Metabolism Open 13 (2022) 100173

Contents lists available at ScienceDirect

Metabolism Open

journal homepage: www.sciencedirect.com/journal/metabolism-open

The effects of gender-affirming hormone therapy on cardiovascular and skeletal health: A literature review

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ARTICLE INFO

Keywords:
Transgender
Gender-affirming hormone therapy
Cardiometabolic
Bone mineral density
Trabecular bone score

ABSTRACT

Approximately 1.5 million people in the United States currently identify as transgender. The use of gender affirming hormone therapy is integral to routine clinical care of transgender individuals, yet our understanding of the effects of this therapy is limited. There are reasons to believe that gender affirming hormone therapy may have important effects on cardiovascular risk and bone health in transgender individuals. The purpose of this review article is to summarize the evidence for the cardiovascular effects (including coronary artery disease, hypertension and stroke) as well as the effects on bone metabolism associated with gender affirming hormone therapy in both transgender men and transgender women.

1. Introduction

Approximately 1.5 million adults in the United States (0.6% of the population in 2016) identify as transgender, with 99.5% of these individuals younger than 65 years [1]. Transgender persons are a diverse group whose gender identity differs from the sex assigned at birth [2]. Some transgender persons undergo medical treatment which includes gender-affirming hormone therapy (GAHT) and/or surgery to align their physical characteristics with their gender identity and to alleviate gender dysphoria. GAHT is provided in order to induce feminizing or masculinizing changes [2].

The prevalence of transgender population in the United States has been increasing. This is likely due to the fact that transgender individuals are now more likely to identify as such in demographics surveys [3]. Understanding the terminology used to describe transgender individuals (Table 1) and the commonly used hormone therapies (Table 2) is essential to improve care for this population. Awareness of the potential side effects of GAHT is needed to make informed decisions and to individualize GAHT. This article reviews the available evidence regarding the effects of GAHT on the cardiovascular and skeletal health in the transgender population.

1.1. Research methodology

We searched online electronic databases (Embase, Medline Cochrane Library, Google Scholar and Pubmed) to identify all relevant studies from 1990 until 2022. We used keywords such as "transgender", "gender", "gender dysphoria", "cisgender", "sex assigned at birth", "natal sex", "gender affirming therapy", "gender affirming surgery", "cardiovascular", "cardiovascular disease", "myocardial infarction", "stroke", "cerebrovascular disease", "cardiometabolic", "diabetes", "lipid", "cholesterol", "dyslipidemia", "body fat", "visceral fat",

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https://doi.org/10.1016/j.metop.2022.100173
Received 13 January 2022; Received in revised form 23 February 2022; Accepted 1 March 2022
Available online 3 March 2022
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Table 1
Definitions of terms [2,53].

Terms	Definition
Sex	Sex is assigned at birth as male or female, usually based on the appearance of the external genitalia
Gender identity	A person's intrinsic sense of being male, female or an alternative gender (e.g., boygirl, girlboy, transgender, genderqueer)
Gender dysphoria	Distress that is caused by a discrepancy between a person's gender identity and sex assigned at birth
Transgender man	Individual assigned female at birth who identifies as male
Transgender woman	Individual assigned male at birth who identifies as female
Gender-affirming hormone therapy (GAHT)	Hormonal therapy aiming to align the physical characteristics of an individual with their gender identity
Gender-affirming surgery	Surgery to change primary and/or secondary sex characteristics to affirm a person's gender identity

Table 2
Gender-affirming hormone therapy (GAHT) used in transgender persons [32,42].

