Therapeutic Advances in Endocrinology and Metabolism Review

Bone health in transgender people: a narrative review

Ther Adv Endocrinol Metab

2022, Vol. 13: 1–15

DOI: 10.1177/20420188221099346

Giulia Giacomelli and Maria Cristina Meriggiola

***Abstract*:** Bone health in transmen and transwomen is an important issue that needs to be evaluated by clinicians. Prior to gender-affirming hormone treatment (GAHT), transwomen have lower bone mineral density (BMD) and a higher prevalence of osteopenia than cismen probably related to external factors, such as hypovitaminosis D and less physical activities. Gonadotropin-releasing hormone (GnRH) analogues in transgender youth may cause bone loss; however, the addition of GAHT restores or at least improves BMD in both transboys and transgirls. The maintenance or increase in BMD shown in short-term longitudinal studies emphasizes that GAHT does not have a negative effect on BMD in adult transwomen and transmen. Gonadectomy is not a risk factor if GAHT is taken correctly. The prevalence of fractures in the transgender population seems to be the same as in the general population but more studies are required on this aspect. To evaluate the risk of osteoporosis, it is mandatory to define the most appropriate reference group not only taking into consideration the medical aspects but also in respect of the selected gender identity of each person.

Keywords: bone health, fracture, gender-affirming hormone therapy, gender-affirming surgery, osteoporosis, transgender

Received: 10 January 2022; revised manuscript accepted: 21 April 2022.

Introduction

The term transgender is an umbrella term that describes a person whose gender expression and identity differs from what is typically expected with the sex assigned at birth.[1] Transgender people may require treatment to affirm their gender identity.[2,3] Treatment for gender affirmation may include social gender transition, psychotherapy, gender-affirming hormone therapy (GAHT) and gender-affirming surgery (GAS).[4] Not all these steps are necessary, and each individual undertakes those required to alleviate distress and to achieve a good quality of life.

GAHT should be modulated according to the patient's goals, the risk/benefit ratio of the drugs, presence of other medical conditions and the assessment of socio-economic issues. GAHT has been proven effective and safe in alleviating dysphoria in most patients.[5] If dysphoria begins in childhood or at puberty, suspending puberty with gonadotropin-releasing hormone (GnRH) analogues (GnRHa) prevents the development of secondary sexual characteristics that are not aligned with the established identity and provides time to explore their own identity. In later adolescence, usually around 16 years of age, GAHT is initiated if gender identity remains incongruent with the sex assigned at birth.[1]

With puberty blockers and in adults treated with GAHT, unintended systemic biological changes may occur which may increase the risk of chronic diseases, such as osteoporosis. Sex hormones are well known in playing a crucial role in bone acquisition at puberty,[6] and in adulthood, it regulates bone homeostasis.[7–9] Therefore, hormone treatments (puberty blockers and GAHT) can affect bone health both in adolescents who undergo puberty suspension and in transgender adults.

This narrative review has the aim of providing an updated description of what is known of the effects of GAHT on bone health, osteoporosis and fracture risk in the transgender people.

Correspondence to:
Maria Cristina Meriggiola
Division of Gynecology and Physiopathology of Human Reproduction, Department of Medical and Surgical Sciences (DIMEC), IRCCS Azienda Ospedaliero-Universitaria Di Bologna. S. Orsola Hospital, University of Bologna, Via Massarenti 13, 40138
cristina.meriggiola@unibo.it

Giulia Giacomelli
Division of Gynecology and Physiopathology of Human Reproduction, Department of Medical and Surgical Sciences (DIMEC), IRCCS Azienda Ospedaliero-Universitaria Di Bologna. S. Orsola Hospital, University of Bologna, Bologna, Italy

Background

Sex steroid hormones and bone physiology

Oestrogens (Es) and testosterone (T) are crucial for bone health.

In ciswomen during puberty, Es stimulate periosteal apposition and the growth spurt through GH-IGF1 axis stimulation.[10] IGF-1 is a bone-trophic hormone that promotes bone formation by acting on osteoblasts and collagen synthesis.[10] During adulthood, Es promote the maintenance of normal bone mineral density (BMD) and trabecular bone mass due to the inhibition of osteoclasts and activation of osteoblasts.[11]

In cismen, bone health is maintained either as a direct anabolic effect of T on bone mediated by the activation of androgen receptor or indirectly through peripheral aromatization to estradiol. Cellular studies document that T stimulates the proliferation of preosteoblasts and differentiation of osteoblasts while the converted E suppresses osteoclast formation.[12] In cismen, bioavailable Es are better correlated with BMD than T and play an important role in male age-associated bone loss.[13]

The effect on muscle mass is another indirect bone benefit of T: T increases lean mass and this gain induces an increased mechanical load on the bone, which may potentially stimulate bone formation.

Hormone treatment in transgender youth

Puberty is marked by the onset of the secretion of gonadal sex hormones and is a crucial period for bone accrual.[14] In young patients with gender dysphoria, blocking puberty prevents the development of unwanted secondary sexual characteristics of the sex assigned at birth and inhibits menstruation in transboys and erection and hair growth in transgirls. Puberty suspension with GnRHa or progestins is indicated as early as Tanner's stage 2 of pubertal development, while hormone therapy with Es or T is typically prescribed around the age of 16 years.[1] Puberty suspension allows time for transgender adolescents to explore their gender identity without experiencing incongruent and often distressing pubertal development.

GnRHa promotes prolonged activation of the receptor, leading to desensitization and consequently to suppression of luteinizing hormone (LH) and follicle stimulating hormone (FSH) secretion with a subsequent reduction in Es or T levels.[15]

Progestins are not able to induce full pubertal suppression but they can also be used to modulate the development of potentially distressing features of incongruent puberty and therefore constitute a valid alternative, especially in countries where GnRHa are not available or restricted by cost or by other reasons. Menstruation in transboys can be suppressed with androgenic progestins and erections or hair growth in transgirls can be suppressed with antiandrogenic progestins.[16]

The accrual of bone mass during puberty is a major determinant of peak bone mass and, thereby, therapy with GnRHa or progestins that block the physiological production of endogenous sex hormones, can affect peak bone mass in early adulthood and increase the risk of osteoporosis and fractures in later life. Little is known, however, about BMD or long-term consequences of early pubertal suppression on skeletal health in these youths.

GAHT in adult transwomen

In transwomen, before gonadectomy, GAHT includes antiandrogen administration or GnRHa plus Es.[1] The most common antiandrogens are spironolactone or, where available, cyproterone acetate (CA). Spironolactone is an antagonist of aldosterone with moderate androgen receptor antagonist activity. Spironolactone is not able to reduce T concentrations to female reference ranges[17] but promotes feminization due to its antiandrogen activity and additional oestrogenic activity. The antiandrogen effects of CA are the result of its antigonadotropic effect that leads to suppression of gonadal T production and of its competitive blocking of androgen action at the androgen receptor.[18]

There is not enough evidence to establish the superiority of one antiandrogen from the other in inducing feminization.[19] Indeed, they work through different mechanisms (suppression of T production or antagonism at the androgen receptor or both) and therefore the serum T level is not a good marker of effectiveness. Instead, breast growth, change in body fat distribution and reduction of facial and body hair should be compared to evaluate effectiveness; however, supporting data regarding this are lacking.

