A, van Trotsenburg M, Rotteveel J.	2015	34 young adults >21 years of age with previous gonadectomy	Lumbar BMD z score decreased from -0.8 to -1.4 in trans women and from 0.2 to -0.3 in trans men.	GAHT given during puberty may increase risk of BMD loss.

	with gender dysphoria					
24	Association between grip strength and bone mineral density in general US population of NHANES 2013-2014	Luo Y, Jiang K, & He M	2020	1850 participants, age 40-80 years old	Grip strength is associated with increased femoral neck and total lumbar spine BMD in men and women.	Grip strength can be predictive of BMD in general US population.
28	A study of changes in bone metabolism in cases of gender identity disorder	Miyajima T, Kim YT, Oda H.	2012	57 trans men and 18 trans women	Trans women: bone resorption was inhibited, L2-4 BMD increased Trans men: bone resorption increased, L2-4 BMD decreased.	BMD increased in trans women but decreased in trans men. Both were influenced by dose of estrogen.
34	Fracture risk assessment in an Italian group of transgender women after gender-confirming surgery	Motta G, Marinelli L, Barale M, Brustio PR, Manieri C, Ghigo E, Procopio M, Lanfranco F.	2020	57 trans women	40% incidence of low bone mass in lumbar spine, low estradiol levels, and increased fracture risk.	Trans women on estrogen replacement therapy (ERT) have higher incidence of low bone mass, likely due to low estradiol levels and ERT non-compliance. While low, there is also an increased risk for fractures.
33	Body composition and bone mineral density in male-to-female transsexuals during cross-sex hormone therapy using gonadotrophin-releasing hormone	Mueller A, Zollver H, Kronawitter D, Oppelt PG, Claassen T, Hoffmann I, Beckmann MW, Dittrich R.	2011	84 trans women (MtF)	There is a significant decrease in testosterone during GAHT but bone mineral density at the lumbar spine was found to be significantly increased. No effect was found on femoral bone density.	There was an increase in spine BMD after GAHT. There was a neutral effect of GAHT on femoral BMD.

	agonist					
17	Pubertal suppression, bone bass, and body composition in youth with gender dysphoria	Navabi B, Tang K, Khatchadourian K, Lawson ML.	2021	51 Trans women (Tanner Stage IV-V) 119 trans men (Tanner Stage IV-V)	Trans women had lower lumbar spine (LS) and total hip (TH) bone mineral density at baseline. After GAHT there was a significant drop in LS an TH in both trans men and trans women.	GAHT, specifically GnRH therapy, negatively effects bone density in transgender girls and boys.
30	Effects of three different testosterone formulations in female-to-male transsexual persons	Pelusi C, Costantino A, Martelli V, Lambertini M, Bazzocchi A, Ponti F, Battista G, Venturoli S, Meriggiola MC.	2014	45 transgender male receiving testosterone	Lean body mass significantly increased, and fat mass decreased in all groups.	Testosterone therapy in trans men appears safe, regardless of testosterone formulation.
25	Testosterone Therapy: Review of Clinical Applications	Petering RC, Brooks NA.	2017	N/A	Low testosterone levels are associated with decreased BMD. Testosterone therapy can increase BMD at lumbar spine.	Testosterone therapy does not have a deleterious effect on BMD and is considered safe in regard to bone health parameters.
13	Bone Development in Transgender Adolescents Treated With GnRH Analogues and Subsequent Gender-Affirming Hormones	Schagen SEE, Wouters FM, Cohen-Kettenis PT, Gooren LJ, Hannema SE.	2020	51 trans girls and 70 trans boys receiving GnRHa AND 36 trans girls and 42 trans boys receiving GnRHa and GAHT	Trans girls showed slight increase in lumbar BMD after 2-4 years of GnRH agonist use. No significant increase or decrease in BMD in trans boys utilizing GnRH agonists.	BMD generally decreased when only using GnRHa but increased when combined with GAHT.
20	Change in grip strength in trans people and its	Scharff M, Wiepjes C, Klaver M, Schreiner T,	2019	249 trans women and 278 trans men.	Grip strength decreased by 1.8 kg in trans women but	Grip strength was shown to decrease in trans women

	association with lean body mass and bone density	T'Sjoen G, & den Heijer M			increased 6.1 kg in trans women. Change in grip strength was associated with change in lean body mass, not BMD.	after 12 months of GAHT. Testosterone was shown to have a positive effect on muscle mass and grip strength.
18	Physical changes, laboratory parameters, and bone mineral density during testosterone treatment in adolescents with gender dysphoria	Stoffers IE, de Vries MC, Hannema SE.	2019	62 adolescents with gender dysphoria using GnRHa and testosterone treatment for > 6 months.	BMD z-scores decreased during treatment.	Testosterone and GnRHa therapy can have a deleterious effect on BMD in adolescents who had already completed linear growth.
15	Proandrogenic and Antiandrogenic Progestins in Transgender Youth: Differential Effects on Body Composition and Bone Metabolism	Tack LJW, Craen M, Lapauw B, Goemaere S, Toye K, Kaufman JM, Vandewalle S, T'Sjoen G, Zmierczak HG, Cools M.	2018	44 trans boys (Tanner Stage 4-5) and 21 trans girls (Tanner Stage 4-5)	LBM and grip strength increased in trans boys. LBM and grip strength decreased in trans girls. BMD was decreased in lumbar spine of trans girls.	GAHT can impede bone mass accrual in the lumbar spine of trans girls.
36	Low bone mass is prevalent in male-to-female transsexual persons before the start of cross-sex hormonal therapy and gonadectomy	Van Caenegem E, Taes Y, Wierckx K, Vandewalle S, Toye K, Kaufman JM, Schreiner T, Haraldsen I, T'Sjoen G.	2013	25 trans women and 25 age matched men (control group)	Transgender women had lower BMD at the hip, femoral neck, total body, and lumbar spine compared with cismen.	Trans women have lower BMD at baseline, which may increase osteoporosis risk after GAHT.
26	Bone mass, bone	Van Caenegem E,	2012	66 trans men with 66 age	Trans men using long-term	Long-term use of testosterone

