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Skeletal considerations in the medical treatment of transgender people

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Recognition of the unique challenges and needs of transgender people is growing within the medical community and several guidelines regarding the care of these patients are available.[1] Beyond the acute care issues of hormonal and possible surgical interventions needed to achieve alignment with the individual's affirmed gender, there is now a growing recognition that long-term cross-sex hormone therapy might affect the risk of developing a number of chronic diseases, including cardiovascular disease[2] and osteoporosis.[3] In this Comment, we discuss the skeletal considerations in the care of transgender people in the context of our understanding of the physiology of sex steroid regulation of bone metabolism.

Since the seminal studies of Albright in the 1940s,[4] oestrogen has been recognised as the dominant sex steroid regulating bone metabolism in cisgender (cis) women. Although testosterone was generally assumed to have an analogous role in regulating the skeleton of cis men, a series of studies (summarised elsewhere[5]) of oestrogen receptor-α (ESR1) and aromatase (CYP19A1) deficient cis men, interventional studies in humans, and observational studies relating sex steroids to bone mineral density or fracture risk have now clearly established that, as in cis women, oestrogen is the dominant sex steroid regulating bone resorption and formation in cis males. For bone, testosterone is largely a prohormone, serving to provide the oestradiol needed via aromatisation to both consolidate the skeleton during growth and prevent bone loss in ageing. However, evolving evidence from bone cell (ie, osteoblast or osteoclast lineage) specific deletions of ESR1 or the androgen receptor (AR) has highlighted a potential independent role for androgens in regulating cancellous bone (ie, the spongy bone, as in the vertebrae) remodelling in cis men, with oestrogen likely mainly regulating cortical bone (ie, the compact bone, as in the long bones) remodelling.[5]

Figure A and B presents a working model of the effects of sex steroids on cancellous and cortical bone in cisgender people based on a synthesis of the existing mouse and human data.[5] This model will be useful in the subsequent discussion regarding the skeletal effects of cross-sex hormone therapy in transgender people and highlight gaps in existing knowledge. In cis women (figure A), at least before menopause, the high endogenous ovarian oestrogen concentration (mainly oestradiol, 15–350 pg/mL) inhibits excessive bone

resorption and helps to maintain bone formation in both cancellous and cortical bone. The role of the low androgen (mainly testosterone, 8–60 ng/dL) concentrations in regulating bone remodelling in females in either cancellous or cortical bone remains unclear, although evidence from AR knock-out mice indicates that androgens might have some effects on cancellous, but not cortical, bone remodelling in cis women.[6] By contrast, in cis men (figure B), the relatively low oestradiol concentration coming both from the testes and peripheral aromatisation of testosterone (a combined 10–40 pg/mL) are likely insufficient to fully prevent excessive bone remodelling and bone loss in cancellous bone, perhaps because cancellous bone also contains considerable amounts of oestrogen receptor β (ESR2), which serves to antagonise ESR1 action and thus make cancellous bone relatively resistant to oestrogen.[5] Cortical bone, which expresses little or no ESR2, might be much more sensitive to oestrogen, which appears to mainly target cortical bone in males.[5] By contrast, the existing mouse and human data is consistent with a substantial effect of testosterone at the concentration found in cis men (240–950 ng/dL), in the absence of aromatisation to oestrogen, in preventing loss of cancellous bone. In addition to this effect, testosterone likely has an important role in driving periosteal bone formation and the larger bone size in cis men achieved during puberty.[7] In this context, one can then make some predictions regarding the skeletal effects of cross-sex hormone therapy and compare these with the existing clinical data, with the caveat that virtually all of the studies to date have made use of dual energy x-ray absorptiometry, which cannot distinguish cancellous from cortical bone. Thus, in trans women the high exogenous oestradiol concentration should be sufficient to protect both cancellous and cortical bone (figure C), although it is possible that there might be some deficits in cancellous bone if no androgens are provided, as testosterone concentration are likely very low in these individuals because of gonadal suppression or orchiectomy. In trans men there should be sufficient exogenous testosterone to protect cancellous bone as well as aromatisation of testosterone to oestradiol to prevent cortical bone loss (figure D), although it is possible that some members of the population have poor aromatisation rates and therefore might not produce adequate amounts of oestradiol from testosterone resulting in deficits in cortical bone. These are individuals who, despite adequate testosterone replacement, would still have relatively low oestradiol concentration, with the definition of low still somewhat unclear, but likely in the range of 16 pg/mL or less using a mass spectroscopy assay. The effects of sex steroids are likely amplified during puberty, as sex steroids clearly regulate bone mass acquisition during this period. Importantly, fusion of the growth plate is dependent on oestrogen in both women and men.[8]

