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Changes in Blood Lipids Following Initiation of Gender Affirming Hormone Therapy: A Systematic Review and Meta-Analysis

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ABSTRACT

Aim: The aim of this study was to conduct a systematic review and meta-analysis of changes in low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), total cholesterol, and triglycerides following initiation of feminizing or masculinizing gender affirming hormone therapy (GAHT).

Methods: A search of Ovid MEDLINE, Embase, Web of Science, SCOPUS, and CINAHL databases identified potentially relevant articles published from 1990 through 2024. Both observational and randomized trials of adults receiving feminizing or masculinizing GAHT with baseline and follow-up measures were included. Articles were reviewed for eligibility using Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 guidelines. The risk of bias in each study was quantified using the NHLBI Study Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group. Random effects models were used to compute the before-and-after meta-differences in mean values for each parameter along with the I^2 statistic to assess heterogeneity of results.

Results: Thirty-five studies met the criteria for inclusion in the meta-analysis. Masculinizing GAHT was associated with significant changes in serum lipids from baseline up through the 60-month timepoint with meta-difference of means (95% CI) estimates of 26.2mg/dL (23.3,29.0) for LDL-C, 26.1mg/dL (22.8,29.4) for total cholesterol, 30.7mg/dL (6.9,54.6) for triglycerides and –9.4mg/dL (–12.1, –6.7) for HDL-C. Studies evaluating the effects of feminizing GAHT on balance demonstrated no notable changes in HDL-C or triglycerides while the results for LDL-C and total cholesterol were inconsistent. Heterogeneity of results ranged from minimal ($I^2 = 0\%$) to substantial ($I^2 = 90\%$).

Conclusions: While the results for transfeminine individuals on GAHT appear somewhat reassuring, transmasculine patients receiving testosterone may benefit from closer monitoring of lipid profiles.

Introduction

Approximately 1.4 million adults in the United States identify as transgender or gender diverse (TGD).[1,2] Some TGD individuals use feminizing or masculinizing gender affirming hormone therapy (GAHT) to induce changes consistent with their gender identity.[3,4].

As reviewed in detail elsewhere,[5–7] GAHT regimens can vary widely depending on patient goals. Feminizing GAHT typically consists of an estradiol-containing compound delivered orally (PO), intramuscularly (IM) or transdermally (TD). Estradiol is often administered with an anti-androgen therapy that may include spironolactone, finasteride or cyproterone acetate. Masculinizing GAHT consists of testosterone-containing compounds. These are most often administered IM, subcutaneously (SQ), or TD. Injectable testosterone can be long-acting (testosterone undecanoate) or short-acting (testosterone cypionate or enanthate).

The current World Professional Association for Transgender Health (WPATH) recommendations for follow up of transfeminine (TF) individuals receiving GAHT include periodic evaluations of sex hormones (testosterone and estradiol) and monitoring of serum electrolytes, especially potassium to avoid severe hyperkalemia if spironolactone is included in the GAHT regimen. For transmasculine (TM) individuals

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receiving GAHT, recommended laboratory monitoring, in addition to sex hormone concentrations, include hemoglobin/hematocrit levels due to the possibility of testosterone-induced polycythemia.[5,8].

Some studies have suggested an elevated risk of cardiovascular disease including myocardial infarction and stroke.[9,10] Whereas cardiovascular and cardiometabolic effects of GAHT constitute an important research priority,[11,12] the magnitude and direction of GAHT-related changes in serum lipids as a contributor to cardiovascular disease burden remain uncertain. This uncertainty is likely attributable to the relatively small size of longitudinal studies capable of tracking changes in various laboratory parameters over time.[13] As a result, the effect estimates in these studies tend to be imprecise. The lack of precision in individual studies motivated the present systematic review and meta-analysis with two specific objectives: 1) to investigate longitudinal changes in blood lipid concentrations at different intervals following GAHT initiation and 2) whenever possible, to examine the influence of specific GAHT characteristics, including medication types, drug combinations, and routes of administration, on observed associations. While doses of both masculinizing and feminizing GAHT are often titrated to achieve optimal gender affirmation, the differences in dosing are beyond the scope of this review.

Methods

We performed a systematic review and meta-analysis to estimate GAHT-related temporal changes in four laboratory measures: low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, and total cholesterol. The study followed protocols consistent with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement on systematic reviews.[14].

