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Impact of Gonadotropin-releasing Hormone Analogue and Gender-affirming Hormone Therapy on Bone Mineral Density in Transgender Adolescents

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Abstract

Background: Sex hormones have a key impact on the development of the human body during puberty, including a significant influence on bone development - their shape, structure, length, and mineral density. Due to the growing number of transgender and gender diverse (TGD) adolescents and the increasing demand for gender-affirming hormone therapy (GAHT), there is rising curiosity about the impact of this therapy on the developing body of a young person.

Purpose: This review aims to summarize the latest scientific reports on the impact of gonadotropin-releasing hormone analogues (GnRHas) and GAHT on the bone mineral density (BMD) of transgender adolescents undergoing gender-changing therapies.

Findings: Low pretreatment BMD is more common among TGD adolescents than in the general population, and this is more prevalent in transgirls than in transboys. BMD Z-scores decline during treatment with GnRHas and respond differentially to GAHT. Regular follow-up and health advice are essential. Further long-term studies of the effects of these therapies on peak bone mass and future fracture risk are needed.

List of abbreviations:

TGD - transgender and gender diverse

GAHT - gender-affirming hormone therapy

BMD - bone mineral density

GnRHa - gonadotropin-releasing hormone analogue

GH/IGF-1 - growth hormone/insulin-like growth factor 1

DXA - dual-energy X-ray absorptiometry

LS - lumbar spine

TBLH - total body less head

FN - femoral neck

ISCD - International Society of Clinical Densitometry

aBMD - areal bone mineral density

BMAD - apparent bone mineral density

DMAB - person who was designated male at birth

DFAB - person who was designated female at birth

TH - total hip

Keywords: transgender and gender diverse youth, puberty suppression, gonadotropin-releasing hormone analogue, gender-affirming hormone therapy, bone health, transgender and bone

Introduction

In recent times, there has been an increase in the number of transgender and gender-diverse (TGD) individuals seeking medical support and gender-affirming hormone therapy (GAHT), including TGD adolescents [1]. As a result, healthcare for transgender individuals and access to gender-changing therapies have improved, and new scientific findings have

emerged in the field. Studies conducted among adolescents show that the prevalence of people identifying as transgender is up to 1.2% [2], while the prevalence of self-reported gender diversity in adolescents ranges from 2.7% to as much as 9% [3,4,5].

A TGD person is a person whose gender is different from the one they were assigned at birth, which includes both binary people (male or female) and non-binary people (people who are neither male nor female or whose gender is not exclusively male or female). On the other hand, a cisgender person is a person whose gender matches the one they were assigned at birth [6]. Transgender individuals may require the use of medically necessary GAHT to accomplish transitions consistent with their gender identity [7]. The overall goal of GAHT is to achieve sex steroid levels at a level associated with an individual's self-identified gender to induce the development of secondary sex characteristics consistent with gender identity [8].

Hormone blocking therapy in TGD adolescents

Early implementation of gender-changing therapies can be effective and helpful for many teens struggling with gender dysphoria. However, those therapies are not indicated for everyone. Children, who have not yet begun endogenous puberty cannot participate in such therapies [7]. Gender-changing treatments for adolescents can be divided into 3 categories: the first is reversible puberty-delaying therapy introduced at the onset of puberty, the second is partially reversible hormone therapy with testosterone and estrogen (GAHT) usually used from the age of 16, and the third is irreversible surgery reserved for adult adolescents [7]. Typically youth therapy consists of 2 stages, first, puberty is blocked and then GAHT is added [7]. Puberty-blocking therapy in adolescents involves the administration of gonadotropin-releasing hormone analogues (GnRHas) or progestogens and is indicated from Tanner stage 2 of puberty [8]. In transboys, puberty can be blocked with androgenic progestins (such as lynestrenol) whereas in transgirls with anti-androgenic progestins (such as cyproterone acetate, bicalutamide, and spironolactone) [7-12]. The purpose of GnRHas or progestogens administration is to regress already developed secondary sexual characteristics, which will allow for gender exploration in adolescents without the appearance of undesirable opposite-sex features [7,13]. This therapy, if administered during early or mid-puberty, usually results in a reduction of one Tanner stage [7]. However, in teenagers who have already finished puberty, it can also bring benefits in the suppression of menstruation and erection [8]. In TGD adolescents with functioning testicles, puberty suppression with GnRHas or progestogens is continued until gonadectomy. In contrast, in TGD adolescents with functioning ovaries, puberty-blocking is usually continued until adequate testosterone levels are achieved [8].

