Bone health in adult trans persons: an update of the literature

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Purpose of review
Hormonal treatment in trans persons can affect bone health. In this review, recent studies published on this topic in adults are discussed.

Recent findings
Before starting hormonal treatment, trans women were found to have lower bone mineral density than cis men, which seems to be related to lower vitamin D concentrations and lower lean body mass, whereas this was not found in trans men. Short-term and long-term studies show that hormonal treatment does not have detrimental effects on bone mineral density in trans women and trans men. Low estradiol concentrations were associated with a decrease in bone mineral density in trans women.

Summary
Based on the reassuring findings in these studies, regularly assessing bone mineral density during hormonal treatment does not seem necessary. This confirms the Endocrine Society Guideline stating that bone mineral density should be measured only when risk factors for osteoporosis exist, especially in people who stop hormonal treatment after gonadectomy. The relationship with estradiol concentrations indicate that hormone supplementation should be adequate and therapy compliance should be stimulated. As vitamin D deficiency frequently occurs, vitamin D supplementation should be considered. Future research should focus on fracture risk and long-term changes in bone geometry.

Keywords
bone, gender dysphoria, sex steroids, trans persons

INTRODUCTION
Transgender people can receive hormonal treatment to adapt their physical characteristics to their experienced gender [1]. Trans women (male sex assigned at birth, female gender identity) can receive estrogens, with or without antiandrogens, which will induce physical changes such as breast growth [2] and changes in body shape [3]. Trans men (female sex assigned at birth, male gender identity) can be treated with testosterone, which among others will lead to an increase in muscle mass [4] and a lower voice [5].

These sex steroids are also known to affect bone health. Before puberty sets in, bone mass is similar in boys and girls. During puberty, boys develop wider bones than girls, because periosteal apposition is stimulated in men, whereas this is inhibited in women. In women, endosteal growth is stimulated, leading to growth of the cortex toward the medullary cavity, whereas this does not occur in men [6,7]. A possible explanation for the difference in periosteal apposition between men and women can be found in the direct effects of testosterone via androgen receptor activation [8]. Another explanation may be the increased muscle mass because of higher concentrations of testosterone [9–11], which increases mechanical loading and therefore increases periosteal growth [12].

Apart from the effects of sex steroids on bone development in men and women, sex steroids are also important for the maintenance of bone health. Estrogens are known to positively affect bone health, primarily by its inhibiting effect on osteoclasts, leading to a decrease in bone resorption [13]. This is supported by the finding that osteoclastic bone resorption increases in postmenopausal
women [14], leading to a decrease in bone mineral density (BMD) [15].

The maintaining effects of testosterone on bone health are less clear. A decrease in BMD was found in men after orchietomy or chemical castration with decreased testosterone concentrations [16]. However, because of aromatization of testosterone into estradiol, the estrogen concentrations also decreased in these people. A recent study performed by Finkelstein et al. [17] found that BMD did not change in men with normal estradiol and normal testosterone levels, but that it decreased in men with normal testosterone and low estradiol levels. This indicates that maintenance of bone health, also in men, is mainly regulated by estrogens.

Hormonal treatment in transgender people can affect bone health. In 2015, an extensive overview of the studies published on BMD and bone geometry in transgender adults until then, was described by van Caenegem et al. [18]. The aim of this current review is to provide an update of the literature on bone health in adult transgender people, by describing the studies published on this topic since then, to discuss these findings in light to earlier studies performed about this topic, and to translate these findings to clinical practice.

LITERATURE SEARCH

A literature search was performed on June 11, 2019 in PubMed using the following search terms: (transgender* OR ‘trans people’ OR ‘trans women’ OR ‘trans men’ OR transsexual* OR ‘trans sex’) AND (‘bone mineral density’ OR ‘bone density’ OR ‘bone health’ OR ‘bone marker’ OR ‘bone turnover’). This search gave 72 results, of which 27 articles were published since the previous review published in 2015. Of these 27 articles, nine articles were reviews, five articles were not about bone health in trans people, two articles were design papers, two studies were in transgender adolescents, one article was a perspective interview, one article was an animal study, and one article was a case report. This led to the inclusion of six articles with original data [19,20,21*,22,23**,24*]. Four studies described short-term effects of hormonal treatment [20,21*,22,24*], two studies described long-term effects of hormonal treatment [19,23**]. Two studies were performed in the Netherlands and included both trans women and trans men [23**,24*], one study was performed in the Netherlands and Belgium in both trans women and trans men [22], one study was performed in trans men in Poland [19], one study was performed in trans women in Brazil [21*], and one study was performed in trans women in Italy [20].