Literature search

We included observational studies and randomized trials of adult TGD patients receiving feminizing GAHT with an estradiol-containing compound or masculinizing hormone therapy with testosterone. Studies were considered eligible for inclusion if they reported laboratory parameters of interest at baseline and at specified intervals of 3, 6, 9, 12, 18, 24, 36, or 60 months following GAHT initiation. Studies were excluded if they did not report the outcomes of interest, did not include both pre- and post-GAHT laboratory values, or did not use pre-specified time points. Studies were also excluded if patients were not GAHT-naïve at baseline, if they were missing data necessary for meta-analysis (e.g., point estimate or variance), or if the study population included patients under 18 years of age (supplementary material Table S1).

We searched Ovid MEDLINE, Embase, SCOPUS, CINAHL, and Web of Science databases (supplementary material Table S2a-d). The search was executed on July 20, 2021, and included studies published since 1990. The search strategy was developed by members of the study team with assistance from an experienced librarian. The list of references from the search was uploaded into Endnote and duplicate references were removed using the protocol outlined by Bramer et al.[15] In an effort to include the most recent publications, we applied the same strategy and search terms and updated the review using Ovid MEDLINE to capture studies published from July 20,2021 through February 27, 2024.

The search results were uploaded into Covidence, an online resource for systematic review management. Two reviewers independently screened all titles and abstracts for eligibility. Discordant reviews were reconciled by consensus. Two reviewers independently reviewed full-text articles for eligibility with discordant reviews reconciled by consensus. If multiple studies used data from the same cohort, only the study with the largest sample size was included. Additional relevant publications were identified through review of secondary references of eligible studies.

Data collection

The information from each eligible publication was extracted using a standardized form. In situations when the required information was missing or unclear the study authors were contacted via email. Of the 14 study authors contacted, 4 responded to inquiries. For studies that only reported results in graphical form and whose authors did not respond to outreach, the required numerical values were extracted using the WebPlotDigitizer application.[16] All data extraction was completed by one reviewer.

The data extracted from each study included author name, year of publication, title, location, study design, start and end date of follow-up, duration of follow-up, eligibility criteria, sample size, demographic characteristics (gender identity, age and race/ethnicity) of participants, BMI at baseline, GAHT type and composition, duration of therapy, route of administration, outcome measure description (median or mean), variance measure description, type of value presented (raw value vs change from baseline), and laboratory parameters of interest including units, baseline, and follow up values. Unless otherwise noted, it was assumed that there was no loss to follow-up in studies with multiple timepoints.

The risk of bias in each study was quantified using the Study Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group.[17] As shown in supplementary material Table S4, the tool includes 12 questions pertaining to various aspects of study design, selection of participants, data collection, and statistical analysis. The response options to each question include yes, no, cannot determine or not applicable. Based on the 12 responses, each study is then characterized as Good, Fair or Poor. The risk of bias was assessed by one reviewer.

Data analysis

From each study, we extracted data on means and standard deviations for LDL-C, HDL-C, total cholesterol, and triglycerides at baseline and at each available follow-up timepoint. All concentrations were expressed in mg/dL to ensure comparability across studies, with conversions from other units where needed. When studies reported only medians and interquartile ranges, means and standard deviations were estimated using the quantile estimation method.[18] We computed the difference in means and the associated variance between baseline and each follow-up timepoint for each study using methods for computation of effect sizes for pre-post scores.[19] We obtained a meta-difference of means (MDM) at each follow-up timepoint using inverse variance random effects restricted maximum likelihood meta-analyses. An MDM at a given timepoint was generated only if there were at least 3 studies reporting the relevant results. We assessed statistical heterogeneity using Cochran's Q test and calculated the I^2 statistic, which was interpreted using cut-offs of 25%, 50%, and 75% for low, moderate, and substantial heterogeneity, respectively.

To assess the trend over time, we fitted a weighted linear regression of the MDM values over time with the weights being the inverse of the variance and the intercept placed at zero.

We also performed a subgroup analysis by route of administration for both TM (IM/SQ) and TF (TD, PO) populations and by testosterone type for TM populations (Long-acting testosterone, short-acting testosterone). Another subgroup analysis was completed comparing the most common co-interventions with femininizing hormone therapy, cyproterone acetate (CPA) and spironolactone. We also performed a sensitivity analysis by excluding studies of TF populations who received estrogen formulations (Premarin, conjugated equine estrogen or ethinyl estradiol) that are no longer recommended by current clinical guidelines.[5,20] Each of the subgroup analyses was performed at the 12 month after GAHT initiation timepoint as this was the only timepoint with enough ($\geq$3) studies.