These antiandrogens are generally given in combination with Es. The dose and type of E molecules used are important for bone maintenance (ethinyl estradiol, conjugated Es, estradiol valerate or micronized estradiol). In transwomen, estradiol can be prescribed using different routes (oral, transdermal and parenteral). Ethinyl estradiol should be avoided due to the increased thromboembolic risk[20] and also it cannot be detected by laboratory assay which therefore makes dose optimization and therapy monitoring difficult.[21] In addition, in functional hypothalamic amenorrhea, current literature suggests that oral ethinyl estradiol is less effective in BMD improvement when compared to transdermal estradiol[22] probably due to a reduction in IGF1 levels. Whether this is also true in transwomen is unknown. There are not enough data on the effectiveness of different oral E formulations on bone health in transwomen.

GAHT in adult transmen

In transmen, T is a lifelong therapy, even after surgery. T can be administered by oral, parenteral or transdermal formulations. Because it requires frequent intake, generates fluctuating T levels, oral T is not used in this population. Short-acting injectable T enanthate or cypionate is often used. They generate supra-physiological levels after injection with a significant decline a few days before the next administration. These fluctuating levels are often perceived by the subjects and may generate mood swings.[23,24] The long-acting intramuscular formulation of T undecanoate maintains more stable T levels and therefore may be preferred because of the lower effect on mood in addition to the advantage of requiring less frequent injections but it is more expensive compared to the short-acting formulations. Transdermal formulations (patch or gel) mimic the physiological male circadian release of T allowing for stable T levels with minimal plasmatic oscillations.[24] We do not currently know how different routes of administration or different formulations may affect bone balance. A short-term study comparing transdermal, short- and long-acting T formulations did not report any difference in BMD after 1 year of administration.[25]

GAS in trans people

Not all trans people require surgery, but for many of them, GAS is an essential step to alleviate dysphoria.[1,2] In trans people, GAS may include surgical removal of the gonads that leads to iatrogenic hypogonadism that can negatively affect bone homeostasis if GAHT is not consistently continued.

Methods

A literature search within the PubMed database was conducted. The search used the terms: 'transgender', 'transmen', 'transwomen', 'transgender youth', 'gender', 'gender dysphoria', 'bone', 'bone mineral density', 'bone health', 'gender affirming hormone therapy', 'osteoporosis', and 'fracture'.

An additional search was completed within the references provided in the included publications.

Bone health in transgender youth

Before GnRHa, in early and late puberty, transgirls have lower BMD Z-score than cisgender reference men. Most, but not all studies, report a slightly lower BMD Z-score also in transboys compared to cisgender reference women. Low BMD Z-score in young trans adolescents has been potentially related to lifestyle, including suboptimal calcium intake, vitamin D deficiency and decreased physical activity, in particular, in transgender girls.[26–28]

In young trans people during GnRHa monotherapy, absolute BMD or bone mineral apparent density (BMAD) does not change over time while BMD Z-score or BMAD Z-score decreases or remains stable[27–33] reflecting a reduction of BMD when compared to peers.

Some authors report a reduction in absolute BMD or BMAD especially in late-pubertal transboys treated with GnRHa.[28,30,32] This may be related to a greater reliance on sex hormones to maintain bone mass during late puberty.

Tack *et al.*[16] investigated the effect on bone mass of the androgenic progestin lynestrenol in transboys and an antiandrogenic progestin CA in transgirls. Lynestrenol did not affect physiological bone development and transboys showed similar increases in BMD as their age-matched female peers and no major changes were seen in cortical thickness. However, with lynestrenol, gonadotropins were not completely suppressed and adverse effects, such as metrorrhagia and

acne, occurred[34] which may increase discomfort in transboys and reduce adherence to therapy.

CA treatment in transgirls appears to be well tolerated with few adverse effects and is capable of inducing feminizing clinical changes.[35] Data on bone health during CA in transgirls showed that CA limited normal bone expansion and reduced pubertal bone mass accrual: prior to starting Z-score for BMD was low and BMD did not increase during the study period, similar to the data in transgirls on GnRHa.[16]

Further studies are therefore needed to establish the feasibility of using these two drugs in young trans people.

It is crucial to investigate whether bone density recovery occurs once GnRHa therapy is combined with GAHT. In transgender youth, after years of combined administration of GnRHa and GAHT, absolute BMD/BMAD and relative Z-score were reported to be significantly increased compared to values obtained during GnRHa monotherapy.[28,31,32] Generally, during GAHT, Z-score normalized in transboys but remained below zero in transgirls according to lower pretreatment values.[28,30,32]

In conclusion, although data are still incomplete on the effects of early treatments in the young trans population, close monitoring of bone health is recommended, together with lifestyle counselling to improve bone health including optimizing dietary calcium and vitamin D intake and exercise, such as weight-bearing. Larger long-term studies are required to evaluate the real impact of these changes in BMD on the fracture risk later in life.

Bone health in transwomen

Before GAHT

A few studies have reported BMD in transwomen before any kind of GAHT or surgery and these suggest that transwomen have lower bone mass and smaller bone size compared to cismen.[36–40]

Van Caenegem *et al.*[40] found that before starting GAHT, transwomen had lower muscle mass and strength and lower areal BMD (aBMD) at lumbar spine, femoral neck and total hip compared with control cismen, in spite of comparable T levels.

Low BMD values at baseline correlate with a higher prevalence of osteopenia and osteoporosis in transwomen than in cismen. Osteopenia, using the female reference range to calculate the T-score, was observed in 28% of the transwomen compared with 12% in age-matched male controls.[36] Osteoporosis was less frequent than osteopenia in transwomen but still showed a prevalence of 8–11%, higher than in male controls (2–4%).[36,40]

A more recent study[39] also reported that 14% of 711 transwomen studied had osteoporosis (T-score $\leqslant -2.5$) and 22% had osteopenia (Z-score < -2.0 for age).

The lower BMD and bone size in transwomen before starting therapy compared to male controls suggest a hormone-independent difference in bone health in this population. The reason for this finding is unclear, but in addition to a genetic predisposition, an interaction with environmental factors has been suggested.[37,38] In various studies, transwomen showed a high prevalence of low vitamin D[36,39,40] and eating disorders.[41] Transwomen participate less in sport and physical activity than age-related control men and women.[36,42] A high prevalence of substance abuse, including alcohol, cannabis, amphetamines and opiates, has been reported in this population.[43] All these factors may contribute to the poor bone health at baseline in transwomen when compared to cismen.

