Bone Health in the Transgenders

6

Yasser El Miedany

Introduction

The United Nations human rights defined "gender identity" as a term which refers to a person's experience of their own gender. The term "transgender" people or "gender nonconforming" refers to subjects who have a gender identity that is different from the sex that they were assigned at birth [1]. In another way, the term "transgender" describes a population experiencing incongruence between their physical sex characteristics (assigned gender) and their gender identity (the extent to which people experience themselves to be like others of one gender) [2]. In some instances, as a result of the incongruence between assigned gender and gender identity, an individual can suffer distress (gender dysphoria), which may be accompanied by physical or mental health issues [3]. A transgender or trans person may identify as a man, woman, transman, or transwoman, or as a non-binary person (Table 6.1). Gender identity is different from sexual orientation, trans people may have any sexual orientation, and, therefore, they can be heterosexual, lesbian, gay, bisexual, asexual or pansexual (attracted to a person of any sex or gender identity).

In the past, being transgender was defined as a mental illness concern and was categorized as such by the World Health Organization in the international Classification of Diseases-10. The recognition of the biologic underpinnings to gender identity has resulted in a major framework shift. Indeed, the latest International Classification of Diseases 11, launched in 2018, changed the term to "gender incongruence" and reclassified it under conditions related to sexual health [4].

The current literature on the number and proportion of transgender people is highly heterogenous. The reported proportions of people self-identified as transgender ranged from 100 to 2000 per 100,000 or 0.1% to 2% among adults. The corresponding range among school children was 1.3% to 2.7%. Causes of heterogeneity may include diverse cultural and legal population-specific contexts as well as how transgender people are perceived and treated in a society [5].

Achieving gender reassignment is not often easy. Psychological implications should be considered carefully and are always addressed as part of the individual assessment. The transitioning process may take several years, usually started by seeking a diagnosis, following which the implications can be discussed and treatment plan is agreed. The implications discussed include:

Y. El Miedany (✉)
Canterbury Christ Church University,
Canterbury, Kent, UK

Y. El Miedany (ed.), *New Horizons in Osteoporosis Management*,
https://doi.org/10.1007/978-3-030-87950-1_6

Table 6.1 Terminology related to sex and gender

Terminology	Definition
Gender identity	Internal sense of being male, female, neither, or along the Spectrum
Sex assigned at birth	Biological characteristics including anatomic phenotype and/ Or chromosomal makeup (usually assigned at birth or shortly thereafter)
Cisgender	Gender identity and expression congruent with sex assigned at birth
Gender dysphoria	Distress that may accompany the incongruence between Experienced or expressed gender and sex assigned at birth
Transgender	A persistent gender identity that differs from sex assigned at birth
Non-binary gender identity	Describes gender identities that are not exclusively masculine Or feminine and therefore outside the "gender binary" of male and female. It may mean the individual feels he/she has no gender
Transgender man (transman)	Sex-assigned female at birth, with masculine Identity
Transgender woman (transwoman)	Sex-assigned male at birth, with feminine Identity
Transvestite (cross-dress)	People who cross-dress are usually comfortable with their assigned Gender and do not wish to change it. (trans people who cross-dress enjoy wearing clothes associated with the opposite sex, often for relatively short periods of time, for personal comfort and pleasure)
Sexual orientation	Gender or genders a person is attracted to
Gender-affirmative healthcare	Include any single or combination of a number of social, psychological, behavioral, or medical (including hormonal treatment or surgery) interventions designed to support and affirm an individual's gender identity

1. Making decisions about whether the person want to commence hormone therapy and be considered for surgery.
2. The need to change the individual's name and gender marker on documentation and explore financial implications.
3. How the person will begin living in the affirmed gender is discussed.

Treatment plan comprises hormone treatment and if the individual has surgery, probably this will involve more than one operation. After surgery, the subject will probably require long-term hormone therapy and regular monitoring for possible side effects.

Studies of mortality and somatic well-being after sex-reassignment surgery of transgenders revealed elevated somatic morbidity as well as mortality in this cohort of people. Long-term follow-up study [6] of individuals undergoing sex-reassignment revealed that 23.1% had somatic morbidity after the reassignment surgery and that of 98% of all transsexuals who officially underwent transgender surgery in Denmark from 1978 through 2010 (total number 104 individuals), one in three had somatic morbidity and approximately 1 in 10 had died. No significant differences in somatic morbidity or mortality were found between male-to-female and female-to-male individuals. The list of somatic morbidities included cardiovascular, cancer, musculoskeletal and bone health, pulmonary, as well as liver diseases. This chapter will focus on bone health in transgenders, the role of sex hormones on bone health, as well as the bone mass effects of cross-sex hormone therapy in transgender people. The chapter will review on the current data available regarding bone health in adult transgender men and women as well as adolescents. It will expand to discuss guidelines for transgender hormone treatment, osteoporosis risk in transgender individuals, as well as approaches toward screening for osteoporosis in transgender individuals. It will conclude by discussing clinical implications for bone health management of transgender people in standard clinical practice.

