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REVIEW

Transgender health and the impact of aging and menopause

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ABSTRACT

Gender affirming hormone therapy (GAHT) is used by many transgender people to reduce gender incongruence and improve psychological functioning. As GAHT shares many similarities with menopausal hormone therapy, clinicians supporting people through menopause are ideally placed to manage GAHT. This narrative review provides an overview of transgender health and discusses long-term effects of GAHT to consider when managing transgender individuals across the lifespan. Menopause is less relevant for transgender individuals who take GAHT (often given lifelong) to achieve sex steroid concentrations generally in the range of the affirmed gender. For people using feminizing hormone therapy, there is an elevated risk of venous thromboembolism, myocardial infarction, stroke and osteoporosis relative to cisgender individuals. For trans people using masculinizing hormone therapy, there is an increased risk of polycythemia, probable higher risk of myocardial infarction and pelvic pain which is poorly understood. Proactive mitigation of cardiovascular risk factors is important for all transgender people and optimization of bone health is important for those using feminizing hormones. With a lack of research to guide GAHT in older age, a shared decision-making approach is recommended for the provision of GAHT to achieve individual goals whilst minimizing potential adverse effects.

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Introduction

Given that menopausal hormone therapy shares many similarities with gender affirming hormone therapy (GAHT), clinicians who support cisgender women through menopause are well placed to support transgender and gender diverse individuals. Transgender and gender diverse, or simply the umbrella term 'trans', refers to someone who has a gender different from that presumed for them at birth and includes binary (male or female) and non-binary (i.e. gender fluid, agender) identities. Population-based samples suggest approximately 0.5 – 3% of the general population are trans [1–6]. The visibility of trans people differs markedly across countries worldwide due to complex social and cultural factors, laws and availability of healthcare services for trans people.

There are many ways in which a trans person may affirm their gender; changing names, pronouns or gender expression, voice therapy, hair removal, using hormone therapy and/or surgery – all of which can significantly improve mental health, gender dysphoria and quality of life [7–11].

Research on the effects and adverse effects of GAHT is evolving and in its infancy. Much of our understanding of the effects and adverse effects of GAHT has been gained from well-characterized retrospective analyses and observational cohort studies from North America and Europe, often compared to population samples which will be summarized in this review. Long-term adverse effects are not definitive and become more relevant as individuals age and develop co-occurring medical conditions. This narrative review aims to provide an overview of transgender health with a focus on masculinizing and feminizing GAHT for clinicians experienced in menopausal hormone therapy and discuss implications of aging when managing trans adults across the lifespan.

Transgender health

Trans people as a whole face significant marginalization worldwide, including in health care. Difficulty accessing basic medical as well as gender affirming care are frequently reported [12]. Even when being able to access gender affirming care, there remains low-quality evidence to guide the medical treatment of trans people overall and health provider knowledge of trans health remains frequently suboptimal [13,14]. Healthcare avoidance because of fear of misgendering, discrimination and mistreatment is extremely

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common, which contributes to poor health. Moreover, the experience of widespread social stressors (social isolation, violence and hate crimes, unemployment) resulting in economic and legal marginalization leads to minority stress, in turn exacerbating poor physical and mental health outcomes [15–17].

It is not surprising that trans people have an elevated risk of many chronic health conditions compared to their cisgender counterparts, including chronic obstructive pulmonary disease, depression, hepatitis, HIV, schizophrenia, substance use disorders as well as obesity and other liver conditions [18,19]. More than 60% report a history of diagnosed depression or anxiety [20] and over 40% have attempted suicide [21–24]. Rates of death by suicide are more than two-fold greater than for cisgender populations [25] and significant disparities exist for all-cause mortality, especially among trans people presumed male at birth (with feminine or non-binary identities) and trans people of color [26–28]. The health inequity faced by trans people globally is a major public health concern.

In 2019, the World Health Organization in its International Classification of Diseases 11th Revision (ICD-11) redefined and reclassified 'Gender Incongruence' from the 'Mental Health' chapter into a newly established 'Sexual Health' chapter, reflecting modern understanding of gender identity [29]. Gender diversity is not a mental health condition, and reclassification sought to reduce stigma and aid access to gender affirming health care. 'Gender Incongruence of Adolescence and Adulthood' is defined as a marked and persistent incongruence between an individual's experienced gender and the assigned sex, which often leads to a desire to 'transition', in order to live and be accepted as a person of the experienced gender, through hormonal treatment, surgery or other healthcare services to make the individual's body align, as much as desired and to the extent possible, with the experienced gender [29].