Transgender Women		Dose
Estrogen	Micronized estradiol, oral	2–4 mg/day
	Estradiol valerate, oral	2–4 mg/day
	17 β-Estradiol transdermal patch, TD	100–200 μg/day
	Estradiol valerate, IM	5–20 mg/2 weeks
	Estradiol cypionate, IM	3 mg/month
Anti-androgens	Spironolactone, oral	100–400 mg/day
	Flutamide, oral	250–500 mg/day
	Bicalutamide, oral	25–50 mg/day
	Enzalutamide, oral	160 mg/day
5α-reductase inhibitor	Finasteride, oral	5 mg/day
	Dutasteride, oral	0.5 mg/day
Progesterone	Cyproterone acetate, oral*	25–100 mg/day
	Medroxyprogesterone, oral	10 mg/day
GnRH agonist	Leuprolide, IM	3.75 mg/4 weeks
	Triptorelin, IM or SC	3.75 mg/4 weeks
	Goserelin, SC	3.8 mg/4 weeks
	Buserelin, SC or intranasal	200–1200 μg/day
	Histrelin, SC	50 μg/day
Transgender Men		**Dose**
Androgen	Testosterone enanthate, IM or SC	250 mg/4 weeks
	Testosterone cypionate, IM or SC	200 mg/4 weeks
	Testosterone undecanoate, IM	1000 mg/12 weeks
	Testosterone gel, TD	5 g/day
	Testosterone transdermal patch, TD	5 mg/day
	Crystalline Testosterone (testosterone pellets; SC depot)	600 mg/4–6 months
	Testosterone undecanoate, oral	80–160 mg/day

Abbreviations: GnRH, Gonadotropin releasing hormone, IM, intramuscularly; SC, subcutaneously; TD, transdermal.
*Not available in the US, Cyproterone acetate is also an anti-androgen.
In transgender women, estrogen is often used together with either anti-androgen or GnRH analog.

"pulmonary embolism", "venous thromboembolism", "bone mineral density", "bone health" in order to screen studies that included gender affirming therapy effects on our desired outcome.

Retrospective studies, prospective studies, observational studies, systematic reviews, meta-analyses and randomized trials were all included when applicable.

A total of 150 articles were screened. 53 articles were retained based on the outcomes related to our review.

2. Cardiovascular health

2.1. Transgender women

2.1.1. Ischemic heart disease

Two early observational studies reported that the crude incidence of myocardial infarction and mortality related to myocardial infarction in transgender women receiving GAHT were not different from sex assigned at birth men [4,5]. Nokoff et al. analyzed the data from a 2015 behavioral risk factor surveillance survey (BRFSS) and found that transgender women on GAHT had a higher risk of myocardial infarction than sex assigned at birth women (OR 2.9; 95% CI 1.6–5.3) but this risk was not higher than in sex assigned at birth men (OR 1.09; 95% CI 0.59–2.03) [6]. Similar results were found by Getahun et al. in a retrospective cohort study of 2842 transgender women (mean study duration: 4 years): transgender women receiving GAHT had higher risk of ischemic heart disease than sex assigned at birth women (HR 1.9; 95% CI 1.3–2.6) but the risk was not different from that of sex assigned at birth men [7].

A case control study showed a higher prevalence of myocardial infarction in transgender women who had received GAHT for an average of 7.7 years compared with sex assigned at birth women (18.7/1000 cases vs. 0; P = 0.001), with the prevalence of myocardial infarction similar to sex assigned at birth men [8]. The incidence of myocardial infarction in transgender women on GAHT was similarly higher than in sex assigned at birth women (SIR 2.64 [95% CI 1.81–3.72]) and similar to sex assigned at birth men in a retrospective cohort [9].

Transgender women were found to have higher mortality rate due to ischemic heart disease than adjusted expected mortality of the general population (SMR 1.64; 95% CI: 1.43–1.87) in a retrospective cohort study. Transgender women treated with ethinyl estradiol had a particularly high event rate with a 3-fold increased risk of cardiovascular mortality compared with former users or never-users (HR 3.12; 95% CI 1.28–7.63) [10].

Overall, the available data indicate that transgender women on GAHT are at a higher risk of ischemic heart disease (including myocardial infarction) compared with sex assigned at birth women, however transgender women appear to have similar cardiovascular risk when compared to sex assigned at birth men.

2.1.2. Cerebrovascular disease

The incidence of cerebrovascular disease in transgender women receiving GAHT was found to be similar to sex assigned at birth men [4] and to the general population [5] in two early retrospective observational studies. In a retrospective cohort study of 966 transgender women receiving GAHT, the mortality related to cerebrovascular disease in transgender women was not statistically different from the general population [10].

In a case-control study of 214 transgender women on GAHT, the prevalence of ischemic stroke in transgender women was however higher than that in sex assigned at birth men (23.4/1000 cases vs. 9.4/1000 cases; P = 0.03), but similar to sex assigned at birth women [8].