Sex Hormones and Bone Health

Sex steroids are major determinants of bone homeostasis. In boys, during puberty, testosterone stimulates periosteal apposition, leading to increased bone width and size compared to girls, despite the similar cortical thickness [7]. In turn, estrogen plays a main regulatory role in bone metabolism in both women and men, acting on bone remodeling and keeping it within physio-

logical limits. Estradiol acts on the lifespan of osteoblasts, decreasing apoptosis and increasing the functional capacity of individual osteoblasts. In osteoclasts, estradiol induces apoptosis and decreases cellular differentiation [8]. Estrogen deficiency is associated with an imbalance between bone resorption and bone formation that is linked to osteoblast apoptosis, oxidative stress, and osteoblastic NF-κB (RANKL) activity [9].

Although the importance of sex steroids in bone health is widely accepted, the differential effects of estrogen and testosterone individually remain a topic of discussion. In the late 1990s, Riggs et al. [10] described a pivotal role for estrogen in the female and male skeleton. Recent research, assessing bone architecture, has questioned this model. Cortical bone loss still seems related with estrogen deficiency, but trabecular bone loss occurs earlier in adulthood, in both men and women, in the presence of normal sex steroid status, indicative that trabecular bone loss is either (partly) estrogen-independent or requires higher levels for its preservation [11–13]. Hence, quantitative computed tomography (QCT) and visualizing bone geometry is a valid tool which can be used for unravelling the interactions of sex steroid with trabecular and cortical bone.

Sex steroids also influence bone size: men develop larger periosteal (outer) and endosteal (inner) circumference than women, partly due to the interplay of sex steroids, mechanical loading, and the growth hormone (GH)/ insulin-like growth factor 1 (IGF1)-axis during puberty [14–16]. In adulthood, periosteal apposition continues, but at a slower rate in women than in men [17]. Sex steroid reversal, as encountered in transmen on testosterone treatment, may shed light on the role of individual contributions of sex steroids in the sexual dimorphism in bone geometry.

Bone Mass Effects of Cross-Sex Hormone Therapy in Transgender People

Animal studies have helped elucidate the role played by estrogen as well as testosterone in bone health. In male mice, estrogen receptor deletion in osteoblasts causes a delay in cortical bone mass accrual during puberty. However, in contrast to female mice, this effect is transient; a few months later, male mice develop normal bone mass, suggesting that androgen action via androgen receptor has a compensatory effect. Interestingly, androgen receptor deletion in osteoblasts and osteocytes has no effect on cortical bone, suggesting an indirect action of androgens. Androgens may also exert anabolic actions via paracrine mechanisms by acting on muscle fibroblasts [18, 19]. In fact, muscle mass is one of the main triggers of periosteal apposition, leading to larger periosteal circumference [20]. It is important to keep in mind that DXA scanning does not provide information on bone volume and that men have larger bones than women, which gives them greater resistance even with similar densities. Volume changes associated with the treatment would not be detected by DXA. However, the use of peripheral quantitative computed tomography, a technique that allows assessment of bone size, has shown increased volumetric BMD in transgender men [21, 22], with larger endosteal and periosteal bone circumference [21] after androgen therapy.

In humans, transmen have a female birth sex but identify as, or desire to be, a member of the male gender. In the case of gender dysphoria, this incongruence causes discomfort or distress often leading to the choice for testosterone treatment and/or sex reassignment surgery (including hysterectomy/salpingo-oophorectomy and mastectomy). A substantially higher muscle mass and a larger periosteal and endosteal circumference, higher trabecular volumetric bone mineral density (vBMD), and lower cortical vBMD was reported earlier in a cross-sectional study using peripheral QCT (pQCT) in adult transmen after long-term testosterone treatment (10 years) and transgender surgery compared with age-matched control women. This larger bone size was probably mostly explained by the higher androgen-induced muscle mass in transmen [23–27]. These data may, at least in part, provide a mechanistic basis for the evidence generated by this meta-analysis regarding the impact of cross-sex hormone therapy on preserving bone mass in transgender men.

Transwomen, conversely, receiving estrogen therapy may lose lean mass in association with androgen deprivation, which over time can lead to smaller bones and higher prevalence of low bone mass. Recent study revealed a prevalence of 18.3% of low bone mass in transwomen after long-term cross-sex hormone therapy, whereas no cases were observed in male or female controls [23, 24]. Also, Lapauw et al. [28] found a prevalence of 35% of low bone mass after a mean of 96 months of estrogen therapy. The studies reporting osteoporosis or low bone mass prevalence >25% included transwomen followed for 5 [29, 30] to 6.3 years [31] after the procedure.

Practical Guidelines for Transgender Hormone Treatment

Both the World Professional Association for Transgender Health (WPATH) and the Endocrine Society have created transgender-specific guidelines [32] to help serve as a framework for providers caring for gender minority patients. These guidelines are mostly based on clinical experience from experts in the field. Guidelines for hormone therapy in transgender men are mostly extrapolations from recommendations that currently exist for the treatment of hypogonadal natal men and estrogen therapy for transgender women is loosely based on treatments used for postmenopausal women.