	geometry, and body composition in female-to-male transsexual persons after long-term cross-sex hormonal therapy	Wierckx K, Taes Y, Dedecker D, Van de Peer F, Toye K, Kaufman JM, T'Sjoen G.		matched women (control group)	testosterone therapy had higher LBM and greater grip strength but decreased BMD at radius and tibia.	therapy can potentially lower BMD in trans men but improved LBM and grip strength.
35	Preservation of volumetric bone density and geometry in trans women during cross-sex hormonal therapy: a prospective observational study	Van Caenegem E, Wierckx K, Taes Y, Schreiner T, Vandewalle S, Toye K, Kaufman JM, T'Sjoen G.	2014	49 trans women with 49 age matched cismen (control group)	Before starting GAHT, trans women had lower BMD. During GAHT, BMD increased at femoral neck, radius, lumbar spine, and total body.	Bone mass is preserved with estrogen therapy.
14	Effect of pubertal suppression and cross-sex hormone therapy on bone turnover markers and bone mineral apparent density (BMAD) in transgender adolescents	Vlot MC, Klink DT, den Heijer M, Blankenstein MA, Rotteveel J, Heijboer AC.	2017	34 trans men and 22 trans women.	There is decreased bone turnover in trans men and trans women when using GnRHa. BMD increased during GAHT, especially in the lumbar spine for trans women.	GnRHa (pubertal suppression) decreases bone turnover markers in both trans men and trans women. GAHT can help to increase BMD.
31	Gender-Affirming Hormone Treatment Decreases Bone Turnover in Trans women and Older Trans men	Vlot MC, Wiepjes CM, de Jongh RT, T'Sjoen G, Heijboer AC, den Heijer M.	2019	121 transwomen and 132 trans men.	Bone turnover increased in younger trans men and decreased in older trans men. Bone turnover decreased in trans women.	Estrogen was found to decrease bone turnover in trans women, thus increasing BMD. No deleterious effects were noted in testosterone therapy for trans men.

32	Bone geometry and trabecular bone score in transgender people before and after short- and long-term hormonal treatment	Wiepjes CM, Vlot MC, de Blok CJM, Nota NM, de Jongh RT, den Heijer M.	2019	535 trans women and 473 trans men.	In trans women and trans men ages 20-49 years old, there were no changes in trabecular bone score. No differences were found in trabecular bone score for different durations of GAHT.	Estrogens may have a positive effect on trabecular bone score, an indicator of bone micro-architecture and osteoporosis risk.
21	Bone Mineral Density Increases in Trans Persons After 1 Year of Hormonal Treatment: A Multicenter Prospective Observational Study	Wiepjes CM, Vlot MC, Klaver M, Nota NM, de Blok CJ, de Jongh RT, Lips P, Heijboer AC, Fisher AD, Schreiner T, T'Sjoen G, den Heijer M.	2017	231 trans women and 199 trans men	BMD increased in trans women at the lumbar spine, total hip, and femoral neck. In trans men, BMD increased in total hip, and remained stable at the lumbar spine and femoral neck.	There was an increase in BMD in both trans men and trans women after 12 months of GAHT.
23	Long-term evaluation of cross-sex hormone treatment in transsexual persons	Wierckx K, Mueller S, Weyers S, Van Caenegem E, Roef G, Heylens G, T'Sjoen G.	2012	100 transgender individuals post gender-affirming surgery.	25% of trans women showed osteoporosis at lumbar spine and radius. Trans men did not show changed risk for osteoporosis.	Trans women were found to be at a higher risk for osteoporosis. This was theorized to be due to use of cyproterone acetate prior to GAHT. This may highlight the importance of GAHT used simultaneously with other treatments. Trans men were shown to maintain BMD throughout GAHT.
3	Effect of Cross-Sex	Yun Y, Kim D, Lee ES.	2021	11 individuals	BMD in the lumbar spine	Estrogen therapy helps

	Hormones on Body Composition, Bone Mineral Density, and Muscle Strength in Trans Women			treated with feminizing GAHT.	significantly increased but had no significant changes in the femoral neck or total femur.	to maintain bone mineralization in trans women. Testosterone therapy did not have significant effects on BMD but did show a slight decrease in hand grip strength in some participants.

Appendix 1: *Individual study information and results with corresponding in-text reference number.*