All analyses were performed using R version 4.2.3 (meta, metafor,

metamedian packages).[21] The results were summarized both in numerical and graphical form.

Results

Study characteristics

As shown in Fig. 1, following screening of 1943 unique titles, 84 studies were selected for full text review and of those 26 studies met the inclusion criteria. With the addition of 5 studies identified through secondary reference review and 4 studies obtained via the updated review of OVID MEDLINE, 35 studies provided data for our meta-analysis.[22–53] The full list of articles excluded from the review during full text review and the reasons for exclusions are provided in the supplementary material Table S3.

Studies included in the systematic review and meta-analysis are summarized in Table 1. Of the 36 studies included in the *meta*-analysis, 17 focused on TM populations only[22,24,31,32,34,36,38,39,42–44,47,48,50,54–56] 8 on TF only[30,35,37,40,41,52,53,57], and 11 on both TF and TM populations.[23,25–29,33,45,46,49,51] The studies represented 13 countries, including Italy (7 publications)[31–33,35,42,43,51], the US (5)[22,23,29,46,48], Spain (6)[24,27,28,44,49,54], Germany (5)[34,36,39,41,52], the Netherlands (4)[26,33,38,50], Austria (2)[25,30], Canada (2)[40], the UK (1)[37], Belgium (1)[33], Sweden (1)[55], Argentina (1)[47], Thailand (1)[56], Israel (1)[57] and Taiwan (1)[45]. Most studies had a maximum follow-up time of 12 months (12 studies)[22,26,28,31,34,38,40,45–47,49,55] or 24 months (10 studies)[24,27,33,39,41,42,51–53,56]. Five studies followed patients for 60 months[23,25,30,32,35], 5 studies for 6 months[29,37,43,50,57], 2 studies for 36 months[36,44], 1 study for 3 months[54], and 1 study for 72 months.[48] The distribution of maximum timepoints included in studies can be found in Table 2. Study periods represented a 40-year interval from 1980 through 2020. Based on the risk of bias assessment one study was rated as "good", 18 studies were "fair", and 16 studies were "poor" (supplementary material Table S4). Figures S1-S4 in the supplementary material display results of individual studies separated by gender, timepoint, and lab of interest.

In the sub-analyses, 4 studies reported results for TD estradiol[25,28,35,51],6 did so for patients taking PO estradiol[25,28,35,51], 7 studies focused on patients taking cyproterone acetate (CPA) as a co-