In the past, the guidelines for hormone therapy initiation recommended that all patients undergo a "real-life test" prior to starting medical therapy. This test required patients to live full-time as their self-affirmed gender for a predetermined period of time (usually 12 months) before starting cross-sex hormones. The recommendation was intended to help patients transition socially. However, both abovementioned societies have recognized that this step is unreasonable for many patients as social transition can be very challenging if there is incongruence between an individual's self-affirmed gender and their physical appearance. As a result, the updated guidelines do not require this step, and instead, the societies recommend that patients transition socially and with medical therapy at the same time [32].

WPATH recommends that hormone therapy should be initiated once psychosocial assessment has been completed, the patient has been determined to be an appropriate candidate for therapy, and informed consent reviewing the risks and benefits of starting therapy has been obtained. Per WPATH, a referral is required by a qualified mental health professional, unless the prescribing provider is qualified in this type of assessment. The criteria for cross hormone therapy include: (1). persistent well-documented gender dysphoria (a condition of feeling one's emotional and psychological identity as male or female to be opposite to one's biological sex) diagnosed by a mental health professional well versed in the field; (2). capacity to make a fully informed decision and to consent for treatment; (3). age of majority; and (4). good control of significant medical and/or mental comorbid conditions [32, 33].

This fourth criterion can sometimes be the most challenging to interpret. Many patients may have concurrent mood disorders related to their gender dysphoria, and experienced providers may have success alleviating the severity of these symptoms by allowing the patient to begin the medical transition process. This is a key concept and should be considered when patients are being evaluated for hormone therapy initiation. Patients with comorbid psychiatric conditions should be closely monitored, and mental health support remains paramount for these patients. Table 6.2 shows hormone options available for transgender men and women, whereas Table 6.3 shows Surveillance recommendations for transgender men on testosterone as well as transgender women on estrogen [34].

There are no unanimous recommendations for the use of anti-androgens. Options are listed in Table 6.2. Spironolactone is one of the most common medications used to suppress endogenous testosterone in transfemale patients. The biggest risk associated with spironolactone is hyperkalemia, and this should be closely monitored. Other options include 5α-reductase inhibitors such as finasteride, but these can be associated with liver

Table 6.2 Hormonal options for transgender men and women

Transgender men			Transgender women		
Route	Formulation	Dose	Route	Formulation	Dose
Oral	Testosterone undecanoate	160–240 mg/day	Oral	Estradiol	2–4 mg daily
Parental (subcutaneous, intramuscular)	Testosterone enanthate, cypionate	50–200 mg/week 100–200 mg/10–14 days	Parental (subcutaneous, intramuscular)	Estradiol valerate	5–30 mg every 2 weeks
Implant (subcutaneous)	Testopel	75 mg/pellet	Transdermal	Estradiol	0.1–0.4 mg twice weekly
Transdermal	Testosterone gel (1%) testosterone patch	2.5–10 g/day 2.5–7.5 mg/day	Anti-androgens	Progesterone Medroxyprogesterone acetate GnRH agonist (leuprolide) Histrelin implant Spironolactone Finasteride	20–60 mg PO daily 150 mg IM every 3 months 3.75–7.5 mg IM monthly 50 mg implanted every 12 months 100–200 mg PO daily 1 mg PO daily

Table 6.3 Surveillance recommendations for transgenders on hormone therapy

Surveillance recommendations for transgender men on testosterone	Surveillance recommendations for transgender women on estrogen
Monitor for virilizing and adverse effects every 3 months for the first year, then every 6–12 months Obtain baseline hematocrit and lipid profile and monitor at follow-up visits Obtain baseline bone mineral density if a patient is at risk for osteoporosis; routine screening after age 60, or earlier if sex hormone levels consistently low Monitor serum estradiol during the first 6 months and thereafter until uterine bleeding has ceased Monitor serum testosterone at follow-up visits; target 300–1000 ng/dL Peak levels for parenteral testosterone measured 24–48 hrs after injection Trough levels for parenteral testosterone measured before injection	Monitor for feminizing and adverse effects every 3 months for the first year, then every 6–12 months Obtain baseline hematocrit and lipid profile and monitor at follow-up visits Obtain baseline bone mineral density if a patient is at risk for osteoporosis; routine screening after age 60, or earlier if sex hormone levels consistently low Obtain prolactin at baseline, at 12 months after initiation of treatment, biennially thereafter Monitor serum testosterone during the first 6 months until levels are <55 ng/dL Monitor serum estradiol at follow-up visits; target 100–200 pg/mL

toxicity and may not be as effective as spironolactone [33]. Gonadotropin-releasing hormone (GnRH) agonists can be very expensive and are not always a good option for patients. Progestins are used by some providers, but should be used with caution as there is a theoretical risk of breast cancer associated with long-term exogenous progesterone use [35].