Gender-affirming hormone therapy (GAHT) in TGD adolescents

The goal of GAHT is to induce the development of secondary sex characteristics consistent with gender identity by achieving levels of sex steroids compatible with internal gender perception [7]. Feminizing GAHT consists of estrogen (17-ß-estradiol is preferred) and in people with testicles also an androgen-lowering drug (either cyproterone acetate, spironolactone, or GnRHas), which is used until the gonadectomy is performed [8]. This therapy causes: breast development, female-like fat distribution, decreased muscle mass and strength, skin softening, reduced libido, decreased facial hair, and increased scalp hair [7,8]. Unfortunately, what remains unchanged is the tone of the voice [7,8]. The main side effects of estrogen use are infertility, an increased incidence of cardiovascular disease, and venous thromboembolism [7,14,15]. On the other hand, masculinizing GAHT which consists of testosterone, causes: cessation of menstruation, deepening of the voice, increased muscle mass and strength, increased facial and body hair, and vaginal atrophy [7,8]. The main side effects of testosterone use include an increased risk of heart attack, infertility, increased blood pressure, reduced high-density lipoprotein (HDL) levels, excess weight, polycythemia, acne, and scalp hair loss [7,8,14,16-18].

The influence of sex hormones on bone development

Sex hormones significantly influence the regulation of bone remodeling, thus regulating the shape, structure, and size of bones and impacting BMD. During maturation, bones reach a mass of 90% of peak adult bone mass [19], and acquiring higher bone mass after puberty is associated with a reduced risk of osteoporosis later in life [20]. The skeleton is formed during puberty, and since it is known that the final skeletal system differs between individuals of the opposite sex, the reason for these differences can be seen in different levels of sex hormones, which affect bone structure differently in pubertal boys and girls. At the end of puberty, males are on average taller, have greater bone mass, a larger cross-sectional area of bones, and a stronger skeleton than females [21]. Sex hormones continuously interact with the growth hormone/insulin-like growth factor 1 (GH/IGF-1) axis and thus affect bone in both direct and indirect ways, such as increasing muscle mass [22]. Both testosterone (and other androgens) and estrogens influence bone growth and mineralization in both sexes, but androgens primarily influence bone growth, while estrogens primarily influence bone mineralization [23]. Androgens increase periosteum adhesion, thereby increasing bone size and strength in men, while estrogens decrease periosteum adhesion and chondrocyte

proliferation in the growth plate, inhibiting longitudinal bone growth [24]. In summary, during puberty, a precise balance between sex hormone levels is needed to achieve proper bone development.

Measurement and interpretation of BMD results in TGD youth

Dual-energy X-ray absorptiometry (DXA) is used to assess bone mineral density and the preferred sites for DXA in children and adolescents are the lumbar spine (LS) and the total body less head (TBLH) [25]. However, most studies of TGD adolescents have primarily assessed the LS and femoral neck (FN). The hip is a cortical bone and grows faster than the spine (which is a trabecular bone), therefore we can see changes in mineralization earlier [26]. The International Society of Clinical Densitometry (ISCD) recommends proximal femur measurements in children with reduced lower extremity weight-bearing who may benefit from continuous measurements into adulthood [27]. Unfortunately, like any other method, DXA has its limitations. Firstly, it is a 2D imaging method assessing areal bone mineral density (aBMD), which is unreliable in short bones [28,29]. In addition, alterations in aBMD may also result from the changing height of adolescents during GAHT [29]. Therefore, in addition to assessing aBMD, many researchers also calculate apparent bone mineral density (BMAD), which is more accurate [29]. According to the ISCD guidelines, it is recommended that all adolescents have their Z-score calculated based on reference values consistent with age and gender identity, whereas, for nonbinary adolescents, it is recommended to use reference values corresponding to the sex assigned at birth [27]. This is because children who started gender-affirming therapy in early puberty did not have time to develop characteristic features of sex recorded at birth, therefore determining the Z-score based on references consistent with birth sex would be inaccurate [25]. In a retrospective cohort study of 322 TGD adolescents, in which the effect of GnRHas and GAHT on bone geometry was examined, it was shown that if GnRHa was started in early puberty, after 2 years of GAHT, bone geometry was similar to experienced gender [30]. Whereas, initiation of GnRHas therapy in mid to late puberty was not associated with changes in bone geometry and such adolescents remained within the reference curve of sex assigned at birth [30]. It is possible that in the future, creating a reference database for transgender people will be necessary [31]. Yet currently most studies rely on reference values of sex assigned at birth.