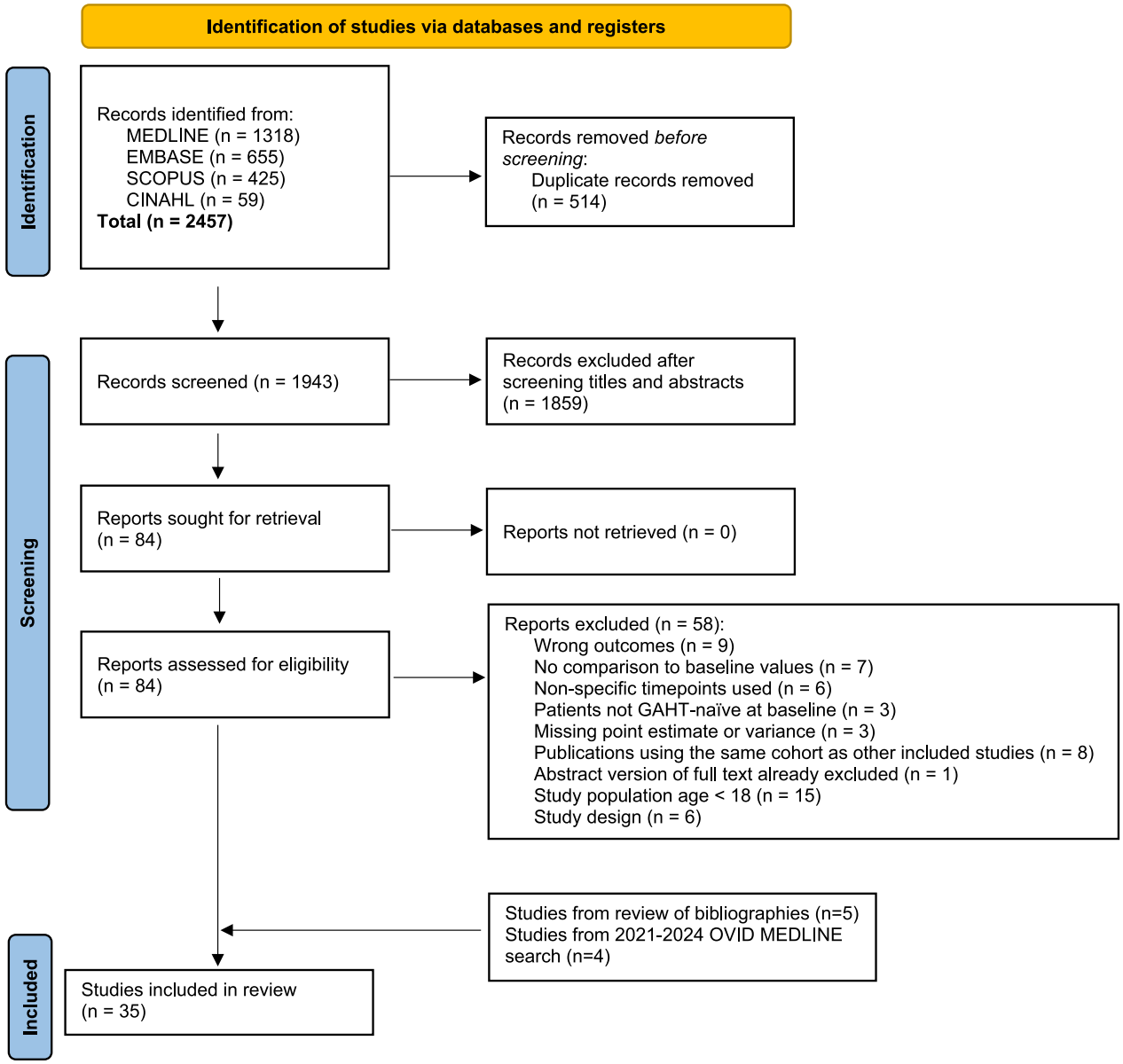

Fig. 1. PRISMA flowchart of the study selection process.

Table 1
Characteristics of Included Studies.

Study	Location	Study Period	Gender	Sample (n)	GAHT Regimen (Dose(s), Routes of Administration, Dose Frequency)	Co-Intervention(s)	Follow-up (months)	Mean/ Median Age (years)	Race/ Ethnicity	Body Mass Index (kg/ m^2)
Chandra et al	USA	NR	TM	12	Testosterone Enanthate or Cypionate (50–125 mg, IM, q2wk)	None	12	29	83% NHW; 8% NHB; 8.3% H	27.5
Allen et al	USA	2007 –2019	TF	126	Estradiol (PO, IM, TD); Conjugated Estrogen (PO)	Spironolactone (80.2%), Finasteride (1.6%), Progesterone (19.8%)	60	31.1	60.3% NHW, 18.2% NHB, 15.1% H, 4.8% A, 1.6% O	27.9
			TM	91	Testosterone Cypionate (IM); Testosterone (TD)	None		27.8	60% NHW, 18% NHB, 17%H, 4% A, 1% O	29
Martinez et al	Spain	2015–2017	TM	19	"Cross-Sex Hormone Therapy"	None	24	23.9	NR	27.12
Ott et al	Austria	1995–2009	TF	49	Estradiol (100ug, TD, biw)	Cyproterone Acetate (50 mg, PO,qd);	60	35.7	NR	22.6
				40	Oral 17-β Estradiol (2–4 mg, oral, qd)	Finasteride (5 mg, PO, qd)				
			TM	80	Testosterone Undecanoate (1000 mg, PO, q3mo)	Lynestrenol (5 mg, PO, qd)		26		23.7
Elbers et al	Netherlands	NR	TF	20	Ethinyl Estradiol (100ug, PO, qd)	Cyproterone Acetate (100 mg, PO, qd)	12	26	NR	20.6
			TM	17	Testosterone Esters (250 mg, IM, q2wks	None		23		21.7
Van Velzen et al	Spain	2010–2017	TM	47	Testosterone Gel (50 mg, TD, qd)	None	12	29	NR	24
				62	Testosterone Esters (250 mg, IM, q2wks	None		25		
				79	Testosterone Undecanoate (1000 mg, IM, q3mo)	None		23		
			TF	98	Estradiol (100ug, TD, biw)	Cyproterone Acetate (50 mg, PO, qd)		41		24
				144	Estradiol Valerate (2 mg, PO, BID)	Cyproterone Acetate (50 mg, PO, qd)		22		
Deutsch et al	USA	2012–2013	TF	16	Micronized 17-β Estradiol (2 mg, SL, BID); Estradiol (100ug, TD, biw); Estradiol Valerate (20 mg, IM, q2wks)	Spironolactone (50 mg, PO, BID)	6	29	69% NHW, 6%NHB, 38% H, 12% A, 12% O	25
			TM	31	Testosterone Cypionate (200 mg/mL, SQ, qwk; Testosterone Gel (1 % 5 g, TD gel, qd); Testosterone Patch (4 mg, TD, qd)	None		27	80% NHW, 10% NHB, 35% H, 6% A, 3% O	29
Aust et al	Austria	NR	TF	55	"Estrogens" (No further information reported)	None	60	37	NR	NR
Pelusi et al	Italy	NR	TM	15	Testosterone Enanthate (100 mg)	None	12	31	87% NHW, 13% O	22.3