However, most of the data that specifically analysed BMD before GAHT come from the studies performed in Northern Europe (Amsterdam, Belgium and Norway) and include mostly white subjects. Only one small study reports lower BMD in eight Korean transwomen.[44] Therefore, whether this is true in other trans female populations is unknown.

Prior to starting GAHT, fracture prevalence in transwomen has been reported to be similar to cismen.[36,40] A less sportive and less active lifestyle in transwomen may be related with a lower risk of traumatic fracture despite the higher prevalence of osteoporosis.[36]

During GAHT

Cross-sectional studies show that BMD does not change significantly or is slightly higher during GAHT compared to the reference population included in the studies (Table 1(a)).[45–48] Only

Table 1. 30-years overview of literature on bone health in transwomen.

a. Cross-sectional studies.

Cross-sectional studies	*N*	Control group	Treatment	Duration of GAHT (mean/range)	Lumbar spine BMD *versus* control group	Femur neck or total hip BMD *versus* control group
Reutrakul *et al.*[46]	11 17	Cismen Cismen	EE or oCEE or EV i.m. or mestranol	⩽2 years >2 years	= ↑	↓ FN ↓ TH ↑ FN
Sosa *et al.*[48]	27	Cismen	CA or LNG or NET + EE or oCEE or EV i.m. or mestranol	3–35 years (average 16.5 years)	↑	↑ FN
Ruetsche *et al.*[45]	24	Cismen Ciswomen	CA before GAS + EE or EV i.m. or micronized 17-beta estradiol	12.5 years	= =	=FN =TH =FN =TH
T'Sjoen *et al.*[50]	50	Cismen	CA (before GAS) + TE or oral EV or EE or estriol	3–33 years (average 7.6 years)	↓	↓ TH
Lapauw *et al.*[49]	23	Cismen	CA (before GAS) + TE or oral EV or oral EE or oCEE	8 years	↓	↓ TH
Miyajima *et al.*[47]	15	Transmen no GAHT	E dipropionate i.m.	19.2 and 32.4 years	↑	n.a.
Dobrolińska *et al.*[51]	68	/	CA (before GAS) + oral E (unspecified) or E s.c.	10 and 15 years	n.a.	↓ TH after 15 *versus* 10 years

b. longitudinal studies.

Longitudinal studies	*n*	Treatment	Duration of follow-up	Lumb ar spine	Femur or total hip
van Kesteren *et al.*[52]	56	Mixed treatments: CA + EE or TE or oCEE or EV	1 year	↑	n.a.
van Kesteren *et al.*[53]	20	EE (+CA before GAS)	1 year 28–36 months	↑ ↓	n.a.
Mueller *et al.*[54]	40	GnRHa + oral EV	1, 2 years	↑	↑ FN
Dittrich *et al.*[55]	60	GnRHa + oral EV	2 years	↑	=FN
Haraldsen *et al.*[38]	12	EE oral	3, 12 months	=	=FN
Mueller *et al.*[56]	84	GnRHa + EV i.m.	1, 2 years	↑	=FN
Van Caenegem *et al.*[40]	49	CA alone (before GAS) or + oral EV or TE	1, 2 years	↑	↑ FN =TH
Gava *et al.*[57]	40	CA or Leu + TE	1 year	=	n.a.
Wiepjes *et al.*[58]	231	CA + EV or TE	1 year	↑	↑ FN ↑ TH
Fighera *et al.*[59]	142	Spironolactone or CA + oral EV or TE or CEE	31.3 ± 6.5 months	=	=FN =TF
Wiepjes *et al.*[39]	102	Spironolactone or CA (before GAS) + oral EV or TE	10 years	=	=FN =TH
Gava *et al.*[60]	50	CA or Leu + oral EV or TE	5 years	↑	n.a.
Yun *et al.*[44]	11	CA or spironolactone + oral or i.m. EV	6 months	↑	=FN =TF

BMD, bone mineral density; CA, cyproterone acetate; EE, ethinyl estradiol; EV, estradiol valerate; FN, femur neck; GAS, gender-affirming surgery; GnRHa, gonadotropin-releasing hormone agonist; Leu, leuprolide; LNG, levonorgestrel; NET, norethisterone; oCEE, oral conjugated oestrogens; TE, transdermal estradiol; TF, total femur; TH, total hip; n.a., data non-available.

two studies report a lower BMD in transwomen after an average of 8 years of GAHT.[49,50] In these studies, low BMD could be related to 1 year of antiandrogen therapy administered alone prior to starting GAHT or to baseline differences observed prior to starting GAHT, such as lower physical activity and muscle mass.[49,50]

A recent cross-sectional study of 68 transwomen who had undergone gonadectomy showed that total hip BMD after 15 years of GAHT was significantly lower compared to 10 years of GAHT.[51] Indeed, transwomen with bone loss are mainly those who did not take GAHT after gonadectomy thus emphasizing the protective role of these treatments.

By definition, cross-sectional studies have no dimension of time; therefore, they cannot support conclusions on the risk of disease or on causal relationships. In cross-sectional studies, it is not possible to define whether the change in BMD is due to GAHT or physiological ageing. Furthermore, the limit of cross-sectional studies is that they do not consider baseline values and currently we know that transwomen have lower BMD than cismen before GAHT. Without longitudinal data, it is not possible to establish a true cause and effect relationship.

When we analyse the short-term longitudinal studies, data show a stable or slightly increased lumbar spine and femur BMD[38,40,44,52,54–60] [Table 1(b)].

Van Kesteren *et al.*[53] report that BMD increased significantly after 1 year of GAHT. However, after 28–63 months, BMD is reduced but remains higher than baseline. The authors suggest that the decrease in BMD could be a result of insufficient E dosage after gonadectomy.

A recent follow-up study found that lumbar spine BMD is similar to baseline after 10 years of GAHT. Lumbar spine Z-score (calculated using the BMD of the sex assigned at birth) is higher when compared to baseline.[39] Normally, BMD decreases after the peak bone mass, but in transwomen, it remains stable after 10 years of GAHT. These data may further suggest that GAHT does not have a negative effect on BMD.[39]

However, no longitudinal study has investigated the effect of GAHT after more than 10 years. This may be due to the limits of these types of studies which are expensive, long and require a large sample size.