In contrast, a subsequent retrospective cohort study (n = 2842) found that the risk of ischemic stroke in transgender women receiving GAHT was higher than that in sex assigned at birth women (HR 1.9; 95% CI 1.4–2.7) but similar to that of sex assigned at birth men (median follow up: 4 years) [7]. In the subgroup analysis, transgender women who had received GAHT for longer than 6 years (n = 853) had higher risk of ischemic stroke than both sex assigned at birth men (HR 9.9; 95% CI 3.0–33.1) and sex assigned at birth women (HR 4.1; 95% CI 1.5–11.4) indicating increased risk of stroke with prolonged exposure to hormone therapy [7]. A similar higher risk of ischemic stroke in transgender women on GAHT compared with both sex assigned at birth men (SIR 1.80 [95% CI 1.23–2.56]) and sex assigned at birth women (SIR 2.42 [95% 1.65–3.42]) was shown in another retrospective cohort of 2517 patients [9].

Overall, the available data for cerebrovascular disease are equivocal. However there seems to be an increased long-term risk of ischemic stroke in transgender women on GAHT compared to both sex assigned at birth men and women.

2.1.3. Cardiometabolic risk factors

A meta-analysis of 29 studies, which included 3231 transgender women, showed no significant differences in total cholesterol (TC), LDL-C, HDL-C or triglyceride levels (TG) in transgender women receiving GAHT at 3–6 months, 12 months or $\geq$ 24 months compared to baseline [11]. Serum TG level was higher than baseline after 24 months of GAHT [11]. A prospective cohort study of 30 transgender women found no significant changes in lipid profiles after 6 months of estrogen therapy compared with baseline [12].

In contrast, a prospective observational study showed that GAHT in transgender women was associated with deleterious alteration in lipid prolife: TC, TG, LDL-C increased and HDL-C decreased after 1 year and 2 years of GAHT compared with baseline [13]. The study also demonstrated alteration in glyco-insulinemic profile in transgender women with homeostatic model assessment-insulin resistance index (HOMA-IR index) of 6.57 (SD 2.69) after 2 years of GAHT compared with baseline HOMA-IR index of 3.63 (SD 0.77) [13]. A higher prevalence of diabetes was observed in transgender women receiving estrogen compared with both sex assigned at birth men and sex assigned at birth women in a case-control study [8]. While data regarding insulin resistance in transgender patients are limited, a recent systematic review of 26 studies showed that in transgender women feminizing hormone therapy (estradiol, with or without anti-androgen agents) decreases lean mass, increases fat mass, and may worsen insulin resistance. However, the data on insulin resistance are not as consistent due to paucity of randomized prospective research, small cohorts and short follow up periods. More data are needed for better and more consistent results [14]. In a recent prospective study, the cardiometabolic profile of 179 transgender women on GAHT was evaluated at 1 year. The authors found that total body fat had increased without a change in visceral fat. These changes were not associated with a change in the lipid profile or HOMA-IR index [15].

Conflicting effects of GAHT on the lipid profile of transgender women were observed in some studies. LDL-C decreased (−12%), HDL-C increased (+24%) while TG increased (+86%) and TC remained unchanged after one year of GAHT compared with baseline in an observational study of 20 transgender women (mean age 26 $\pm$ 6)[16]. Reductions in TC, LDL-C, TG, HDL-C were observed after one year of GAHT compared with baseline in a prospective cohort study of 53 transgender women [17]. A similar pattern compared to baseline was seen in another cohort study of 242 transgender women after one year of GAHT [18].

In summary, the existing literature related to dyslipidemia and cardiometabolic profiles in transgender women is mixed and it is difficult to draw conclusions about any consistent effects of estrogen therapy on lipid profile in transgender women. While data on total cholesterol, LDL-C and insulin resistance are equivocal, there seems to be consistent evidence for the increase in TG levels and total body fat.

2.1.4. Blood pressure

The incidence of hypertension (defined then as BP > 160/90 mmHg) in transgender women receiving GAHT was shown to be similar to sex assigned at birth men (crude incidence 14 [95% CI 7.8–23.1] vs. 18.708) in a study reported in 1989 [4]. A small prospective observational study in 1993 found significantly decreased level of endothelin in transgender women after 4 months of GAHT [19]. The effect of lower endothelin level on blood pressure, however, remains unclear. Modest reduction of blood pressure was seen in transgender women receiving GAHT in multiple observational studies lasting 6 months to one year [17,18,20]. The subjects in these studies were taking various formulations of GAHT including oral estradiol valerate and transdermal estradiol.