Osteoporosis Risk in Transgender Individuals

There is a broad spectrum of transgendered persons, not all of whom choose to become transsexual by transitioning physically to the opposite sex. Therefore, many transgendered individuals, from a biological perspective, conform to their

natal sex. Of those who have chosen transition, some may be either taking or may have taken sex hormones surreptitiously and self-regulated, whereas others may be undergoing or may have completed medically supervised hormonal and surgical therapy. Surgical therapies include either male orchiectomy or female oophorectomy. In addition to this, there is a high prevalence of exposure to modifiable risk factors for osteoporosis among transgender individuals. Smoking is highly prevalent among transgender individuals [36]. A national survey revealed that 30.7% of transgender individuals smoke and many work in smoke-filled bars resulting in significant exposure levels to passive smoking. An estimated 25% of transgender individuals misuse alcohol or drugs to cope with the discrimination they face because of their gender identity or expression [37].

Like the cisgender population, transgender individuals experience these modifiable risk factors as part of their multiple, interacting, and cumulative lifestyle habits [38]. These risk factors along with transgender individuals use of cross-sex hormones may put them at increased risk for osteoporosis. In addition, because of the complex interactions between the sex hormones and bone metabolism, both in the achievement of peak bone mass leading up to skeletal maturity and then in the subsequent loss of bone with aging, as well as the increased risk behavior; the risk of developing osteoporosis varies widely among transgendered persons.

On another front, transgender individuals often delay accessing healthcare, placing them at risk for poor short- and long-term health outcomes [39]. The World Professional Association for Transgender Health Standards of Care emphasizes access to evidence-based healthcare as a right for transgender individuals. In concordance, the American Academy of Nursing published a position statement on healthcare services for transgender individuals [40]. Although there has been an abundance of research addressing bone health and osteoporosis prevention, the individuals' knowledge and health beliefs for carrying out health behaviors; there is no research on transgender individuals' knowledge, health beliefs, or osteoporosis preventing behaviors in this disparate cohort of population who are often using self-administered cross-sex hormones. Therefore, it would be a logical step to consider examining these variables in transgender individuals.

Use of cross-sex hormones is the most common body modification that transgender individuals can access to bring endocrine and psychological systems into balance [40], but this can potentially affect one's bone mineral density (BMD). The stigma surrounding transgenders has led to growing numbers of individuals obtaining hormones and hormone blockers via the Internet and self-medicating [40, 41]. Self-treatment with cross-sex hormones therapy may increase the risk for developing osteoporosis [42]. The research is limited on the use of non-physician, unprescribed cross-sex hormones [43]. Without medical advice and knowledge required to minimize health risks from self-prescribed use of cross-sex hormones, transgenders may develop misperceptions and inaccurate health beliefs that may lead to unhealthy behaviors with severe risks that include cardiovascular complications, altered bone health, and osteoporosis. There are no randomized controlled trials on the use of long-term cross-sex hormones, and little is known about the long-term effects [44]. With the increasing numbers of adolescents and young adults who are taking cross-sex hormones, effects of pubertal suppression on BMD have not been systematically explored and need to be studied over the long term [45].

The research on fractures in transgender individuals is also sparse. In a systematic literature review by Weinand and Safer [46] on cross-sex hormones safety for adult transgenders, results indicated that a considerable amount of the existing data has been generated from case reports with very few large cohort studies addressing long-term effects of hormone therapy. A cross-sectional study conducted in Belgium by [44], a pioneer in transgender research, explored the side effects of cross-sex hormones use in 100 transgenders after sex assignment surgery who had on average a 10-year use of these hormones. Results indicated that transmen did not have osteoporosis as a side effect, but transwomen had significantly

more low bone density and osteoporosis at the lumbar spine and radius.

The evolution of bone density, geometry, and bone turnover in transwomen during the initial 2 years of monitored use of cross-sex hormones was investigated by Van Caenegem et al. [47] and is recognized as one of the first prospective studies in this area. Transwomen at the onset of the study before using cross-sex hormones had lower bone density and smaller bone size compared with age matched control men. With the monitored use of prescribed cross-sex hormones, bone turnover decreased, but there was a significant decrease in muscle mass and strength. Research recommendations include lengthening the time of follow-up for addressing the long-term effects of cross-sex hormones on bone and the effect in older individuals. In fact, the time is ripe for educating transgenders about the use of cross-sex hormones to increase knowledge about osteoporosis prevention and bone health awareness [48].

Furthermore, adaptation of recommendations for osteoporosis screening to transgender populations is complicated by existing recommendations that vary widely for non-transgender people, including lack of consensus about screening for non-transgender men, and lack of recommendations on the frequency of screening.

Screening for Osteoporosis in Transgender Individuals

The Endocrine Society recommends that both male-to-female and female-to-male transgendered persons on cross-hormone therapy be considered for BMD testing at baseline if clinical risk factors for osteoporotic fractures are present. In individuals at low risk, screening for osteoporosis should be conducted at 60 years of age and in those who are not compliant with hormone therapy [49]. Screening between ages 50 and 60 should be considered for those with established risk factors for osteoporosis. Transgender people (regardless of birth assigned sex) who have undergone gonadectomy and have a history of at least 5 years without hormone replacement should also be considered for bone density testing, regardless of age (Grading: X C W). There are three main reasons to perform central DXA: (1) diagnosing osteoporosis; (2) determining fracture risk (50 years of age or older); and (3) monitoring response to treatment [50]. Of these indications, only the monitoring of treatment response (i.e., determining change in BMD over time) is sex or gender neutral. The subject is being compared with him- or herself and any observed change in the BMD has the same statistical relevance as if the person's sex had been maintained between serial scans.