A meta-analysis and systematic review of 812 transwomen showed a significant increase in lumbar spine BMD at 12 and 24 months after initiation of GAHT while changes in femoral neck or total neck BMD were not statistically significant.[61]

After GAS

In transwomen, Es are considered a lifelong therapy and are generally administrated in monotherapy after gonadectomy. Current literature agrees that the reduction of BMD after gonadectomy seems to be related to poor compliance or underdosing of GAHT rather than being a direct effect of gonadectomy. In support of this, years after surgery, transwomen with reduced BMD values have lower estradiol or higher LH levels that reflect the incorrect GAHT intake. Some authors found that BMD correlated inversely with LH levels to support the use of LH to monitor GAHT on bone,[45,51,53] but these data have not been supported by other studies.[39,49,50]

Influence of GAHT on osteoporosis and fracture risk

Osteopenia and osteoporosis are not uncommon in transwomen despite GAHT. Current literature shows that low bone mass (Z-score that matches gender assigned at birth) has been observed in 12.9–40% of transwomen during GAHT and is related to lower basal BMD, lower lean body mass, lower estradiol levels and lower compliance to GAHT.[49,50,59,62,63]

The prevalence of osteoporosis (according to male reference) is around 20% in transwomen after more than 10 years of GAHT.[45,51,64]

The direct consequence of a weak bone is an increased risk of fracture but transwomen do not seem to experience this.[48,65] In a nationwide cohort study, Wiepjes *et al.*[66] analysed fracture incidence in transgender people using long-term GAHT compared to an age-matched reference population. A total of 1089 transwomen younger than 50 years of age and 934 transwomen older than 50 years of age using GAHT for a median time of 8 and 19 years, respectively, were included. Globally, fractures occurred in 3.3% of the transwomen (67 out of 2023 patients) and the overall

fracture incidence was no greater in transwomen compared with age-matched reference men or women. Interestingly, after stratification of patients according to age (younger/older than 50 years), transwomen younger than 50 years tended to have an increased fracture risk compared with age-matched reference women although not when compared with men. Transwomen above 50 years of age had a similar fracture risk compared with age-matched reference women (4.4% *versus* 4.2%, respectively) but higher compared to age-matched reference men (2.4%). The higher fracture risk in young transwomen compared to ciswomen may be explained by lower initial BMD even before the start of GAHT while similar fracture risk in older transwomen and ciswomen may be explained by the decrease in BMD in control women due to the loss of Es after menopause. Furthermore, fracture location reported among transwomen showed more frequent involvement of hip, spine, forearm and humerus, which was comparable to the fracture distribution among ciswomen (low BMD) rather than cismen (fractures due to accidents).[66]

Another cross-sectional study showed that the 10-year fracture risk was in the low-risk range on average according to DeFRA (adapted version of FRAX score based on Italian epidemiological studies)[63] and only one out of seven transwomen in this study showed an intermediate to high 10-year fracture risk but none of the patients had fragility fractures.

Long-term longitudinal studies reporting fracture risk in this population have not been carried out.

Bone health in transmen

Before GAHT

In contrast to transwomen, transmen do not seem to have low BMD before starting GAHT.[38,67] Areal BMD, trabecular and cortical BMD and cortical bone size in transmen are similar to ciswomen.[68] The rates of osteoporosis or osteopenia before GAHT are low (2.4% and 4.3%, respectively)[39] and are in line with the general population. Participation in sports and physical activity is higher in transmen than in transwomen with a preference for sports that develop body muscles, such as bodybuilding.[69] Physical activity correlates with the development of muscle mass and strength which are the key factors for healthy bone growth and the reaching of peak bone mass.[70,71] The high rate of participation in physical activity could lead to proper bone mineralization in transmen but studies are required to prove this.

Fracture prevalence is similar to matched controls and this may be related to a preserved BMD before GAHT.[68]

During GAHT

Cross-sectional studies show that lumbar spine and femur neck BMD after many years of GAHT in transmen are in line with the reference population included in the studies [Table 2(a)].[45,65,67] According to Dobrolińska *et al.*,[51] total hip BMD was highest between 10 and 15 years of GAHT and significantly lower after 15 years. This long-term data, even if it resulted from a cross-sectional study, suggest that GAHT has no negative effect on bone. Two studies showed lower BMD in transmen than controls [47,72] but this could be due to poor compliance with the therapy.[72] A recent small case–control study found a lower femur neck BMD in 19 transmen compared to 19 cismen and attributed it to the lower muscle mass found in transmen.[73] Overall, the authors claimed that T therapy had a positive effect on bone as the remaining parameters (lumbar spine and total femur BMD, and the respective T-score and Z-score) were similar to the reference population.[73]

The results of cross-sectional studies are reinforced by longitudinal studies [Table 2(b)]. In fact, some short-term follow-up studies show that the femur, lumbar and total body BMD do not change.[25,38,52,75,77] Also, T therapy may have a positive effect on the bone demonstrated by a slight improvement of BMD.[58,68,74,76] Wiepjes *et al.*[58] reported that in post-menopausal transmen, lumbar spine BMD increased more than other age groups after 1 year of GAHT in respect to baseline values. At baseline, post-menopausal transmen had lower estradiol levels than transmen of other age groups. During GAHT, T levels increased in both post-menopausal and younger transmen, while estradiol levels (due to T aromatization) increased only in post-menopausal transmen. We can assume therefore that the increase in BMD in transmen may be related to the concentration of estradiol rather than a direct effect of T.

Table 2. 30-years overview of literature on bone health in transmen.

a. Cross-sectional studies.

Cross-sectional studies	*N*	Control group	Treatment	Duration of GAHT (mean/range)	Lumbar spine BMD *versus* control group	Femur neck or total hip BMD *versus* control group
Goh *et al.*[72]	5	Transmen before GAHT and ciswomen	T i.m.	1–3 years	↑	n.a.
	27	Transmen before GAHT and ciswomen	T i.m.	2–12 years	↓	n.a.
	32	Transmen before GAHT and ciswomen	T i.m. non-compliant or stopped GAHT	0.5–8 years	↓	n.a.
Ruetsche *et al.*[45]	15	Ciswomen Cismen	T i.m.	7.6 years	= =	=FN =TH =FN =TH
Van Caenegem *et al.*[67]	50	Ciswomen	T i.m. or TD	9.9 (range 3.2–27.5) years	=	=FN =TH
Miyajima *et al.*[47]	50	Transmen no GAHT	T i.m.	15.2 and 33.4 years	↓	n.a.
Broulik *et al.*[65]	35	Cismen Ciswomen	T i.m. or oral	18 years	= ↑	=FN ↑ FN
Dobrolińska *et al.*[51]	43	/	T i.m. or TD	10, 15 years	n.a.	↓ TH after 15 years *versus* 10 years
Andrade *et al.*[73]	19	Cismen	T i.m. or TD	2 years	=	↓ FN =TH

b. Longitudinal studies.