Pre-treatment bone health in TGD adolescents

Some studies conducted to date have reported that low BMD may occur in TGD adolescents even before initiating gender-changing therapies. Studies show that this phenomenon affects more transgirls who were designated male at birth (DMAB) than transboys who were designated female at birth (DFAB) [32-38]. In most studies conducted to date, transgirls were found to have baseline aBMD Z-scores well below 0, while transboys had baseline aBMD Z-scores around 0 [35-38]. There may be many reasons for reduced BMD in TGD adolescents. Still, they certainly include decreased physical activity, which may result from excluding TGD adolescents from sports among peers, poor eating habits, and low exposure to sunlight causing vitamin D and calcium deficiencies [8,32,39]. Less is known about the difference in BMD Z-scores between transgender girls and boys but it has recently been shown that transgender girls are less physically active and consume more processed foods than transgender boys [40].

Because the first gender-changing therapies for adolescents were introduced recently there is little data available on the long-term effects of this therapy on target bone mass. Since then, however, several studies have evaluated the impacts of these therapies on adolescents, including studies assessing the influence on the skeletal system of young people. Unfortunately, these have usually been cross-sectional or observational studies that usually lack cisgender control groups.

Impact of monotherapy of GnRHas on BMD in TGD adolescents

As described above, sex hormones have a major impact on developing bone during puberty, and therefore, blocking sex hormone secretion, through the use of GnRHas, to disrupt puberty in transgender adolescents may result in impaired bone development and reduced peak bone mass.

Transgirls

Numerous studies show that absolute aBMD/BMAD do not change in transgirls during GnRHa monotherapy, but aBMD/BMAD Z-scores decrease, which indicates a reduction in transgirls BMD compared to their peers [35-38,41-43]. In particular, the first retrospective study of 15 transgirls (mostly in late puberty) showed that after a mean duration of GnRHa monotherapy of 1.3 years, absolute LS and FN aBMD/BMAD values did not change [38]. In contrast, corresponding Z-scores decreased but not significantly [38].

Subsequent studies have confirmed this relationship, although they differed in the duration of GnRHa monotherapy. In another retrospective study of 31 transgirls (at different stages of puberty: 57% early puberty and 43% late puberty), researchers performed LS and hip scans during 3 years of GnRHa treatment [41]. They found that LS and hip aBMD/BMAD Z-scores decreased dramatically during the first year of therapy, with a smaller decrease thereafter [41]. They observed no changes in absolute aBMD/BMAD values over 3 years [41]. Some studies have organized their results by the puberty stage at the start of therapy. Vlot et al. in their study divided transgirls into two groups based on bone age: younger (age < 15 years) and older (age ≥ 15 years) [35]. After a mean duration of GnRHa therapy of 2.5 years, a significant decrease in LS BMAD Z-scores (but not in FN) was observed only in the younger transgirls group [35]. In yet another study, investigators divided transgirls at the time of initiation of GnRHas therapy into early (Tanner stage 2-3) and late (Tanner stage 4-5) puberty groups [36]. LS BMAD Z-scores decreased in both groups after 2 years of GnRHas therapy, but hip BMAD Z-scores reduced only in the late puberty group [36]. Interestingly, a significantly smaller Z-score decline was observed after 3 years of this therapy [36].

Due to its effective feminizing effects and high safety profile, cyproterone acetate has been proposed as an alternative to GnRHas [10]. However, studies show that cyproterone acetate, similarly to GnRHas, causes decreases in hip and LS aBMD Z-scores in transgirls [9].

Transboys

As in transgirls, absolute aBMD/BMAD in transboys does not change during GnRHa monotherapy, but the corresponding Z-scores decrease, indicating a reduction in BMD in transboys compared to their peers [35-38,41-44]. However, some researchers have observed that absolute aBMD/BMAD in transboys may decrease, especially in those who started GnRHa therapy in late puberty [35,36,38,44], which may be due to the greater influence of sex hormones on maintaining bone mass in late puberty [45]. In the first retrospective study of 19 transboys (mostly in late puberty), it was noted that after an average of 1.5 years of GnRHa therapy, both absolute aBMD/BMAD for LS and FN and the corresponding Z-scores decreased [38]. In the study by Vlot et al., after 2 years of GnRHa therapy, a decrease in absolute aBMD/BMAD values was observed only among transboys belonging to the older group in terms of bone age (age ≥ 14 years) [35]. It was also noted that in the older group of transboys, there was a decrease in BMAD Z-score in both LS and FN, while in the younger group (bone age < 14 years) a decrease was observed only in LS [35]. In one observational prospective study, which divided TGD adolescents at the beginning of GnRHas