Given the marked vulnerability of the trans community, many with experiences of trauma in healthcare settings, respectful and culturally sensitive health care which uses language tailored to what is most comfortable for the individual (including names and pronouns) is essential. A consultation for gender affirming care is often an opportunity to holistically address social, medical and mental healthcare needs.

Gender affirming hormone therapy

GAHT (masculinizing or feminizing) is desired by many (but not all) trans people to induce physical characteristics of a person's affirmed gender. Commencement of hormone therapy is typically a highly considered decision after balancing potential benefits on psychological functioning with potential medical and social risks [8,30]. GAHT can significantly improve mental health, gender dysphoria and quality of life [7,8,30].

Masculinizing hormone therapy

Trans people presumed female at birth who commence masculinizing hormone therapy will generally achieve serum testosterone concentrations in the typical cisgender male reference range [11,31]. Testosterone therapy is given in the same manner as that for hypogonadal cisgender men. This induces lowered voice, body and facial hair growth, as well as changes in body composition with increase in muscle mass and reduction in fat mass. Non-binary individuals may desire a more androgynous appearance and may use low-dose testosterone therapy for more gradual effects, often achieving testosterone concentrations above the cisgender female reference range but not necessarily in the cisgender male reference range [32]. Adverse effects of testosterone therapy include polycythemia, reduced high-density lipoprotein cholesterol, androgenic alopecia, acne, gynecological effects such as pelvic pain and genital dryness, and cardiovascular effects as discussed further in the following [33].

Feminizing hormone therapy

Trans people presumed male at birth who commence feminizing hormone therapy will generally achieve serum estradiol and testosterone concentrations in the cisgender female range [11,31]. This most often involves estradiol with antiandrogen agents such as cyproterone acetate, spironolactone or gonadotropin-releasing hormone analogues for people who do not undergo orchiectomy. Depending on the mechanism of action, peripheral androgen receptor antagonists such as spironolactone or bicalutamide may not necessarily lower the testosterone concentrations [34,35]. Feminizing hormone therapy induces breast growth, increases in fat mass and redistribution to a gynoid pattern, reduction in muscle mass, reduction in body and facial hair growth and reduction in sexual function. Some physical characteristics induced by male puberty do not change, such as lowered voice pitch and bone structure [11]. Adverse effects include an increased risk of venous thromboembolism (VTE), weight gain, compromised bone structure and cardiovascular disease (CVD) relative to cisgender women and men [33,36].

Aging and menopause

Aging trans adults have unique challenges. Fear of mistreatment in older care, isolation and loneliness exacerbated by trans identity, increased vulnerability to financial stressors, perceived lack of agency, and healthcare system and provider inclusivity are major concerns [37,38]. This is compounded by a need for increased healthcare provider interaction with the multiple chronic disease burden exacerbated with aging [19]. Alzheimer's disease and related dementia diseases may be more prevalent among trans people [39], but the impact of GAHT on cognitive functioning remains unclear [40].

The term menopause whereby oocyte production and menstruation ceases is framed around cisgender women and is relevant only for older trans people presumed female at birth who do not use GAHT. There has only been one study published examining trans women's experiences and beliefs about menopause [41]. Sixty-seven trans women of mean age 49 years expressed positive views about GAHT, including

treatment importance and personal and mental health benefits, but also concerns about long-term effects. Most expected to use GAHT indefinitely and 96% were taking GAHT at the time of the study. As such, trans women did not feel menopause was relevant [41]. No studies have been undertaken with trans people using testosterone therapy, but from a clinical perspective, many would continue therapy lifelong.