In contrast, an observational study of 79 transgender women showed an increase in blood pressure (both systolic and diastolic) after 1 year and 2 years of GAHT compared with baseline [13]. A similar increase in blood pressure was seen in another prospective observational study of 20 transgender women [16].

In summary, evidence for the effects of GAHT on BP in transgender women remains scarce and equivocal making it difficult to draw definite conclusions.

2.1.5. Venous thromboembolism

Two early observational studies showed increased risk of VTE and pulmonary embolism in transgender women: one study showed a 45-fold increase in risk compared to sex assigned at birth men (crude incidence 19 [95% CI 11.7–29.4] vs. 0.42) [4] while another showed a 20-fold increase in risk compared to general population (SIR 19.56 [95% CI 12.27–26.18])[5]; all cases of VTE occurred in patients using oral ethinyl estradiol except for one patient using transdermal 17 β-estradiol in the latter study.

Similarly, a retrospective cohort study of 2842 transgender women found higher risk of VTE in transgender women receiving GAHT compared to sex assigned at birth men (HR 1.9 [95% CI 1.4–2.7]) and sex assigned at birth women (HR 2.0; 95% CI 1.4–2.8) with the highest risk seen with longer exposure to hormone therapy [7]. In a recently published retrospective observational study of 6793 transgender persons, higher incidence of VTE was seen in transgender women receiving GAHT compared with both sex assigned at birth men (SIR 4.55 [95% CI 3.59–5.69]) and sex assigned at birth women (SIR 5.52 [95% CI 4.36–6.90]) [9].

In contrast to the studies described above, no cases of VTE were detected in a retrospective cohort study of 162 transgender women who received GAHT for a mean duration of 4.4 years. Of note, all the subjects in this study received transdermal 17β-estradiol along with cyproterone acetate and finasteride rather than oral estrogen, suggesting that the increased risk of VTE with estrogen therapy applies to oral formulations [21].

In regards to progesterone in transfeminine care, it is not currently recommended by clinical guidelines for routine GAHT. This is mostly due to lack of efficacy and safety data. However, there are increasing data in favor of the use of progesterone and its derivatives in transgender women for feminization, bone health and mood disorders. Data regarding cardiovascular safety remain scarce [22,23].

In summary, the data for VTE in transgender women are consistent and show an increased risk of VTE and pulmonary embolism in transgender women compared to both sex assigned at birth men and women.

2.2. Transgender men

2.2.1. Ischemic heart disease and cerebrovascular disease

A retrospective observational study of 293 transgender men taking GAHT in the Netherlands found a similar incidence of myocardial infarction between transgender men and the general Dutch population over 2418 patient-years (SIR 0.34 [0.01–1.92]) [5]. Multiple observational studies have not found an increased risk of myocardial infarction or increased mortality related to myocardial infarction in transgender men receiving GAHT compared with sex assigned at birth men or sex assigned at birth women [6–8,10]. Similarly, a cohort study that followed 50 transgender men receiving testosterone (mean age 37 $\pm$ 8.2 years) for an average of 10 years (range 2–35 years) did not report any cases of myocardial infarction [24].

One cross-sectional study using population-based data (BRFSS data from 2014 to 2017) found that transgender men had a >4-fold and 2-fold increased risk of myocardial infarction compared with sex assigned at birth women (OR 4.90 [95% CI 2.21–10.90], P < 0.01) and sex assigned at birth men (OR 2.53 [95% CI 1.14–5.63], P 0.02) [25]. Information regarding specific hormone therapy was not provided in this study making it difficult to assess the factors related to this increased

risk [25]. The risk and prevalence of ischemic stroke in transgender men on GAHT were also shown to be similar to those of sex assigned at birth men and sex assigned at birth women [7,8,10].

In summary, while data are scarce and not consistent, there seems to be no increased risk of cardiovascular disease, myocardial infarction or stroke in transgender men on hormone therapy.