However, the scanner software determines the subject's standard scores (T-scores and Z-scores) based on the sex entered by the technologist. For any given BMD measurement, the corresponding standard score will be different for men and women because their reference population databases differ. There are as yet no specific reference databases for transgendered persons. The T-score is used to diagnose osteoporosis by determining diagnostic category as defined by the World Health Organization. It is also a key measurement used in the estimation of fracture risk in the widely used FRAX (Fracture Risk Assessment Tool, World Health Organization, Geneva, Switzerland) fracture risk prediction tool, as well as in other such tools as Canadian Association of Radiologists and Osteoporosis Canada (CAROC) system, Foundation for Osteoporosis Research and Education Fracture Risk Calculator (FORE FRC), and the Garvan Fracture Risk Prevention Tool, all of which require that either male or female sex be entered into the calculator [51]. It follows that both parameters (i.e., diagnostic category and estimated fracture risk) might not accurately reflect the bone health of individuals whose sex/ gender identity as recognized by the scanner differs from their actual biological sex. A similar dilemma exists in interpreting the laboratory results of transgendered persons on hormonal therapy [52].

It is probable that most technologists and physicians performing and interpreting DXA scans will not be fully aware of the treatment protocols of the transgendered patients referred to them for assessment. The densitometrist's report can confidently indicate serial changes in BMD irrespec-

tive of the recorded sex of the patient, but the assignment of a diagnostic category and estimation of 10-year fracture risk are problematic because our normative databases assume that the individual conforms to his or her natal sex.

A solution for the DXA technologist might be to process each transgendered patient twice, the first time based on the sex declared on the patient questionnaire and the second time based on the opposite sex. This will provide two sets of T-scores, 1 for each sex. The reporting physician can then decide how to best interpret and report on the data. For example, diagnostic category and fracture risk could be calculated twice using the standard male and female reference databases. Both reports could be issued to the referring clinician, who is likely the individual best positioned to determine if the transgendered person is biologically male or female, and to assess the clinical implications of the DXA results. It has been suggested that in some individuals, the clinician may wish to assign a fracture risk that is intermediate between the biological male and female values [53]. However, there are disadvantages of such an approach, in terms of added time, inaccuracy, inapplicability for monitoring, as well as the potential for creating confusion. Clearly, individual facilities will need to determine the most appropriate policy for each to adopt.

Advice should be given to modify risk factors for osteoporosis, including tobacco cessation, correct low vitamin D levels, maintain calcium intake in line with current guidelines for non-transgender people, weight bearing activity, and moderation of alcohol consumption [54].

Implications for Standard Clinical Practice

Currently, there is no published research on transgenders' bone health and osteoporosis prevention. This is an important area for future research, with the growing number of transgenders who are not only at risk for osteoporosis and possible fractures just as the general public is at risk, but who are at an additional risk because of long-term use of cross-sex hormones. Little is known about the long-term use of cross-sex hormones, particularly when initiated in young adulthood and continued into adulthood.

Determining transgenders' health belief perceptions of bone health and osteoporosis is important because of their unique healthcare issues. Improving osteoporosis-preventing behaviors, particularly dietary calcium intake and weight-bearing exercise, are issues that both men and women face during aging as bone density decreases [38]. However, the transgender population is faced with compounding issues of cross-sex hormone use, particularly when they self-manage use of hormones. Self-management can result in hormone imbalance, which can have a long-term effect on bone health. Earlier study revealed that transgenders lack knowledge about bone health and behaviors that promote bone health and prevent osteoporosis [55]. Therefore, it is important that healthcare providers consider the transgenders' knowledge deficits in relation to osteoporosis prevention and bone health promotion. Clinical implications include conducting appropriate assessments and providing education when caring for transgenders. Thorough assessments are needed to screen the transgenders for their use of cross-sex hormones (self-regulated or regulated by a health professional) and determining the transgender' knowledge and health beliefs regarding osteoporosis prevention and promotion of bone health [56].

It is vital to establish a respectful communicating approach with the transgenders so that conversations about risk behaviors and hormone use can easily occur. By identifying gaps in the transgenders' knowledge, healthcare providers can educate this at-risk minority population on how to be proactive in maintaining bone health through awareness of risk factors (such as hormone use) and prevention behaviors (diet, exercise) [57]. Healthcare providers can influence positive bone health behaviors by taking on critical roles as a caregiver, educator, and advocate. By identifying knowledge gaps for transgenders, devising better prevention and wellness

plans, not only for bone health but also for the overall health and well-being, would be achievable [48, 58].