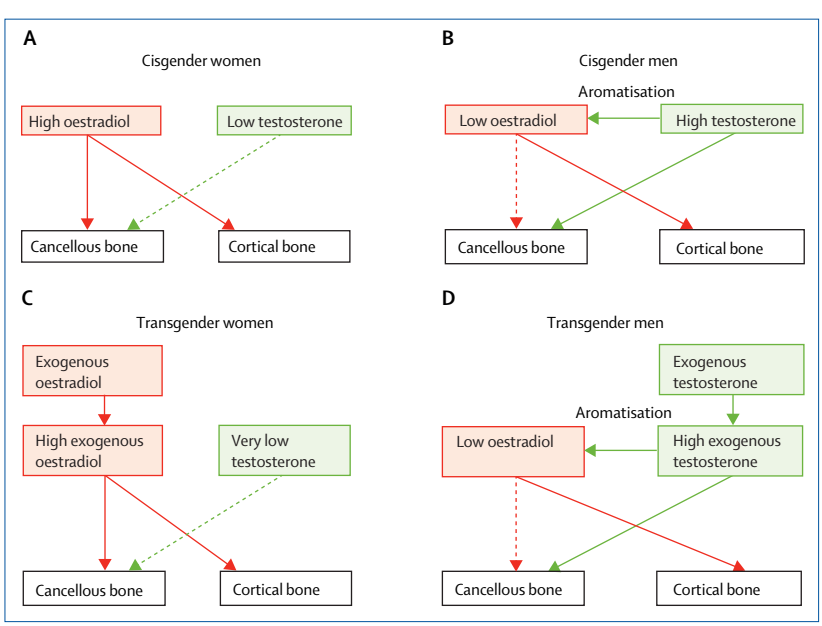

Figure: **Working model for sex steroid action on cancellous versus cortical bone in cis gender women (A) and cisgender men (B) and the analogous models in transgender women (C) and transgender men (D) placing the models in the context of exogenous hormone therapies. Red indicates oestrogen effects and green indicates testosterone effects, with dashed lines showing relatively small effects.**

This working model would predict that, assuming compliance with cross-sex hormone therapy, the skeleton should be relatively well protected in both trans women and trans men. This prediction appears to be generally true, at least in terms of bone mineral density by dual energy x-ray absorptiometry, with some caveats.[3] Thus, compared with cis men, trans women have lower bone mass and cortical size even before the initiation of hormone treatment, suggesting sex steroid-independent effects in these individuals.[3] Among causal factors, these individuals are more likely to have vitamin D deficiency and less likely to be involved in sport than cis men.[3] Second, although bone mineral density is generally preserved in both trans women and

trans men, data on fracture risk is sparse. In the largest fracture study to date, which included 2023 trans women (1089 aged <50 years and 934 aged ≥50 years) and 1036 trans men,[9] fracture risk was not increased in trans men compared with either the cis men or cis women, but tended to be increased in young (<50 years old) trans women compared with age-matched cis women (odds ratio (OR) 1·49, 95% CI 0·96–2·32) but not when compared with age-matched cis men. In trans women older than 50 years, fracture risk was similar to age-matched cis women, but was increased compared with age-matched cis men (OR 1·90, 1·32–2·74). Thus, if one limits the reference group to the affirmed gender, trans men did not have an increase in fracture risk compared with age-matched cis men, and young, but not older, trans women had an increase in fracture risk when compared with age-matched reference cis women. Whether this is related to the underlying skeletal deficits in trans women even before the initiation of hormone treatment noted earlier remains to be determined. However, the observation period for this fracture cohort was only 3 years.[9]

Although generally reassuring, several important research and clinical issues are unresolved regarding bone health in transgender people, and further studies are needed to address the knowledge gaps. First, additional data on fracture risk is needed, particularly longer-term fracture studies in larger cohorts of transgender people, likely requiring pooling of data from multiple sites, and perhaps involving a central registry not only including skeletal health but also other chronic diseases, such as cardiovascular disease. Second, given the model in figure, studies evaluating skeletal status in transgender people must include the use of techniques that can distinguish cancellous from cortical bone (eg, high resolution peripheral or standard resolution central quantitative CT) because deficits in specific bone compartments that might effect fracture risk might not be detected by dual energy x-ray absorptiometry. Third, additional longitudinal studies evaluating compartment specific changes in cancellous versus cortical bone in transgender versus cisgender people of varying ages are needed. Finally, given the concerns regarding long-term postmenopausal oestrogen therapy,[10] studies evaluating the known skeletal benefits versus non-skeletal (eg, cardiovascular disease and breast cancer) risks of continuing older trans women on relatively high doses of oestrogen treatment are needed.

In summary, our understanding of the physiology of sex steroid action on bone in cis women and cis men suggests that the skeleton should be relatively well protected, assuming adequate compliance with hormone therapy, in trans women and trans men, but areas of uncertainty remain. These areas require continued clinical vigilance and additional research about the maintenance of bone health in these individuals.

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