2.2.2. Cardiometabolic risk factors

Deleterious changes in lipid profile were observed in two prospective cohorts: TC, LDL-C and TG increased and HDL-C decreased in transgender men after one year of GAHT compared with baseline values [17,18]. A similar pattern of changes in lipid profile was seen in transgender men in another prospective cohort study after two years of GAHT compared with baseline [13].

This unfavorable trend in lipid profile in transgender men was supported by a meta-analysis of 29 studies, which included 1500 transgender men. The authors concluded that LDL-C and TG increased and HDL-C decreased significantly while TC remained unchanged after 2 years of GAHT compared with baseline, with mixed results seen before 2 years of GAHT, indicating that longer duration of GAHT is associated with undesirable effects on lipid profile [11].

Unfavorable changes in lipid profile in transgender men receiving GAHT were fairly consistent in multiple studies despite some mixed results: a cross-sectional study of 111 transgender men showed that transgender men treated with testosterone had higher TC, TG and lower HDL-C compared with transgender men not treated with testosterone [26]; two additional prospective observational studies showed that TG increased and HDL-C decreased in transgender men after one year [16] and two years [27] of GAHT compared to baseline while TC and LDL-C remained unchanged. Another prospective study reported decreased HDL-C in transgender men after one year of GAHT with other lipid parameters unchanged [28].

The data on the risk for diabetes mellitus in transgender men are mixed. A case-control study showed increased prevalence of diabetes in transgender men receiving GAHT compared with sex assigned at birth women but it was not different from sex assigned at birth men [8]. Conversely, HOMA-IR in transgender men was not different from baseline after one year and two years of GAHT in a prospective observational study [13]. HbA1c was similar in transgender men treated with GAHT and those not treated with GAHT in a cross-sectional study [26]. In a recent prospective study, the cardiometabolic factors of 162 transgender men was evaluated before and after 1 year of GAHT. The authors found that total body fat decreased without changes in visceral fat. Those changes were not related to changes in blood lipids or HOMA-IR index [15]. The investigators concluded that cardiometabolic effects of GAHT are not related to changes in visceral fat and total body fat.

In summary, GAHT seems to increase LDL-C, TGL and decease HDL-C in transgender men. Some studies indicate that these changes are more pronounced after 2 years of therapy.

2.2.3. Blood pressure

Two observational studies published in 1989 and 1997 did not find an increased incidence of hypertension (defined then as blood pressure >160/95 mmHg and >160/90 mmHg) respectively in transgender men receiving GAHT compared with the general population [4,5]. Chandra et al. also found no changes in mean arterial blood pressure in a prospective cohort study of 12 transgender men after one year of GAHT [28]. Giltay et al. demonstrated a slightly decreased blood pressure in transgender men after 3–4 months of GAHT in an observational study [29].

In contrast, a cross-sectional study of 111 transgender men (48 on IM testosterone esters and 63 not on any hormone therapy) showed that transgender men treated with androgens had significantly higher blood pressure (systolic, diastolic, and mean arterial pressure) than those who were not treated over mean study duration of 45 ± 38.1 months [26]. A variable increase in systolic blood pressure (+4.1–13.4 mmHg) was seen in transgender men after receiving GAHT for 1–2 years compared with baseline across observational studies ranging in sample size from 43 to 50 individuals [13,17,27].

In summary, data on blood pressure in changes in transgender men on GAHT remain controversial and it is thus difficult to draw definite conclusions without better data. Table 3 summarizes the effect of GAHT on the cardiovascular risk and different cardiometabolic parameters in transgender men and women.

3. Skeletal health

Bone strength, which determines fracture risk, reflects the integration of bone density and bone quality. Dual energy X-ray absorptiometry (DXA), a noninvasive measurement of bone density, is the current standard of care to diagnose osteoporosis and to assess fracture risk [30]. Bone quality assessment involves macro- and microarchitectural characteristics of bone tissue and can be conducted invasively (using a bone biopsy), or noninvasively (using a program to measure the trabecular bone score, a marker of variation obtained from the lumbar spine bone density image).

Sex steroids are major determinants of bone homeostasis. Estrogen plays a significant role in bone remodeling [31]. A deficiency in estrogen is associated with increased bone resorption, increased bone loss, and increased fracture risk in the general population. Testosterone plays an important role in bone gain and maintenance in sex assigned at birth men, and testosterone deficiency is associated with increased bone resorption, bone loss, and fracture risk.