For trans people who take GAHT, whether it be testosterone or estradiol, there remain minimal data on how to manage GAHT with aging, whether there are higher risks with commencement in older age or whether the dose needs to be reduced over time. There is no age at which GAHT is absolutely contraindicated, and in fact, trans people who commence GAHT in older age report higher quality of life scores compared to younger individuals [42]. In trans people using testosterone therapy, there is a complete absence of data, so an individualized approach is needed. In trans people using feminizing hormone therapy, a retrospective chart review of 296 individuals compared estradiol formulations and serum estradiol concentrations in those aged $\geq$45 years ($n = 55$) and <45 years ($n = 241$) in Australia [43]. Despite recommendations for transdermal estradiol in individuals aged $\geq$45 years [44], oral estradiol was the predominant estradiol formulation used by 58% of those aged $\geq$45 years. However, the median oral estradiol valerate dose was lower (4 mg vs. 6 mg, $p = 0.01$), and a higher proportion of individuals aged $\geq$45 years used transdermal estradiol (31% vs. 8%, $p < 0.01$). There was no difference in serum estradiol concentration between groups (300 pmol/l vs. 328 pmol/l, $p = 0.22$). Notably, it is unclear whether the recommendations from the menopausal hormone therapy literature are applicable to trans individuals who are typically treated with higher oral and transdermal estradiol doses, and further research is needed.

Venous thromboembolism

VTE is a rare but serious side-effect of exogenous oral estrogens including oral contraceptives and menopausal hormone therapy [45]. Estradiol therapy used in GAHT is no exception. No elevated risk of VTE has been observed with masculinizing hormone therapy and, as such, this section will focus on the risk of VTE with feminizing hormones [33,36].

Two large cohort studies from the USA and the Netherlands comparing trans people to reference cisgender men and women in the general population have consistently demonstrated a two-fold to five-fold elevated risk of VTE in trans people using feminizing hormone therapy relative to reference populations [33,36]. Retrospective cohort studies report a 0–5% incidence of VTE during feminizing hormone therapy [46–48]. The largest cohort from the Netherlands of 816 individuals using oral (ethinyl estradiol) and transdermal estradiol followed for a total of 10,152 patient-years found that 0.4% had a VTE [47]. The highest risk of VTE appears to occur in the first year of treatment, in those aged >40 years, with ethinyl estradiol use, smoking and obesity [47,48]. Based on these studies, transdermal estradiol has been recommended for those with risk factors, and the use of oral ethinyl estradiol is no longer recommended [11,31]. However, trans people on feminizing hormone therapy have hypercoagulable global coagulation assays relative to cisgender men, but there was no difference between those on oral compared to transdermal estradiol [49]. Whilst this was a very small pilot study, the hypercoagulability seen with transdermal therapy is different to menopausal hormone therapy [50], potentially because of higher doses of transdermal estradiol used in GAHT (typically 100–200 μg/24 h estradiol patches) [48,49].

In trans people over the age of 40 years, an individualized shared decision-making approach to estradiol therapy is needed, taking into consideration comorbidities, medication adherence and, importantly, goals of care. Despite knowledge of an elevated risk of VTE, many trans people elect to use oral estradiol therapy due to an inability to tolerate transdermal therapy or for quality of life benefits [43].

In those who have had a VTE on GAHT, treatment with therapeutic anticoagulation should be based on current guidelines for cisgender individuals [51]. There are no specific data to guide treatment of VTE in trans people, nor are there data to guide cessation or continuation of estradiol during an acute VTE event.

Similarly, there are minimal data to guide the perioperative use of feminizing hormone therapy. A single-center retrospective review of 407 trans people having vaginoplasty found no VTE events in those who continued estradiol therapy, with a mean postoperative follow-up of 285 days [52]. Previous reviews have not found any evidence to support or refute routine discontinuation of estradiol therapy prior to surgery (which may carry negative psychological consequences) [53–55]. The physical and mental health benefits of estradiol therapy may outweigh the risk of VTE [56]. Overall, treatment decisions for the formulation, dose, duration and route of hormone therapy should be individualized.

Cardiovascular disease

Many early studies described a higher risk of cardiovascular morbidity and mortality in trans women, but many earlier studies utilized ethinyl estradiol which is no longer used as GAHT [48,57–60]. More recently, larger cohort studies and registry studies with population-based comparison groups have been more informative, but not all are entirely consistent.