Longitudinal studies	*n*	Treatment	Duration of follow-up	Lumb ar spine	Femur or total hip
van Kesteren *et al.*[52]	35	T i.m. or oral	1 year	=	n.a.
van Kesteren *et al.*[53]	19	T i.m. or oral	1 year	=	n.a.
			28–36 months	↓	
Turner *et al.*[74]	15	T i.m.	1 year	=	=FN
			2 years	=	↑ FN
Haraldsen *et al.*[38]	21	T i.m.	1 year	=	=FN
Meriggiola *et al.*[75]	15	T i.m.	1 year	=	n.a
Mueller *et al.*[76]	45	TU i.m.	1, 2 years	=	=FN
Pelusi *et al.*[25]	45	T i.m. or TU i.m. or TD	1 year	=	n.a.
Van Caenegem *et al.*[68]	23	TU i.m.	1 year	=	=FN ↑ TH
Wiepjes *et al.*[58]	199	T i.m. or TD	1 year	↑	=FN ↑ TH
Wiepjes *et al.*[39]	70	T oral, TD and T i.m.	10 years	=	=FN =TH
Gava *et al.*[77]	16	TU i.m.	1 year	=	=

BMD, bone mineral density; FN, femur neck; GAHT, Gender-affirming hormone therapy; i.m., intramuscular; n.a., not available; T, testosterone; TD, transdermal testosterone; TH, total hip; TU, testosterone undecanoate.

Again, one follow-up study (average 3.5 years of GAHT) reported a significantly lower BMD measured after 1 year of therapy suggesting an inadequate uptake of GAHT.[53]

In support of the fact that T treatment has no negative effects on bone health, a longitudinal study demonstrated that after 10 years of GAHT, lumbar spine BMD maintains values similar to baseline whereas lumbar spine Z-score increased.[39]

A short-term meta-analysis of 487 transmen confirmed that femur neck BMD, total neck BMD and lumbar spine BMD do not differ significantly after GAHT.[61]

After GAS

Ovariectomy affects BMD but T therapy may mitigate this effect in transmen. In ovariectomized transmen, circulating estradiol is also important. According to peripheral aromatization of T to estradiol, the addition of letrozole (aromatase inhibitor) to T therapy leads to lower BMD than T alone, whereas the addition of dutasteride (5a-reductase inhibitor) to T does not affect BMD.[75]

Therefore, a reduction in BMD is possible in transmen who have undergone gonadectomy,[47] particularly if they are not maintained at adequate post-operative T levels. In fact, operated transmen on regular GAHT showed no changes in BMD during follow-up, whereas operated transmen who either had stopped or were on irregular GAHT showed a lower BMD which increased again when treatment was resumed regularly.[72] The decrease in BMD correlated with the increased LH levels but not with the time between ovariectomy and the last visit.[53]

Influence of GAHT on osteoporosis and fracture risk

The low prevalence of osteopenia and osteoporosis at baseline combined with BMD values maintained during GAHT results in a low rate of osteoporosis after years of GAHT.[64,73]

In transmen, data on fractures are scarce possibly due to the fact that osteoporosis is infrequent in transmen.

A cross-sectional study found no difference in fracture between transmen and controls.[65]

The largest fracture risk study showed that after a median time of 9 years of GAHT, the fracture risk was not increased in young transmen and was similar to age-matched reference women but lower compared with age-matched reference men. Authors suggest that transmen may be more careful or participate less in physical activities than the general male population leading to fewer accident fractures.[66]

More studies are needed to investigate the prevalence of osteoporosis and the fracture risk in transmen.

Z-SCORE: gender identity or sex assigned at birth?

To assess the risk of osteopenia/osteoporosis in transgender people, the most important question is whether to use the sex of the gender identity or the sex assigned at birth as the reference population.

In 2019, the International Society of Clinical Densitometry (ISCD) determined how to calculate T-score and Z-score to better define the diagnosis and bone care in the trangender population.[78] According to this position statement, T-score should be calculated using a Caucasian genotypic female reference for all transgender people aged 50 years or older regardless of ethnicity while Z-score should be used in transgender people below the age of 50 years and calculated using the database that matches the patient's gender identity.[78]

The main problem is that most trans people start GAHT after puberty and therefore they have already reached the age of peak bone mass that is in line with the sex assigned at birth. A recent study shows that in young trans people, the reference curves for subperiosteal width and endocortical diameter are in line with that of the gender experienced only when puberty was stopped at an early stage.[79] Participants who start puberty blockers during mid-to-late puberty remain within the reference curve of the gender assigned at birth.[79]

Currently, the debate on which reference should be used remains open. For this reason, when performing dual-energy x-ray absorptiometry (DXA), it may be appropriate to request Z-score calculated from both male and female normative databases.

Novel imaging techniques

DXA is the gold standard imaging tool in assessing BMD, osteoporosis and fracture risk but this technique has limitations. One of these is that it measures areal BMD by only two-dimensional analysis and does not evaluate bone structure, which is a necessary parameter in defining bone strength.

Recent advances in imaging permit a more accurate assessment of bone. Peripheral quantitative computed tomography (pQCT) is a three-dimensional imaging technique that quantitatively measures volumetric BMD (vBMD) at the peripheral skeletal sites (distal radius and distal tibia) and has the capacity to differentiate between cortical and trabecular bone compartments.[80] pQCT has already been successfully used in many contexts[81] and it could be useful in transgender population to understand if and how structural changes occur in the bone after GAHT.

The data with the use of this technique in the transgender population are still scanty, but a recent cross-sectional study showed that transwomen on GAHT had a lower cross-sectional area (CSA), cortical vBMD and trabecular bone volume than cismen at the tibia and radius. Furthermore, bone had less thickness and greater porosity at the cortical level while the trabecular component had thicker trabeculae than controls.[82] These findings are in line with previous cross-sectional studies.[49,50] Lower cortical and trabecular vBMD values were recorded even before GAHT in transwomen[36] suggesting the importance of environmental and social factors as previously discussed. In support of this hypothesis, a longitudinal study showed that cortical and trabecular bone is preserved during the first 2 years of GAHT.[40]

In transmen using T increased bone size, trabecular vBMD and thicker trabeculae were reported with the use of pQCT while cortical parameters remain unchanged.[67,68,82]

The modification of trabecular vBMD may be related to the indirect effects of T therapy, such as peripheral aromatization to estradiol or increased muscle mass and mechanical load on bone.

Clinical education

How and when to check BMD during puberty suspension in transgender youth?	• Performing a DXA before starting therapy and repeating it every 1–2 years until the start of GAHT[1]
How and when to check BMD during puberty induction with GAHT in transgender youth?	• Performing a DXA every 1–2 years at least until peak bone mass is reached (around 25–30 years)[1]
How and when to check BMD during GAHT in adult transwomen?	• Consider performing a DXA at baseline[1] • If there are no risk factors for osteoporosis, repeat it at 60 years.[1] • In case of risk factors, such as past use of puberty blockers, poor compliance or suspension of GAHT after GAS, evaluate execution of DXA every 1–2 years (up to at least stable BMD values, then extend the intervals).[1,78]
How and when to assess BMD during GAHT in adult transmen?	• In case of presence of risk factors, such as past use of puberty blockers, poor compliance or suspension of GAHT after GAS, evaluate execution of DXA every 1–2 years (up to stable BMD values, then extend the intervals).[1,78]
What reference should be used to calculate the Z-score?	• No agreement exists and according to ISCD, the Z-scores of the gender identity could be used.[78] Both gender identity and sex assigned at birth should be used as a reference population to better define the bone profile assessment because data are lacking.
How to support bone health?	• Vitamin D and physical activity should be encouraged for transgender youth and adults. • Encourage proper intake of GAHT especially after GAS • There is no evidence on the safety and efficacy of antiresorptive or anabolic therapy in the treatment of osteoporosis in transgender populations. Clinicians are encouraged to follow the guidelines for cisgender populations.[83]

BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry; GAHT, gender-affirming hormone treatment; GAS, gender-affirming surgery; ISCD, International Society of Clinical Densitometry.