In conclusion, many healthcare professionals have not received formal training in dealing with transgendered patients and may not be comfortable in interacting with and providing care for them. Having surgical therapies such as male orchiectomy or female oophorectomy, cross-hormone therapy, as well as the high prevalence of exposure to modifiable risk factors for osteoporosis would have a negative impact on the transgenders' bone health and make them prone to develop osteoporosis. Until expert guidelines are developed, facilities that deal regularly with transgendered patients may wish to consider the following policy: When assessing a declared transgendered person for a DXA scan, the densitometrist should follow current social convention and respect the patient's chosen gender identity by entering the sex declared by the patient. After the scan has been completed, the initial printout will reflect this declared identity. The densitometrist should then change the recorded sex, issuing a second printout. Both documents are made available to the physician reporting the scan, who may wish to consider issuing 2 reports for the patient, assigning diagnostic category and fracture risk for both a female and a male individual. This is a policy decision that will need to be made locally. However, interval change in BMD, if the scan is a follow-up, will be identical on the two documents. Future longitudinal studies to investigate the long-term impact of cross-sex hormones use on bone health. A larger sample would provide the opportunity to analyze daily calcium and vitamin D intake by participant age. Most importantly, intervention studies are needed to determine the best ways to access and educate this historically private population regarding bone health and osteoporosis preventing behaviors. Including ethnic and cultural considerations of transgenders in future research would provide a diverse perspective of the use of cross-sex hormones and bone health and prevention of osteoporosis. Healthcare providers can play a key role in helping promote transgender' awareness for bone health.

References

1. Transgender. United Nations Human Rights. https://www.unfe.org/wp-content/uploads/2017/05/UNFE-Transgender.pdf. (Accessed on 26th July 2019).
2. Beek TF, Cohen-Kettenis PT, Kreukels BP. Gender incongruence/gender dysphoria and its classification history. Int Rev Psychiatry. 2016;28:5–12.
3. Levine SB. Ethical concerns about emerging treatment paradigms for gender dysphoria. J Sex Marital Ther. 2018;44:29–44.
4. WHO/Europe brief – transgender health in the context of ICD-11. http://www.euro.who.int/en/health-topics/health-determinants/gender/gender-definitions/whoeurope-brief-transgender-health-in-the-context-of-icd-11 (Accessed on 26th July 2019).
5. Goodman M, Adams N, Corneil T, Kreukels B, Motmans J, Coleman E. Size and distribution of transgender and gendr nonconforming populations. A narrative review. Endocrinol Metabl Clin N Am. 2019;48:303–21.
6. Simonsen R, Hald G, Kristensen E, Giraldi A. Long-term follow-up of individuals undergoing sex-reassignment surgery: somatic morbidity and cause of death. Sex Med. 2016;4:e60–8.
7. Neu CM, Rauch F, Manz F, Schoenau E. Modeling of cross-sectional bone size, mass and geometry at the proximal radius: a study of normal bone development using peripheral quantitative computed tomography. Osteoporos Int. 2001;12(7):538–47.
8. Khosla S, Oursler MJ, Monroe DG. Estrogen and the skeleton. Trends Endocrinol Metab. 2012;23(11):576–58.
9. Fighera TM, Ziegelmann PK, Rasia da Silva T, Spritzer PM. Bone Mass effects of cross-sex hormone therapy in transgender people: updated systematic review and meta-analysis. J Endocr Soc. 2019;3(5):943–64. Published 2019 Mar 15. https://doi.org/10.1210/js.2018-00413.
10. Riggs BL, Khosla S, Melton LJ III. A unitary model for involutional osteoporosis: estrogen deficiency causes both type I and type II osteoporosis in postmenopausal women and contributes to bone loss in aging men. J Bone Miner Res. 1998;13:763–73. https://doi.org/10.1359/jbmr.1998.13.5.763.
11. Khosla S, Melton LJ, Riggs BL. The unitary model for estrogen deficiency and the athogenesis of osteoporosis: is a revision needed? J Bone Miner Res. 2011;26:441–51. https://doi.org/10.1002/jbmr.262.
12. Khosla S, Melton LJ III, Achenbach SJ, Oberg AL, Riggs BL, Melton LJ. Hormonal and biochemical determinants of trabecular microstructure at the ultra-distal radius in women and men. J Clin Endocrinol Metab. 2006;91:885–91. https://doi.org/10.1210/jc.2005-2065.
13. Kirmani S, Christen D, van Lenthe GH, Fischer PR, Bouxsein ML, McCready LK, Melton LJ III, Riggs BL, Amin S, Muller R, et al. Bone structure at the distal radius during adolescent growth. J Bone Miner