therapy into early puberty (Tanner stage 2-3) and late puberty (Tanner stage 4-5), it was noted that in both groups there was a significant decrease in BMAD Z-scores in LS and hip after 2 years of GnRHa monotherapy [36]. It was also observed that in the early puberty group, the absolute BMAD value in LS did not change and in the hip, it decreased, while in the late puberty group, the absolute BMAD value decreased in both LS and the hip [36]. In studies that assumed a longer period of GnRHa therapy, similar to transgirls, the greatest decrease in Z-scores values was observed in the first year of GnRHa treatment. In contrast, in the following years, the decrease was significantly smaller with possible stabilization of results at some point [36,41].

Progestogens (such as lynestrenol) were also evaluated as an alternative to GnRHa use in transboys [9]. It was surprisingly found that lynestrenol does not affect bone development, however, since it does not cause full suppression of gonadotropins, it may provoke numerous side effects such as metrorrhagia and acne [10]. Further studies are needed to thoroughly evaluate the efficacy and safety of lynestrenol use, particularly in transboys at risk for osteoporosis and fractures.

Impact of GAHT on BMD in TGD adolescents

Typically, after the age of 16, GAHT is added to GnRHa to achieve secondary sexual characteristics consistent with gender identity. The level of sex hormones increases following internal gender perception, which may positively affect bone development in TGD adolescents. However, it remains to be determined whether bone density fully recovers from puberty blocking in both transgirls and transboys after the addition of GAHT.

Transgirls

Some studies on the effect of estrogen administration after puberty suppression with GnRHa have shown that absolute aBMD/BMAD values as well as corresponding Z-scores increase after the first 2-3 years of GAHT, however, Z-scores often remained below baseline values [35,36,38,42,43,46]. Vlot et al. examined the BMD of TGD adolescents at three-time points - at the beginning of GnRHa therapy (lasting an average of 2.5 years), at the beginning of GAHT, and 2 years after the start of GAHT [35]. They observed that in both younger and older transgirls, absolute BMAD and Z-scores for LS increased after 2 years of GAHT, but Z-scores remained below 0 and were lower than at the beginning of GnRHa therapy in the younger group of transgirls [35]. Shagen et al., in their study, found that after 3 years of GAHT (preceded by 2 years of GnRHa therapy), there was an increase in the

absolute value of BMAD and Z-scores in LS and FN in transgirls in both early (Tanner stage 2-3) and late puberty (Tanner stage 4-5) groups [36]. As in previous studies, Z-scores remained well below 0 in both groups of transgirls. However, in transgirls in the early puberty group, the scores after 3 years of GAHT were higher than the scores after 2 years of GAHT in the study by Vlot et al., which may indicate better results after longer GAHT [36]. In turn, in the study conducted by Klink et al., it was noted that in transgirls aged 22 years after an average of 5.8 years of GAHT (preceded by GnRhas lasting an average of 1.3 years), the aBMD Z-scores for LS increased but remained lower than at the initiation of GnRHa therapy, while the aBMD Z-scores for FN normalized [38]. Interestingly, as many as 40% of transgirls aged 22 years had an LS BMD Z-score below -2 [38]. In a recent study by van der Loos et al., evaluating BMD in TGD adolescents after GnRHa treatment and subsequent long-term GAHT therapy (median duration in transgirls was 11.6 years), it was observed that BMD Z-scores in transgirls did not differ from the baseline (before GnRHa treatment) in total hip (TH) and FN, but were still lower than the baseline in LS [46]. These results may suggest that GnRHa therapy followed by long-term estrogen administration may still not be safe for bone health in transgirls, which requires special attention and further studies [46].

Transboys

Similar to transgirls, recent studies have reported that in transboys after years of combined therapy consisting of GnRha monotherapy followed by the addition of GAHT, absolute aBMD/BMAD values , and corresponding Z-scores increased relative to those achieved after GnRHa monotherapy [35,36,38,42-44,46]. There is more disagreement about whether Z-scores return to pre-GnRHa therapy values. In the study by Vlot et al., it was noted that after an average duration of GAHT of 2 years (with preceding GnRHa therapy lasting an average of 2.5 years), transboys experienced an increase in absolute values and BMAD Z-scores for LS and FN [35]. Interestingly, similar to transgirls, Z-scores after 2 years of GAHT did not reach pre-GnRha values in the majority of transboys [35]. In another retrospective study of 62 transboys receiving GAHT (after previous GnRHa treatment), it was observed that after 1–2 years of testosterone treatment, the absolute aBMD/BMAD results for the left hip and LS were no longer significantly different from those measured at the beginning of GnRHa treatment [44]. In contrast, aBMD/BMAD Z-scores for LS increased but remained lower than at baseline [44]. Shagen et al. in their study found that after 3 years of GAHT use, BMAD Z-scores for LS and FN increased significantly, especially in transboys from the early pubertal group (Tanner stage 2–3), whose Z-scores after 3 years of testosterone