Conclusion

The medical care of transgender persons is a field of medicine that has been neglected for a long time and, as a consequence, still presents numerous challenges due to the scarcity of scientific evidence. GAHT may affect the health of various physiological systems, the skeleton being one of these. Data reported thus far are quite reassuring suggesting that, with adequate compliance, bone health is preserved in adult trans people undergoing GAHT.[84] However, data on fracture risk are still sparse and the long-term effects of puberty blockers on bone health remain uncertain.

The impaired bone health in young and adult transgender people before GAHT when compared to cisgender people highlights that neglecting the needs of transgender people, including difficulties in social acceptance, psychological fragilities and poor medical care, plays an important – probably the most important – role in their health. Scientists should aim to fill this gap in knowledge and sensitize the entire medical community towards the needs of these persons.

Future research to improve current knowledge on bone health in transgender people should include the following:

- Long-term longitudinal studies on transgender youth undergoing puberty blocking and subsequent GAHT.
- Evaluation of factors, such as physical activity, social behaviour and vitamin D intake, that could influence bone health in hormone-naive transgender population.
- Understand the effects of different hormonal formulations or dosages on bone health
- Evaluation of fracture risk in the transgender population
- Implementation of research on bone morphology using new technologies, such as pQCT

Author contribution(s)

Giulia Giacomelli: Investigation; Methodology; Project administration; Visualization; Writing – original draft; Writing – review & editing.

Maria Cristina Meriggiola: Conceptualization; Data curation; Funding acquisition; Project administration; Supervision; Validation; Writing – review & editing.

ORCID iD

Maria Cristina Meriggiola https://orcid.org/0000-0003-0061-9834

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

1. Hembree WC, Cohen-Kettenis PT, Gooren L, *et al*. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2017; 102: 3869–3903.
2. World Professional Association for Transgender Health (WPATH). *Standards of care for the health of transsexual, transgender, and gender nonconforming people*. 7th ed., 2012, https://www.wpath.org/publications/soc
3. American Psychiatric Association (APA). *Diagnostic and statistical manual of mental disorders*. 5th ed. Washington, DC: American Psychiatric Association, 2013.
4. Hadj-Moussa M, Ohl DA and Kuzon WM Jr. Evaluation and treatment of gender dysphoria to prepare for gender confirmation surgery. *Sex Med Rev* 2018; 6: 607–617.
5. Heylens G, Verroken C, De Cock S, *et al*. Effects of different steps in gender reassignment therapy on psychopathology: a prospective study of persons with a gender identity disorder. *J Sex Med* 2014; 11: 119–126.
6. Rothman MS and Iwamoto SJ. Bone health in the transgender population. *Clin Rev Bone Miner Metab* 2019; 17: 77–85.
7. Vandenput L and Ohlsson C. Estrogens as regulators of bone health in men. *Nat Rev Endocrinol* 2009; 5: 437–443.
8. Cauley JA. Estrogen and bone health in men and women. *Steroids* 2015; 99: 11–15.
9. Hammes SR and Levin ER. Impact of estrogens in males and androgens in females. *J Clin Invest* 2019; 129: 1818–1826.

10. Dixit M, Poudel SB and Yakar S. Effects of GH/IGF axis on bone and cartilage. *Mol Cell Endocrinol* 2021; 519: 111052.

11. Emmanuelle N-E, Marie-Cécile V, Florence T, *et al*. Critical role of estrogens on bone homeostasis in both male and female: from physiology to medical implications. *Int J Mol Sci* 2021; 22: 1568.

12. Mohamad NV, Soelaiman IN and Chin KY. A concise review of testosterone and bone health. *Clin Interv Aging* 2016; 11: 1317–1324.

13. Drake MT and Khosla S. Male osteoporosis. *Endocrinol Metab Clin North Am* 2012; 41: 629–641.

14. Saggese G, Baroncelli GI and Bertelloni S. Puberty and bone development. *Best Pract Res Clin Endocrinol Metab* 2002; 16: 53–64.

15. Ortmann O, Weiss JM and Diedrich K. Gonadotrophin-releasing hormone (GnRH) and GnRH agonists: mechanisms of action. *Reprod Biomed Online* 2002; 5(Suppl. 1): 1–7.

16. Tack LJW, Craen M, Lapauw B, *et al*. Proandrogenic and antiandrogenic progestins in transgender youth: differential effects on body composition and bone metabolism. *J Clin Endocrinol Metab* 2018; 103: 2147–2156.

17. Burinkul S, Panyakhamlerd K, Suwan A, *et al*. Anti-androgenic effects comparison between cyproterone acetate and spironolactone in transgender women: a randomized controlled trial. *J Sex Med* 2021; 18: 1299–1307.

18. Kuijpers SME, Wiepjes CM, Conemans EB, *et al*. Toward a lowest effective dose of cyproterone acetate in trans women: results from the ENIGI study. *J Clin Endocrinol Metab* 2021; 106: e3936–e3945.

19. Angus LM, Nolan BJ, Zajac JD, *et al*. A systematic review of antiandrogens and feminization in transgender women. *Clin Endocrinol* 2021; 94: 743–752.

20. Asscheman H, Giltay EJ, Megens JA, *et al*. A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. *Eur J Endocrinol* 2011; 164: 635–642.

21. Meriggiola MC and Gava G. Endocrine care of transpeople part II. A review of cross-sex hormonal treatments, outcomes and adverse effects in transwomen. *Clin Endocrinol* 2015; 83: 607–615.

22. Roberts RE, Farahani L, Webber L, *et al*. Current understanding of hypothalamic amenorrhoea. *Ther Adv Endocrinol Metab* 2020; 11: 2042018820945854.

23. Bui HN, Schagen SE, Klink DT, *et al*. Salivary testosterone in female-to-male transgender adolescents during treatment with intra-muscular injectable testosterone esters. *Steroids* 2013; 78: 91–95.

24. Meriggiola MC and Gava G. Endocrine care of transpeople part I. A review of cross-sex hormonal treatments, outcomes and adverse effects in transmen. *Clin Endocrinol* 2015; 83: 597–606.

25. Pelusi C, Costantino A, Martelli V, *et al*. Effects of three different testosterone formulations in female-to-male transsexual persons. *J Sex Med* 2014; 11: 3002–3011.