One of the largest studies reviewed medical records of all 6793 trans individuals attending the Amsterdam Gender Clinic over a 43-year period [33]. It was found that trans women had an elevated incidence of stroke and myocardial infarction relative to cisgender women, and an elevated incidence of stroke relative to cisgender men. Trans men had an elevated risk of myocardial infarction relative to cisgender women but not cisgender men [33]. Findings were almost entirely consistent with Getahun et al.'s analysis of US Kaiser Permanente's electronic medical record data which found that trans women had an elevated risk of ischemic stroke (adjusted hazard ratio 1.9; 95% confidence interval [CI] 1.3–2.6) and myocardial infarction (adjusted hazard ratio 1.8; 95%

CI 1.1–2.9) relative to cisgender women but not cisgender men [36]. For trans men, the evidence was insufficient to draw conclusions about cardiovascular events [36]. These retrospective chart reviews were limited in not being able to completely account for potential confounders such as smoking, HIV status or minority stress.

In an attempt to control for potential confounding cardiovascular risk factors, two separate analyses of the Behavioral Risk Factor Surveillance System data from 2014 to 2017 were used to evaluate the odds of being trans and myocardial infarction [61,62]. Multivariable analyses adjusted for CVD risk factors including age, diabetes mellitus, hypertension, hypercholesterolemia, chronic kidney disease, smoking and exercise. Trans women had a more than two-fold increase in the rate of myocardial infarction compared with cisgender women (odds ratio, 2.56; 95% CI 1.78–3.68; $p < 0.01$) but not compared with cisgender men [61]. Trans women also had a higher rate of angina/coronary heart disease (adjusted odds ratio 1.90, 95% CI 1.34–2.68) and stroke (adjusted odds ratio 1.88, 95% CI 1.16–3.03) relative to cisgender women and any CVD than cisgender men (adjusted odds ratio 1.38, 95% CI 1.01–1.88) [62].

Data on trans men remain conflicting, with no elevated risk of myocardial infarction or CVD reported in some studies [36,62], but an elevated risk of myocardial infarction relative to cisgender women but not cisgender men in others [33] Alzahrani et al. showed an increased rate of myocardial infarction relative to both cisgender men and women of more than two-fold [61].

Two national registry studies from Sweden and Denmark have attempted to analyze the mediating effect of GAHT on CVD [63,64]. Due to the young age of included participants, both studies used very broad definitions of CVD which included conduction disorders. Both studies demonstrated an elevated risk of CVD in trans men and in trans women relative to cisgender counterparts. Testosterone therapy in trans men was shown to explain part of the elevated risk of CVD [63]. In contrast, Karalexi et al. found similar results whether trans people were on GAHT or not on GAHT, suggesting that CVD risk is mediated by factors unrelated to hormonal therapy [64].

Mechanistically, several studies have tried to explain the potential increased CVD risk in trans women. In cisgender men, elevated estradiol concentrations and testosterone deprivation have been shown to be associated with elevated CVD risk [65–68]. In trans women, increased body fat and insulin resistance, compromised endothelial function [69], altered biomarkers such as advanced glycation end products associated with systemic inflammation and CVD [70] as well as platelet activation and increased concentrations of coagulation markers and inflammation markers [71] may all potentially contribute. In trans men, several studies have shown unfavorable lipid changes with increased total cholesterol, triglycerides and low-density lipoprotein and decreased high-density lipoprotein [72–74] as well as increased high-sensitivity C-reactive protein [71]. Moreover, hematocrit rises with testosterone therapy [75], and it is unclear if higher hematocrit, which is associated with venous and arterial thrombosis risk and long-term mortality in the general population, may account for increased CVD risk in trans men [76–79]. Higher intima-media thickness in the carotid artery has also been observed in trans men [73]. Increasing research has revealed that cardiovascular risk factors at the individual level do not fully account for the increased cardiovascular risk, and minority stress itself is associated with higher odds of CVD and behaviors such as smoking, poor sleep and inadequate nutrition [80,81].

Screening for cardiometabolic derangements and risk reduction are important for all aging individuals but even more so for both trans women and men across the lifespan.

Bone health

Given the importance of sex steroid concentrations in bone remodeling, bone health is an area of concern for aging trans individuals. Only one nationwide cohort study of >3000 trans people has examined fractures (obtained from emergency department visit data) compared to reference men and women [82]. Fracture risk was higher in older trans women (occurring in 4.4%) compared to age-matched reference men (odds ratio 1.90, 95% CI 1.32–2.74) but not to reference cisgender women. Fracture risk was lower in trans men compared to reference cisgender men (odds ratio 0.57, 95% CI 0.35–0.94) but the numbers of fractures were small ($n = 18$) [82]. Fracture type and lifestyle risk factors were not available.