Res. 2009;24:1033–42. https://doi.org/10.1359/jbmr.081255.
14. Vandewalle S, Taes Y, Fiers T, Toye K, Van Caenegem E, Roggen I, De Schepper J, Kaufman JM. Associations of sex steroids with bone maturation, bone mineral density, bone geometry and body composition: a cross-sectional study in healthy male adolescents. J Clin Endocrinol Metab. 2014;99:E1272–82. https://doi.org/10.1210/jc.2013-3887.
15. Vanderschueren D, Venken K, Ophoff J, Bouillon R, Boonen S. Clinical review: sex steroids and the periosteum – reconsidering the roles of androgens and estrogens in periosteal expansion. J Clin Endocrinol Metab. 2006;91:378–82. https://doi.org/10.1210/jc.2005-1766.
16. Szulc P, Seeman E. Bone fragility: failure of periosteal apposition to compensate for increased endocortical resorption in postmenopausal women. J Bone Miner Res. 2006;21:1856–63. https://doi.org/10.1359/jbmr.060904.
17. Coleman E, Bockting W, Botzer M, Cohen-Kettenis P, DeCuypere G, Feldman J, Fraser L, Green J, Knudson G, Meyer WJ, et al. Standards of care for the health of transsexual, transgender, and gender-nonconforming people, version 7. International J Transgender. 2012;13:165–232. https://doi.org/10.1080/15532739.2011.700873.
18. Almeida M, Laurent MR, Dubois V, Claessens F, O'Brien CA, Bouillon R, Vanderschueren D, Manolagas SC. Estrogens and Androgens in Skeletal Physiology and Pathophysiology. Physiol Rev. 2017;97(1):135–87.
19. Cauley JA. Estrogen and bone health. Steroids. 2015;99(Pt A):11–5.
20. Frost HM. Bone's mechanostat: a 2003 update. Anat Rec A Discov Mol Cell Evol Biol. 2003;275(2):1081–101.
21. Van Caenegem E, Wierckx K, Taes Y, Dedecker D, Van de Peer F, Toye K, Kaufman JM, T'Sjoen G. 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(7):2503–11.
22. Van Caenegem E, Wierckx K, Taes Y, Schreiner T, Vandewalle S, Toye K, Lapauw B, Kaufman JM, T'Sjoen G. 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(2):163–71.
23. Elbers JM, Asscheman H, Seidell JC, Gooren LJ. Effects of sex steroid hormones on regional fat depots as assessed by magnetic resonance imaging in transsexuals. Am J Physiol. 1999;276:E317–25.
24. Haraldsen IR, Haug E, Falch J, Egeland T, Opjordsmoen S. Cross-sex pattern of bone mineral density in early onset gender identity disorder. Horm Behav. 2007;52:334–43. https://doi.org/10.1016/j.yhbeh.2007.05.012.
25. Mueller A, Haeberle L, Zollver H, Claassen T, Kronawitter D, Oppelt PG, Cupisti S, Beckmann MW, Dittrich R. Effects of intramuscular testosterone undecanoate on body composition and bone mineral density in female-to-male transsexuals. J Sexual Med. 2010;7:3190–8. https://doi.org/10.1111/j.1743-6109.2010.01912.x.
26. Meriggiola MC, Armillotta F, Costantino A, Altieri P, Saad F, Kalhorn T, Perrone AM, Ghi T, Pelusi C, Pelusi G. Effects of testosterone undecanoate administered alone or in combination with letrozole or dutasteride in female to male transsexuals. J Sexual Med. 2008;5:2442–53. https://doi.org/10.1111/j.1743-6109.2008.00909.x.
27. van Caenegem E, Wierckx K, Taes Y, Schreiner T, Vandewalle S, Toye K, Lapauw B, Kaufman J-M, T'Sjoen G. 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). European J Endocrinol. 2015;172:163–71.
28. Lapauw B, Taes Y, Simoens S, Van Caenegem E, Weyers S, Goemaere S, Toye K, Kaufman JM, T'Sjoen GG. Body composition, volumetric and areal bone parameters in male-to-female transsexual persons. Bone. 2008;43(6):1016–21.
29. Fighera TM, da Silva E, Lindenau JD, Spritzer PM. Impact of cross-sex hormone therapy on bone mineral density and body composition in transwomen. Clin Endocrinol. 2018;88(6):856–62.
30. T'Sjoen G, Weyers S, Taes Y, Lapauw B, Toye K, Goemaere S, Kaufman JM. Prevalence of low bone mass in relation to estrogen treatment and body composition in male-to-female transsexual persons. J Clin Densitom. 2009;12(3):306–13.
31. Wierckx K, Mueller S, Weyers S, Van Caenegem E, Roef G, Heylens G, T'Sjoen G. Long-term evaluation of cross-sex hormone treatment in transsexual persons. J Sex Med. 2012;9(10):2641–51.
32. World Professional Association for Transgender Health. Standards of care for the health of transsexual, transgender, and gender nonconforming people. 7th ed; 2011. Available online: https://s3.amazonaws.com/amo_hub_content/Association140/files/Standards%20of%20Care%20V7%20-%202011%20WPATH%20(2)(1).pdf (Accessed on 27th July 2019).
33. Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, et al. Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2009;94:3132–54.
34. Unger CA. Hormone therapy for transgender patients. Transl Androl Urol. 2016;5(6):877–84. https://doi.org/10.21037/tau.2016.09.04.
35. Gooren LJ, Giltay EJ, Bunck MC. Long-term treatment of transsexuals with cross-sex hormones: extensive personal experience. J Clin Endocrinol Metab. 2008;93:19–25.
36. Burkhalter JE, Warren B, Shuk E, Primavera L, Ostroff JS. Intention to quit smoking among lesbian,