26. Lee JY, Finlayson C, Olson-Kennedy J, *et al*. Low bone mineral density in early pubertal transgender/gender diverse youth: findings from the trans youth care study. *J Endocr Soc* 2020; 4: bvaa065.

27. Navabi B, Tang K, Khatchadourian K, *et al*. Pubertal suppression, bone mass, and body composition in youth with gender dysphoria. *Pediatrics* 2021; 148: e2020039339.

28. Schagen SEE, Wouters FM, Cohen-Kettenis PT, *et al*. Bone development in transgender adolescents treated with GnRH analogues and subsequent gender-affirming hormones. *J Clin Endocrinol Metab* 2020; 105: dgaa604.

29. Joseph T, Ting J and Butler G. The effect of GnRH analogue treatment on bone mineral density in young adolescents with gender dysphoria: findings from a large national cohort. *J Pediatr Endocrinol Metab JPEM* 2019; 32: 1077–1081.

30. Klink D, Caris M, Heijboer A, *et al*. Bone mass in young adulthood following gonadotropin-releasing hormone analog treatment and cross-sex hormone treatment in adolescents with gender dysphoria. *J Clin Endocrinol Metab* 2015; 100: E270–E275.

31. Delemarre-Van De Waal HA and Cohen-Kettenis PT. Clinical management of gender identity disorder in adolescents: a protocol on psychological and paediatric endocrinology aspects. *Eur J Endocrinol* 155(Suppl.): S131–S137.

32. Vlot MC, Klink DT, den Heijer M, *et al*. Effect of pubertal suppression and cross-sex hormone therapy on bone turnover markers and bone mineral apparent density (BMAD) in transgender adolescents. *Bone* 2017; 95: 11–19.

33. Carmichael P, Butler G, Masic U, *et al*. Short-term outcomes of pubertal suppression in a selected cohort of 12 to 15 year old young people with persistent gender dysphoria in the UK. *PLoS ONE* 2021; 16: e0243894.

34. Tack LJ, Craen M, Dhondt K, *et al*. Consecutive lynestrenol and cross-sex hormone treatment in biological female adolescents with gender dysphoria: a retrospective analysis. *Biol Sex Differ* 2016; 7: 14.

35. Tack LJW, Heyse R, Craen M, *et al*. Consecutive cyproterone acetate and estradiol treatment in late-pubertal transgender female adolescents. *J Sex Med* 2017; 14: 747–757.

36. Van Caenegem E, Taes Y, Wierckx K, *et al*. Low bone mass is prevalent in male-to-female transsexual persons before the start of cross-sex hormonal therapy and gonadectomy. *Bone* 2013; 54: 92–97.

37. Van Caenegem E and T'Sjoen G. Bone in trans persons. *Curr Opin Endocrinol Diabetes Obes* 2015; 22: 459–466.

38. Haraldsen IR, Haug E, Falch J, *et al*. Cross-sex pattern of bone mineral density in early onset gender identity disorder. *Horm Behav* 2007; 52: 334–343.

39. Wiepjes CM, de Jongh RT, de Blok CJ, *et al*. Bone safety during the first ten years of gender-affirming hormonal treatment in transwomen and transmen. *J Bone Miner Res* 2019; 34: 447–454.

40. Van Caenegem E, Wierckx K, Taes Y, *et al*. Preservation of volumetric bone density and geometry in trans women during cross-sex hormonal therapy: a prospective observational study. *Osteoporos Int* 2015; 26: 35–47.

41. Nagata JM, Murray SB, Compte EJ, *et al*. Community norms for the Eating Disorder Examination Questionnaire (EDE-Q) among transgender men and women. *Eat Behav* 2020; 37: 101381.

42. Bishop A, Overcash F, McGuire J, *et al*. Diet and physical activity behaviors among adolescent transgender students: school survey results. *J Adolesc Health* 2020; 66: 484–490.

43. Reback CJ and Fletcher JB. HIV prevalence, substance use, and sexual risk behaviors among transgender women recruited through outreach. *AIDS Behav* 2014; 18: 1359–1367.

44. Yun Y, Kim D and Lee ES. Effect of cross-sex hormones on body composition, bone mineral density, and muscle strength in trans women. *J Bone Metab* 2021; 28: 59–66.

45. Ruetsche AG, Kneubuehl R, Birkhaeuser MH, *et al*. Cortical and trabecular bone mineral density in transsexuals after long-term cross-sex hormonal treatment: a cross-sectional study. *Osteoporos Int* 2005; 16: 791–798.

46. Reutrakul S, Ongphiphadhanakul B, Piaseu N, *et al*. The effects of oestrogen exposure on bone mass in male to female transsexuals. *Clin Endocrinol* 1998; 49: 811–814

47. Miyajima T, Kim YT and Oda H. A study of changes in bone metabolism in cases of gender identity disorder. *J Bone Miner Metab* 2012; 30: 468–473.

48. Sosa M, Jódar E, Arbelo E, *et al*. Bone mass, bone turnover, vitamin D, and estrogen receptor gene polymorphisms in male to female transsexuals: effects of estrogenic treatment on bone metabolism of the male. *J Clin Densitom* 2003; 6: 297–304.

49. Lapauw B, Taes Y, Simoens S, *et al*. Body composition, volumetric and areal bone parameters in male-to-female transsexual persons. *Bone* 2008; 43: 1016–1021.

50. T'Sjoen G, Weyers S, Taes Y, *et al*. Prevalence of low bone mass in relation to estrogen treatment and body composition in male-to-female transsexual persons. *J Clin Densitom* 2009; 12: 306–313.

51. Dobrolińska M, van der Tuuk K, Vink P, *et al*. Bone mineral density in transgender individuals after gonadectomy and long-term gender-affirming hormonal treatment. *J Sex Med* 2019; 16: 1469–1477.

52. van Kesteren P, Lips P, Deville W, *et al*. The effect of one-year cross-sex hormonal treatment on bone metabolism and serum insulin-like growth factor-1 in transsexuals. *J Clin Endocrinol Metab* 1996; 81: 2227–2232.

53. van Kesteren P, Lips P, Gooren LJ, *et al*. Long-term follow-up of bone mineral density and bone metabolism in transsexuals treated with cross-sex hormones. *Clin Endocrinol* 1998; 48: 347–354.

54. Mueller A, Dittrich R, Binder H, *et al*. High dose estrogen treatment increases bone mineral density in male-to-female transsexuals receiving gonadotropin-releasing hormone agonist in the absence of testosterone. *Eur J Endocrinol* 2005; 153: 107–113.

55. Dittrich R, Binder H, Cupisti S, *et al*. Endocrine treatment of male-to-female transsexuals using gonadotropin-releasing hormone agonist. *Exp Clin Endocrinol Diabetes* 2005; 113: 586–592.