use were slightly higher than those at the beginning of GnRHa treatment [36]. However, the Z-scores of transboys after testosterone treatment remained around 0 throughout [36]. In turn, in the study conducted by Klink et al., it was observed that in transboys there was a trend for a decrease in LS aBMD Z-score between the beginning of GnRHa therapy and the age of 22 years (after an average duration of GnRHa therapy of 1.5 years followed by GAHT lasting an average of 5.4 years) [38]. A recent study evaluating the effect of long-term GAHT treatment (mean duration of 11.9 years in transboys) on BMD in adults who underwent puberty suppression during adolescence showed that BMD Z-scores reached pre-GnRHa treatment values in LS, TH, and FN [46]. These results may suggest that GnRHa treatment followed by long-term GAHT in individuals receiving testosterone is safe for bone health [46]. Another recent study assessed the effect of 12 months of testosterone therapy on bone mineral density and whether changes in the results were related to prior puberty-suppressing treatment [47]. The GnRHa-treated group was observed to have lower BMD at the time of initiation of GAHT than the non-GnRHa group. Still, the BMD after 12 months of testosterone therapy was similar between the groups, suggesting a more rapid BMD recovery in the GnRHa-treated group [47].

Monitoring and clinical aspects

Bone development in TGD adolescents may be impaired even before any gender-changing therapy begins and this is more prevalent in transgirls than in transboys [34]. Long-term hypogonadism may further negatively affect bone health, therefore the BMD of TGD adolescents who start GnRHa therapy followed by GAHT should be closely monitored, as delayed bone development may be associated with an increased risk of fractures and osteoporosis later in life. Regular DXA scans are necessary - at the initiation of GnRHa therapy, then every 1-2 years during GnRHa and GAHT until age 25-30 or peak bone mass is reached [27]. However, bone mass accrual is a multifactorial process, influenced not only by sex hormones but also by other hormones, as well as genetic and lifestyle factors [7]. Regular basic examinations in TGD adolescents and active counseling on lifestyle changes are therefore also necessary. It is important to change eating habits - eating less processed food, adequate calcium intake, and vitamin D supplementation [8]. Greater exposure to sunlight and increased physical activity, especially weight-bearing exercises, which promote bone development, are also recommended [8]. Particular attention should be paid to adolescents with chronic diseases that may impair bone development (e.g. chronic steroid therapy,

hypoparathyroidism) and adolescents who do not intend to start GAHT after GnRHa therapy [25].

Conclusion

Evaluating the impact of puberty suppression with GnRHa therapy and subsequent GAHT on bone health is crucial due to the significant contribution of sex hormones to bone development in adolescents. Current research suggests that although GnRHa therapy is effective in suppressing unwanted secondary sexual characteristics, it may lead to a decrease in BMD Z-scores in TGD adolescents, indicating a reduction in BMD compared to cisgender peers [35-38,41-44]. This phenomenon may be more pronounced in transgirls due to the significant decrease in BMD before any treatment [34]. Adding GAHT to GnRHa usually improves bone density, but unfortunately, pre-GnRHa levels are rarely achieved, especially in adolescents receiving estrogens. Long-term GAHT after prior puberty suppression may be effective and safe in adolescents treated with testosterone. Still, adolescents receiving estradiol often do not achieve pre-GnRHa baselines even after prolonged GAHT [46]. Regularly monitoring bone development and encouraging lifestyle changes in TGD adolescents is crucial.

Studies evaluating the bone effects of GnRHas and subsequent GAHT on TGD adolescents have often yielded inconsistent outcomes, due to various factors influencing the results - pubertal stage at the time of initiation of therapy, duration of GnRHas and GAHT, and others. Nonetheless, there is a lack of studies on the effects of GnRHa monotherapy initiated early in puberty (Tanner stage 2-3) and on the results of long-term (>2 years) GnRHa use on bone health. Furthermore, long-term studies with larger numbers of participants and a cisgender control group are needed to assess peak bone mass and the risk of osteoporosis and fractures later in life.

Disclosure

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