There are currently no estimates on the prevalence of osteoporosis or low bone mass in transgender persons. Screening for osteoporosis in transgender individuals should be performed with DXA similar to the general population according to the Endocrine Society Clinical Practice Guidelines [32]. Risk factors to be assessed to determine the need for DXA screening include age, medical conditions and or medications that increase the risk of osteoporosis [33]. The T-score represents the number of standard deviations above or below the average bone density of a young healthy Caucasian sex assigned at birth woman. The T-score establishes fracture risk and the need for further treatment and lifestyle modifications.

A recent study evaluating BMD in pre-pubertal transgender youth showed decreased BMD in the transgender group compared to their sex assigned at birth counterparts, suggesting the need for BMD surveillance at an even earlier stage [34].

There are limited data on the long-term risks of GAHT on skeletal health. Most of the studies in transgender individuals have been cross-sectional or retrospective, with very few prospective or longitudinal

Table 3
The effect of GAHT on the cardiovascular health in transgender women and men.

Conditions	Effects of GAHT	
	Transgender Women	Transgender Men
Ischemic heart disease	↑↔	↔
Cerebrovascular disease	↑	↔
Blood pressure	∴	↑↔
Venous thromboembolism	↑	↔
Total cholesterol	↓↔	↑↔
HDL-C	↓↔	↓
LDL-C	↓↔	↑↔
Triglycerides	∴	↑↔
Diabetes	↔	↔

Abbreviation: LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol.
↑ denotes a significant increase.
↓ denotes a significant decrease.
↔ denotes no significant change.
∴denotes inconclusive results.
Table format adapted from Connelly PJ et al. Hypertension.2019 [53].

studies and data prior to 2019 were summarized in 2 large meta-analyses. Below we provide a review of those two meta-analyses.

A systematic review and meta-analysis [35,36]of the effects of gender affirming hormone therapy on bone mass in transgender individuals were performed in 2017 [35] and later updated in 2019 [36]. A single study has been performed using trabecular bone score in transgender individuals [37]. The 2017 systematic review and meta-analysis examined 13 studies published from 1980 to 2015. [35]The outcomes of interest were bone mineral density and the incidence of fractures. 392 transgender women and 247 transgender men were identified. The updated 2019 systematic review and meta-analysis selected 19 studies published before August 2018. The quality of the studies was assessed by the National Institutes of Health scale to be fair and/or good. 812 transgender women and 487 transgender men were identified. A list of individual studies is shown in Table 4.

The study on trabecular bone score reviewed patient data from the American University Medical Center in the Netherlands from 1972 to 2016. DXA scan results along with additional clinical data corresponding to bone health were retrieved. The trabecular bone score was calculated based on lumbar spine DXA imaging. 535 transgender women and 473 transgender men were included.

3.1. Transgender women

In both meta-analyses, transgender women showed an increase in bone mineral density in the lumbar region at 12 and 24 months. Fracture rates were only evaluated in a single cohort study with no reported events in either gender. The trabecular bone scores (TBS) in transgender women regardless of age, were found to be higher compared to baseline (+0.04, 95%CI + 0.00; +0.08). TBS, calculated from the lumbar region of the DXA scan, in both meta-analyses had an associated increase in bone mineral density.

3.2. Transgender men

In both meta-analyses transgender men showed no statistically significant changes in bone mineral density in the lumbar spine, femoral neck, or total hip at 12 or 24 months. Most transgender men received IM preparations of testosterone, and some received transdermal or oral androgens. All patients had a baseline DXA scan prior to initiation of GAHT. Among the transgender men less than 40 years of age, TBS tended to be lower in those who used GAHT compared to the baseline groups. For transgender men greater than 40 years of age, TBS was lower in those using 5 years GAHT versus baseline (−0.05, 95%CI −0.08; −0.01) [37]. Although there was evidence of a decrease, the score remained above 1.3, which is in normal architectural range. There was no obvious increase in fracture risk.

In summary, the available data show that in transgender women, GAHT increases bone mineral density and TBS. In transgender men, there was a decrease in TBS which nevertheless remained above 1.3, still in normal architectural range. There was no increase in fracture risk in both populations. Those results are also summarized in Table 5.