56. Mueller A, Zollver H, Kronawitter D, *et al*. Body composition and bone mineral density in male-to-female transsexuals during cross-sex hormone therapy using gonadotrophin-releasing hormone agonist. *Exp Clin Endocrinol Diabetes* 2011; 119: 95–100.

57. Gava G, Cerpolini S, Martelli V, *et al*. Cyproterone acetate vs leuprolide acetate in combination with transdermal oestradiol in transwomen: a comparison of safety and effectiveness. *Clin Endocrinol* 2016; 85: 239–246.

58. Wiepjes CM, Vlot MC, Klaver M, *et al*. Bone mineral density increases in trans persons after 1 year of hormonal treatment: a multicenter prospective observational study. *J Bone Miner Res* 2017; 32: 1252–1260.

59. Fighera TM, da Silva E, Lindenau JD, *et al*. Impact of cross-sex hormone therapy on bone mineral density and body composition in transwomen. *Clin Endocrinol* 2018; 88: 856–862.

60. Gava G, Mancini I, Alvisi S, *et al*. A comparison of 5-year administration of cyproterone acetate or leuprolide acetate in combination with estradiol in transwomen. *Eur J Endocrinol* 2020; 183: 561–569.

61. Fighera TM, Ziegelmann PK, Rasia da Silva T, *et al*. Bone mass effects of cross-sex hormone therapy in transgender people: updated systematic review and meta-analysis. *J Endocr Soc* 2019; 3: 943–964.

62. Chrisostomo KR, Skare TL, Chrisostomo HR, *et al*. Transwomen and bone mineral density: a cross-sectional study in Brazilian population. *Br J Radiol* 2020; 93: 20190935.

63. Motta G, Marinelli L, Barale M, *et al*. Fracture risk assessment in an Italian group of transgender women after gender-confirming surgery. *J Bone Miner Metab* 2020; 38: 885–893.

64. Wierckx K, Mueller S, Weyers S, *et al*. Long-term evaluation of cross-sex hormone treatment in transsexual persons. *J Sex Med* 2012; 9: 2641–2651.

65. Broulik PD, Urbánek V and Libanský P. Eighteen-year effect of androgen therapy on bone mineral density in trans(gender) men. *Horm Metab Res* 2018; 50: 133–137.

66. Wiepjes CM, de Blok CJ, Staphorsius AS, *et al*. Fracture risk in trans women and trans men using long-term gender-affirming hormonal treatment: a nationwide cohort study. *J Bone Miner Res* 2020; 35: 64–70.

67. Van Caenegem E, Wierckx K, Taes Y, *et al*. Bone mass, bone geometry, and body composition in female-to-male transsexual persons after long-term cross-sex hormonal therapy. *J Clin Endocrinol Metab* 2012; 97: 2503–2511.

68. Van Caenegem E, Wierckx K, Taes Y, *et al*. Body composition, bone turnover, and bone mass in trans men during testosterone treatment: 1-year follow-up data from a prospective case-controlled study (ENIGI). *Eur J Endocrinol* 2015; 172: 163–171.

69. López-Cañada E, Devís-Devís J, Valencia-Peris A, *et al*. Physical activity and sport in trans persons before and after gender disclosure: prevalence, frequency, and type of activities. *J Phys Act Health* 2020; 17: 650–656.

70. Orsso CE, Tibaes JRB, Oliveira CLP, *et al*. Low muscle mass and strength in pediatrics patients: why should we care? *Clin Nutr* 2019; 38: 2002–2015.

71. Strope MA, Nigh P, Carter MI, *et al*. Physical activity-associated bone loading during adolescence and young adulthood is positively associated with adult bone mineral density in men. *Am J Mens Health* 2015; 9: 442–450.

72. Goh HH and Ratnam SS. Effects of hormone deficiency, androgen therapy and calcium supplementation on bone mineral density in female transsexuals. *Maturitas* 1997; 26: 45–52.

73. Andrade SRL, Mucida YM, Xavier JDC, *et al*. Bone mineral density, trabecular bone score and muscle strength in transgender men receiving testosterone therapy versus cisgender men. *Steroids* 2022; 178: 108951.

74. Turner A, Chen TC, Barber TW, *et al*. Testosterone increases bone mineral density in female-to-male transsexuals: a case series of 15 subjects. *Clin Endocrinol* 2004; 61: 560–566.

75. Meriggiola MC, Armillotta F, Costantino A, *et al*. Effects of testosterone undecanoate administered alone or in combination with letrozole or dutasteride in female to male transsexuals. *J Sex Med* 2008; 5: 2442–2453.

76. Mueller A, Haeberle L, Zollver H, *et al*. Effects of intramuscular testosterone undecanoate on body composition and bone mineral density in female-to-male transsexuals. *J Sex Med* 2010; 7: 3190–3198.

77. Gava G, Armillotta F, Pillastrini P, *et al*. A randomized double-blind placebo-controlled pilot trial on the effects of testosterone undecanoate plus dutasteride or placebo on muscle strength, body composition, and metabolic profile in transmen. *J Sex Med* 2021; 18: 646–655.

78. Rosen HN, Hamnvik OR, Jaisamrarn U, *et al*. Bone densitometry in transgender and gender

non-conforming (TGNC) individuals: 2019 ISCD official position. *J Clin Densitom* 2019; 22: 544–553.

79. van der Loos MA, Hellinga I, Vlot MC, *et al*. Development of hip bone geometry during gender-affirming hormone therapy in transgender adolescents resembles that of the experienced gender when pubertal suspension is started in early puberty. *J Bone Miner Res* 2021; 36: 931–941.
80. Fonseca A, Gordon CL and Barr RD. Peripheral quantitative computed tomography (pQCT) to assess bone health in children, adolescents, and young adults: a review of normative data. *J Pediatr Hematol Oncol* 2013; 35: 581–589.
81. van den Bergh JP, Szulc P, Cheung AM, *et al*. The clinical application of high-resolution peripheral computed tomography (HR-pQCT) in adults: state of the art and future directions. *Osteoporos Int* 2021; 32: 1465–1485.
82. Bretherton I, Ghasem-Zadeh A, Leemaqz SY, *et al*. Bone microarchitecture in transgender adults: a cross-sectional study. Epub ahead of print 3 January 2022. *J Bone Miner Res off J Am Soc Bone Miner Res*. DOI: 10.1002/jbmr.4497.
83. Lewiecki EM, Binkley N, Clark P, *et al*. Core principles for fracture prevention: North American Consensus from the National Osteoporosis Foundation, Osteoporosis Canada, and Academia Nacional de Medicina de Mexico. *Osteoporos Int* 2020; 31: 2073–2076.
84. Lewiecki EM, Anderson PA, Bilezikian JP, *et al*. Proceedings of the 2021 Santa Fe Bone Symposium: advances in the management of osteoporosis and metabolic bone diseases. *J Clin Densitom* 2022; 25: 3–19.