TRANS WOMEN

Before the start of hormonal treatment

Wiepjes et al. [23**] found that of 711 hormone-naive trans women, 22% had a low bone mass for age (Z-score < −2.0) at baseline, and the low median 25-hydroxy-vitamin D concentrations (42 nmol/l; 17 ng/ml) indicates a high prevalence of vitamin D deficiency (<50 nmol/l; 20 ng/ml). Fighera et al. [21*] included 142 trans women during the first 3 months of estrogen treatment and found that the BMD of the lumbar spine, total hip, and femoral neck in trans women was lower than cis (nongender) men. Eighteen percent of the trans women had low bone mass for age (Z-score < −2.0), compared with 0% of the cis men. Trans women had lower lean body mass than cis men. Lumbar spine BMD was associated with lean body mass in trans women. This might indicate that the high prevalence of low bone mass for age is related to the lower lean body mass.

These two new studies support the earlier findings of studies from Belgium [25] and Norway [26] that trans women have lower BMD, lower muscle mass, and more often vitamin D deficiency prior to hormonal treatment compared with cis men. Possibly, a less active lifestyle because of social isolation in trans women may explain these differences.

Short-term effects of hormonal treatment

Gava et al. [20] found no changes in BMD in 40 hormone-naive trans women during their first year of hormonal treatment, even as no changes in osteocalcin, bone-specific alkaline phosphatase, and
25-hydroxy-vitamin D concentrations. A small increase in parathyroid hormone was found in a subgroup of 20 trans women also using gonadotropin-releasing analogs, whereas this was not found in the subgroup of 20 trans women also using cyproterone acetate. Fighera et al. [21*] found that total body fat increased and lean body mass decreased in 46 trans women after 2.5 years of hormonal treatment, but BMD did not change. Wiepjes et al. [22] found small increases in lumbar spine, total hip, and femoral neck BMD in 231 trans women after their first year of hormonal treatment. These increases were positively associated with the mean estradiol concentrations during hormonal treatment. Trans women who also received vitamin D supplements apart from hormonal treatment had even larger increases in BMD. No differences in change in BMD were found for different age groups. Vlot et al. [24*] found that the bone turnover markers alkaline phosphatase, CTx, P1NP, and sclerostin decreased in 121 trans women during their first year of HT. In trans women with low estradiol concentrations (115 pmol/l), no or less change in bone turnover markers were observed. No differences in change in BTMs for different age groups were found. Changes in BTMs were weakly associated with change in BMD.

These studies are in line with previous studies in trans women describing a maintenance or increase in BMD [26–32] after short-term hormonal treatment. The effects of age and estradiol concentrations have not been studied before and are new findings of these studies. The association with estradiol concentrations indicates that hormone substitution should be adequate and therapy compliance should be stimulated.

Long-term effects of hormonal treatment

Wiepjes et al. [23**] described that lumbar spine BMD increased initially in 711 trans women after the start of hormonal treatment, but decreased thereafter. After 10 years of hormonal treatment, the BMD was similar to baseline. However, as the population also increased ten years in age and a control group was lacking, the Z-score was analyzed. This Z-score increased initially and stabilized thereafter, indicating that the decrease in BMD was because of the aging of the population. The change in BMD was associated with estradiol concentrations: larger increases in BMD were found in the middle and higher estradiol tertile (238 and 443 pmol/l, respectively), whereas BMD decreased in those with lower estradiol concentrations (mean 118 pmol/l). No associations were found between change in BMD and age, testosterone concentrations, or LH concentrations.

This study is the first long-term follow-up study investigating the change in BMD in trans women. An earlier long-term study was a cross-sectional study, in which trans women had lower BMD compared with cis men [33]. However, baseline differences were not taken into account in this study. The maintained BMD in trans women in the study of Wiepjes et al. [23**] indicates that the low BMD after long-term hormonal treatment was already present at baseline.

TRANS MEN

Before the start of hormonal treatment

Wiepjes et al. [23**] described that in 543 hormone-naive trans men the baseline Z-score was 0.0 and only 4% had a low bone mass for age (Z-score < −2.0). The finding that trans men, in contrast to trans women, do not have low BMD at baseline is in agreement with earlier baseline studies performed in trans men. These studies found that trans men had similar or slightly higher BMD than cis women, and similar muscle mass, physical activity, and 25-hydroxy vitamin D concentrations than cis women [4,26].