gay, bisexual, and transgender smokers. Nicotine Tob Res. 2009;11(11):1312–20.
37. Grant JM, Mottet LA, Tanis J with Herman JL, Harrison J, Keisling M. National transgender discrimination survey: Report on health and health care. Findings of a Study by the National Center for Transgender Equality and the National Gay and Lesbian Task Force. 2010. Retrieved from http://www.thetaskforce.org/static_html/downloads/resources_and_tools/ntds_report_on_health.pdf.
38. Institute of Medicine. Institute of Medicine. Dietary reference intakes for calcium and vitamin D. Washington, DC: The National Academies 2011. Retrieved from http://www.ncbi.nlm.nih.gov/books/NBK56070/pdf/Bookshelf_NBK56070.pdf.
39. Thrasher AD, Clay OJ, Ford CL, Stewart AL. Theory-guided selection of discrimination measures for racial/ethnic health disparities research among older adults. J Aging Health. 2012;24(6):1018–43. https://doi.org/10.1177/0898264312440322.
40. Sedlak CA, Boyd CJ. American Academy of Nursing Lesbian, Gay, Bisexual, Transgender, Queer Health Expert Panel . American Academy of Nursing on Policy Health care services for transgender individuals: Position Statement. Nursing Outlook. 2016;64(5):510–2. https://doi.org/10.1016/j.outlook.2016.07.002.
41. Center of Excellence for Transgender Health at the University of California San Francisco [COE]. 2012. General prevention and screening. Retrieved from http://transhealth.ucsf.edu/trans?page=protocol-screening.
42. Institute of Medicine. The health of lesbian, gay, bisexual, and transgender people: Building a foundation for better understanding. 2011. Washington, DC: The National Academies. Retrieved from http://www.nap.edu/catalog.php?record_id=13128.
43. Mepham N, Bouman WP, Arcelus J, Hayter M, Wylie KR. People with gender dysphoria who self-prescribe cross-sex hormones: prevalence, sources, and side effects knowledge. J Sex Med. 2014;11:2995–3001. https://doi.org/10.1111/jsm.12691.
44. Wierckx K, Mueller S, Weyers S, Van Caenegem E, Roef G, Heylens G, T'sjoen G. Long-term evaluation of cross-sex hormone treatment in transsexual persons. J Sex Med. 2012;9(10):2641–51. https://doi.org/10.1111/j.1743-6109.2012.02876.
45. Smith KP, Madison CM, Milne NM. Gonadal suppressive and cross-sex hormone therapy for gender dysphoria in adolescents and adults. Pharmacotherapy. 2014;34(12):1282–97. https://doi.org/10.1002/phar.1487.
46. Weinand JD, Safer JD. Hormone therapy in transgender adults is safe with provider supervision: a review of hormone therapy sequelae for transgender individuals. J Clin Translat Endocrinol. 2015;2(2):55–60. https://doi.org/10.1016/j.jcte.2015.02.003.
47. Van Caenegem E, Wierckx K, Taes Y, Schreiner T, Vandewalle S, Toye K, T'Sjoen G. 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. doi:https://doi.org/10.1007/s00198-014-2805-3.
48. Sedlak CA, Roller CG, Van Dulmen M, Alharbi HA, Sanata JD, Leifson MA, Veney AJ, Alhawatmeh H, O'Bryan Doheny M. Transgender individuals and osteoporosis prevention. Orthop Nurs. 2017;36(4):259–68.
49. Hembree WC, Cohen-Kettenis P, Delemarre-Van De Waal HA, et al. Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2009;94:3132e54.
50. Blake G, Adams JE, Bishop N. DXA in adults and children. In: Rosen CJ, editor. ASBMR primer on the metabolic bone diseases and disorders of mineral metabolism. 8th ed. London, UK: Wiley-Blackwell; 2013. p. 251.
51. Bonnick SL, Lewis LA. Bone densitometry for technologists. 3rd ed. New York, NY: Springer; 2013.
52. Roberts TK, Kraft CS, French D. Interpreting laboratory results in transgender patients on hormone therapy. Am J Med. 2014;127:159e62.
53. Radix A, Deutsch MB. Bone health and osteoporosis. 2016. Available at: http://transhealth.ucsf.edu/trans?page¼guidelines-bone-health. Accessed 28 July 2019.
54. Hammond I, Lentle B, van den Berg L, Vitols-McKay M. Gender identity and bone densitometry. Can Assoc Radiol J. 2017;68:267e269.
55. Williams B, Cullen L, Barlow JH. "I never realised how little I knew!": a pilot study of osteoporosis knowledge, beliefs, and behaviours. Health Care Women Inter. 2002;23(4):344–50.
56. Hsieh C, Novielli KD, Diamond JJ, Cheruva D. Health beliefs and attitudes toward the prevention of osteoporosis in older women. Menopause: The Journal of The North American Menopause Society. 2001;8(5):372–6.
57. Singh S, Foster R, Khan K. Accident or osteoporosis? Survey of community follow-up after low-trauma fracture. Canadian Family Physician 2011. 2011;57(4):e128–33.
58. Roller CG, Sedlak C, Draucker CB. Navigating the system: how transgender individuals engage in health care services. J Nurs Scholarsh. 2015;47(5):417–24. https://doi.org/10.1111/jnu.12160.