Consistent with the fracture data are cross-sectional bone microarchitecture data measured by high-resolution peripheral quantitative computed tomography, an imaging modality which predicts fracture risk better than standard dual X-ray absorptiometry [83]. Trans women on feminizing hormone therapy for a median of 39 months had compromised bone microarchitecture relative to cisgender men with lower total volumetric bone mineral density (BMD), higher cortical porosity, lower trabecular density and number as well as greater trabecular separation. Trans men conversely had preserved bone microarchitecture with higher total volumetric BMD, and higher trabecular thickness compared to cisgender women [83].

Compromised bone density appears inherent even prior to commencement of GAHT. Trans women have lower areal BMD at baseline relative to cisgender men. In addition, lower hand grip strength, lower forearm muscle area and lower 25-hydroxyvitamin D concentrations suggest that lower areal BMD may be related to lifestyle factors such as less physical activity or social isolation [84].

Estradiol concentrations achieved with GAHT are also important. Trans women with low estradiol (<182 pmol/l) have significant reductions in areal BMD over time [85] and increased bone remodeling markers [86]. In trans men who started GAHT aged <50 years, bone remodeling markers increased, but in those aged >50 years (presumed postmenopausal) bone remodeling markers decreased over the first 12 months of testosterone therapy [86].

Concerns regarding compromised bone microstructure and fracture risk appear to be relevant for trans women only and lifestyle factors may reduce attainment of peak bone mass [84]. In young trans people, the role of routine measurement of BMD is not clear. However, all trans women

should be encouraged to optimize their bone health through engaging in regular weight-bearing exercise, smoking cessation, optimization of vitamin D levels and ensuring adequate dosing of GAHT to achieve estradiol concentrations >182 pmol/l.

Pelvic pain with testosterone use

Masculinizing hormone therapy induces significant genital and reproductive system changes, including menstrual cessation, clitoral enlargement, vulvovaginal atrophy and increase in libido [30]. Trans people using testosterone also frequently report pelvic pain, which is most often described as cramping in nature, and occurring in the suprapubic region or less occasionally the right and left iliac regions [87–89]. The cause of this pelvic pain is poorly understood.

While menstrual cessation typically occurs within the first 6 months of masculinizing therapy [90], breakthrough bleeding is not uncommon, and some may experience persistent menstruation [91]. Persistent menstruation along with pain with orgasm are both associated with an increased likelihood of pelvic pain [87]. The association between pelvic pain and pain with orgasm also indicates the possibility of bladder neck contractions, uterine neuro-inflammation, uterine contractions and/or pelvic floor musculature dystonia [92,93]. The pelvic floor muscles are enriched with androgen receptors and exquisitely androgen-sensitive, with androgens causing anabolic effects on pelvic floor muscles [94]. It is therefore plausible that masculinizing hormones may affect the pelvic floor and perineal muscles, and it is hypothesized that pelvic floor muscle dysfunction may contribute to pelvic pain.

Many trans people seek hysterectomy and/or oophorectomy but effects on pelvic pain are inconsistent, with some small studies reporting improvements and little to no change in pelvic pain [87,95].

Without a clear understanding of the causes of pelvic pain in people using masculinizing hormones, a multidisciplinary biopsychosocial approach is required. This may include simple analgesia with paracetamol and non-steroidal anti-inflammatory drugs and pelvic floor physical therapy with release of myofascial trigger points which has been used in cisgender individuals [96]. There also appears to be a link between pelvic pain and current or previous post-traumatic stress disorder diagnosis [87], highlighting the need for trauma-informed approaches to address possible psychological factors [97].

Summary

Provision of safe, affirming healthcare environments is essential to reduce health disparity and optimize health outcomes for trans people. GAHT has significant mental health, physical health and quality of life benefits regardless of age at commencement and is often continued lifelong. With aging, the mitigation of cardiovascular risk factors is important for all individuals, and optimization of bone health through ensuring adequate vitamin D levels, dietary calcium intake and regular weight bearing exercise is additionally important for trans people on feminizing hormone therapy. Given a lack of research on the management of GAHT with aging, a shared decision-making approach is recommended to ensure individual goals are attained whilst minimizing potential medical risks.

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