Short-term effects of hormonal treatment

Wiepjes et al. [22] found in 199 trans men small increases in lumbar spine and total hip BMD during their first year of hormonal treatment, and no changes in femoral neck BMD. These changes were not associated with estradiol or testosterone concentrations. However, age differences were found. In trans men ≥50 years of age, BMD increased more compared with trans men less than 50 years of age. These first mentioned trans men were postmenopausal at baseline and had low estradiol concentrations, whereas the younger trans men had higher estradiol concentrations. Because of the aromatization of testosterone into estradiol, not only the testosterone concentrations increased in the trans men ≥50 years, but also the estradiol concentrations. In the younger trans men, only testosterone concentrations increased, whereas no change in estradiol concentrations was observed. This finding indicates that the change in BMD in trans men is mainly the result of the change in estradiol concentrations instead of direct testosterone effects. This finding was also observed by Vlot et al. [24*] investigating the bone turnover markers in 132 trans men. In trans men less than 50 years, bone turnover markers increased, with relatively more increase in bone formation markers than bone resorption makers, whereas all studied bone turnover markers
decreased in trans men ≥50 years. This finding indicates that an increase in estradiol concentrations leads to a decrease in osteoclast activity, therefore inhibition of bone resorption and increase in BMD.

The findings that BMD remains stable or slightly increases in trans men are in line with earlier short-term studies [4, 26, 31, 34–36]. The finding that BMD increased more in the postmenopausal trans men is in line with a randomized study of Meriggiola et al. [36]. They found that BMD did not change in trans men using testosterone, but decreased in those who were treated with testosterone in combination with an aromatase inhibitor. This supports the finding that the bone-preserving effect of testosterone is mainly because of the aromatization into estradiol.

**Long-term effects of hormonal treatment**

Wiepjes et al. [23**] found that lumbar spine BMD did not change, but T-score increased during the first 10 years of hormonal treatment in 543 trans men. This change was not associated with estradiol or testosterone concentrations but was associated with LH concentrations. Trans men with suppressed LH concentrations (<1 U/l) showed an increase in BMD, whereas no change in BMD was observed in trans men with higher LH concentrations (>1 U/l). In addition, age was associated with change in BMD: older trans men showed a larger increase in BMD than younger trans men, as explained above.

Broulik et al. [19] investigated 35 trans men who were treated with testosterone for 18 years. They found that the T-score of the lumbar spine was similar to cis women, but T-score of the femoral neck was higher than cis women. Bone turnover markers were not different between trans men and cis women, but vitamin D concentrations were lower in trans men. As lumbar spine mainly consists of trabecular bone and the hip mainly consists of cortical bone, they conclude that testosterone treatment particularly affects cortical bone.

This last finding is in agreement with earlier long-term studies in trans men, which found that trans men have a larger cortical bone size or cortical thickness than cis women [37, 38]. This might be explained by the increased muscle mass following testosterone treatment, which could stimulate bone formation.

**DISCUSSION**

Although the Endocrine Society Guideline [1] advises to measure BMD only when risk factors exist, the clinical practice is sometimes different. In the gender identity clinics of Amsterdam, the Netherlands, and Ghent, Belgium, until recently a DXA was performed in every trans person at baseline and thereafter every two to five years. However, based on the results of the studies described in this review, DXA scans are no longer regularly performed. Currently, a DXA scan is only performed in trans women who are hormonal treatment compliant after gonadectomy or if other risk factors exist, such as low body mass index (BMI), long-term use of antiandrogens, the presence of osteoporosis in family members, social isolation, or the use of corticosteroids. In trans women without these risk factors, or in trans men, DXA scans are not standard performed. However, all trans people...
receive information about bone health and are advised to start with vitamin D supplementation, use dairy products, and remain or become physically active. In addition, more attention is paid to therapy compliance and adequate hormone substitution, based on the estradiol concentrations.

We acknowledge that the availability of a bone densitometer in both research centers influenced the frequency of these examinations. This gave us the opportunity, on the basis of our findings, to advise colleagues working in this field and transgender people. Knowledge in adolescent bone density changes is still quite limited and will definitely be a topic for future research.

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REFERENCES AND RECOMMENDED READING
Papers of particular interest, published within the annual period of review, have been highlighted as: • of special interest • of outstanding interest

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