4. Discussion

GAHT is a collective term that encompasses androgen and estrogen therapy in different formulations and routes of administration along with other endocrine therapies. The inconsistent and conflicting results found in the current literature can be explained by the highly heterogenous GAHT used in different studies as well as lack of information on lifestyle and psychosocial aspects of the included transgender individuals.

Transgender women appear to have higher risk of myocardial

Table 5
The effects of GAHT on Skeletal health in transgender women and men.

Parameters		Effects of GAHT	
		Transgender Women	Transgender Men
BMD	**Lumbar spine**	↑	↔
	Femoral neck	↔	↔
TBS		↑	↓ˆ

Abbreviation: GAHT, gender affirming hormone therapy; BMD, bone mineral density; TBS, trabecular bone score.
↑ denotes a significant increase.
↓ denotes a significant decrease.
↔ denotes no significant change.
ˆ TBS decreases but is still within normal range.

Table 4
Studies included in the 2017 and 2019 Meta-analyses of Studies Examining Skeletal Health in Transgender Individuals.

Studies included in 2017 Systematic Review [35]

Study	**Country**	**Design**	**Patients**	**N**	**Mean Age** (years)	**Duration**
Dittrich 2005	Germany	Cohort	Transgender women	60	38.37	24 mos
Klink 2015	Netherlands	Cohort	Transgender women/Transgender men	15/19	14.9/15	7.1/6.9 yrs
Mueller 2011	Germany	Cohort	Transgender women	84	36.3	24 mos
Mueller 2010	Germany	Cohort	Transgender men	45	30.4	12 and 24 mos
Pelusi 2014	Italy	Cohort	Transgender men	45	29.4	12 mos
Reutraku1998	Thailand	Cohort	Transgender women	11	21.2	<24 mos
Sosa 2003	Spain	Cohort	Transgender women	17/27	24.1/43	>24 mos
Turner2004	USA	Cohort	Transgender men	8	33.1	24 mos
VanCaenegem 2015	Belgium	Cohort	Transgender men/Transgender women	23/49	27/33	12 and 24 mos
VanCaenegem 1996	Belgium	Cohort	Transgender women/Transgender men	56/35	33/25	12 mos
VanCaenegem 1998	Netherlands	Cohort	Transgender women/Transgender men	20/19	25.4/25	45.5/38.2 mos
Wierckx 2014	Belgium	Cohort	Transgender women	47/6	31.7/19.3	12 mos
Wierckx 2014	Belgium	Cohort	Transgender men	27/26	27.3/21.7	12 mos

Additional Studies included in 2019 Systematic Review [36]

Study	**Country**	**Design**	**Patients**	**N**	**Mean Age** (years)	**Duration**
Haraldsen 2007	Norway	Cohort	Transgender men/Transgender women	21/12	25.1/29.3	12 mos
Wiepjes 2017	Belgium	Cohort	Transgender men/Transgender women	199/231	23.9/22.5	12 mos
Gava 2016	Italy	Cohort	Transgender women	40	32.9	12 mos
Fighera 2018	Brazil	Cohort	Transgender women	46	33.7	31 mos
Van Kesteren 1996	Netherlands	Cohort	Transgender men/Transgender women	35/56	25/33	12 mos
Van Kesteren 1998	Netherlands	Cohort	Transgender men/Transgender women	19/20	25/25.4	38.2 mos

Abbreviations: mos, months; yrs, years.
Adapted and expanded from Singh-Ospina N et al. J Clin Endocrinol Metab. 2017 [35].

infarction than sex assigned at birth women but not sex assigned at birth men and higher risk of ischemic stroke than both sex assigned at birth men and sex assigned at birth women. It is unclear if the increase in cardiovascular morbidity and mortality in transgender women is due to alterations in cardiovascular risk factors or a direct effect of GAHT. The current literature, however, has not shown a consistent undesirable alteration in conventional cardiovascular risk factors (i.e., hypertension, hyperlipidemia, and diabetes) in transgender women receiving GAHT.

Administration of GAHT to transgender women suppresses the natal androgens resulting in reduced testosterone levels in transgender women compared with sex assigned at birth men. Sex assigned at birth men with low testosterone levels have a high prevalence of cardiovascular disease [38,39] and low baseline testosterone levels are inversely related to cardiovascular mortality in sex assigned at birth men [40]. Suppressed testosterone levels in transgender women along with the greater plaque burden of the natal gender [41] might be one of the mechanisms responsible for the increased cardiovascular morbidity and mortality in this population.

GAHT is associated with increased risk of VTE in transgender women. Oral ethinyl estradiol is now less commonly prescribed due to this recognized higher risk, with micronized estradiol and estradiol valerate now the preferred forms of oral estrogen [42]. To the best of our knowledge, no study had demonstrated increased risk of VTE in transgender men receiving GAHT.

Alteration in the lipid profile, particularly an increase in TG and a decrease in HDL-C, was found to be fairly consistent in transgender men receiving GAHT along with mixed results for TC and LDL-C. Blood pressure was also found to be elevated in some studies although there are conflicting results. The evidence of elevated cardiovascular risk in transgender men is limited. .

It is important to note that transgender men initiate GAHT at ages younger than transgender women. The individuals in the current studies are relatively young and reported study durations are too short to detect cardiovascular events in the primary prevention setting. A prospective study of longer duration or a registry that collects data on lifestyle and psychosocial history would be ideal to assess the cardiovascular effects of GAHT in transgender individuals. Addition of “gender identity” variable to the national health registry may also help assess long-term cardiovascular and metabolic risk in this population [43].

Transgender individuals experience stress due to minority identity, self-stigma, and discrimination [44] and may be more likely to smoke tobacco, drink alcohol and be less physically active compared with cisgender population [43]. A study has also shown that transgender patients are more likely to suffer from drug use disorder, with the highest risk seen with amphetamine (aOR 2.22, 95% CI 1.82–2.70), but also cocaine (aOR 1.59, 95% CI 1.29–1.95), and cannabis (aOR 1.82, 95% CI 1.62–2.05) [45]. Transgender individuals are also more likely to have poor mental health [46]. There is evidence that mental health improves in both transgender men and transgender women after gender affirming therapy, including surgery although not necessarily with GAHT [47].

Additional evidence documents a link between discrimination and cardiovascular health indexes (e.g., tobacco use, hypertension, and obesity) in this stigmatized population [48,49].

Fracture risk in transgender individuals remains uncertain. Estrogen therapy has a positive correlation with TBS and bone mineral density in the lumbar region of transgender women but not elsewhere. Testosterone therapy produces no significant changes in bone mineral density in transgender men. The decrease in the trabecular bone score in transgender men had no significant association with fracture risk since TBS remained in the normal range. The studies conducted so far have been mainly retrospective and of short duration. The average age of the patients was young (20–30 years), and they were followed for about 12–24 months (Table 4). The analysis of additional factors that affect bone health such as smoking, physical activity and vitamin D status was limited. There are limited fracture data.

Further prospective and longitudinal studies are necessary to obtain useful data to assess risk of osteoporosis in the transgender population. Additional factors that can affect bone mineral density need to be assessed. Bone mineral density as considered in the studies and practice is compared to natal reference ranges. With further research, guidelines with reference values for bone mineral density should be established for transgender individuals.

5. Conclusion

Current limited evidence from non-randomized studies suggests that transgender women taking GAHT have increased risks of myocardial infarction, ischemic stroke and VTE. The current evidence does not indicate increased cardiovascular risk in transgender men receiving GAHT. Estrogen therapy has a positive correlation with trabecular bone score and bone mineral density in the lumbar region of transgender women but not elsewhere. The literature should be interpreted with caution due to the risk of bias in these studies.

The evidence shows that GAHT decreases or resolves gender dysphoria in transgender individuals and improves their quality of life [50,51]. Awareness of the potential risk of GAHT by clinicians can help transgender individuals make better informed decisions and can guide clinicians towards early intervention to prevent adverse cardiovascular outcomes. Transgender individuals receiving GAHT should be monitored for conventional cardiovascular risk factors and managed according to current guidelines with lifestyle programs and optimal preventive medical therapy [52]. The psychological well-being of transgender individuals should also be addressed with referral to mental health professionals as needed. Prospective randomized controlled studies are needed to elucidate the mechanisms and effects on GAHT on cardiovascular and skeletal health.

Declaration of competing interest

The authors disclose no conflict of interest related to this manuscript. This work was supported by the Empire Clinical Research Investigator Program (ECRIP) from the New York State Department of Health.

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