(*continued on next page*)

Table 1 (*continued*)

Study	Location	Study Period	Gender	Sample (n)	GAHT Regimen (Dose(s), Routes of Administration, Dose Frequency)	Co-Intervention(s)	Follow-up (months)	Mean/ Median Age (years)	Race/ Ethnicity	Body Mass Index (kg/ m^2)
				15	Testosterone Gel (50 mg, TD, qd)			29	93% NHW 7% O	23.9
				15	Testosterone Undecanoate (1000 mg, IM, q3mo)			28	93% NHW 7% O	22.1
Gava et al (2018)	Italy	NR	TM	25	Testosterone Undecanoate (1000 mg, IM, q3-4mo)	None	60	29.8	NR	22.5
				25	Testosterone Enanthate or Cypionate (100–200 mg, IM, q2-4wks)			30.4		23.3
Cocchetti et al	Belgium, Netherlands, and Italy	2010 – (not indicated)	TF	144	102 participants on Estradiol Valerate (2–6 mg, PO, BID); 6 participants on Estradiol Patch (25-50mcg, TD, qd); 3 participants on Estradiol Hemihydrate or valerate gel (1–3 mg/day, TD, qd)	136 participants on cyproterone acetate (50–100 mg, PO, qd)	24	31.84	NR	23.46
			TM	165	156 participants on Testosterone Undecanoate (1000 mg, IM, q12wks);6 participants on Testosterone Enanthate (250–500 mg, IM, q4wks);3 participants: Testosterone gel (50–60 mg, TD, qd)	None		26.78		25.06
Mueller et al (2007)	Germany	NR	TM	35	Testosterone Undecanoate (1000 mg, IM, q3mo)	None	12	29.63	NR	23.94
Gava et al (2020)	Italy	2012–2020	TF	25	Estradiol (1–2 mg, TD, qd);	Cyproterone Acetate (50 mg, PO, qd)	60	31.1	100% "Caucasian"	22.2
				25	Estradiol valerate (PO, qd)	Leuprolide (3.75 mg, IM, q1mo)		32.5	100% "Caucasian"	21.9
Jacobeit et al	Germany	2007–2009	TM	17	Testosterone Undecanoate (IM)	None	36	34	NR	28.3
Wilson et al	United Kingdom	NR	TF	23	Conjugated Equine Estrogen (1.25–2.5 mg, PO, qd)	Finasteride or Cyproterone Acetate added 4 months after start	6	36	NR	NR
				7	Estradiol (40ug, TD, biw); Estradiol (50ug, TD, biw)			47		
Cupisiti et al	Netherlands	2006–2009	TM	29	Testosterone Undecanoate (1000 mg, IM, q3mo)	None	12	29.9	NR	23.5
Mueller et al (2010)	Germany	NR	TM	45	Testosterone Undecanoate (1000 mg, IM, q3mo)	None	24	30.4	100% NHW	24.1
Fung et al	Canada	2009–2015	TF	82	"Oral or transdermal estrogen"	Cyproterone acetate	12	32.9	NR	25

(*continued on next page*)

Table 1 (*continued*)

Study	Location	Study Period	Gender	Sample (n)	GAHT Regimen (Dose(s), Routes of Administration, Dose Frequency)	Co-Intervention(s)	Follow-up (months)	Mean/ Median Age (years)	Race/ Ethnicity	Body Mass Index (kg/ m^2)
				31	"Oral or transdermal estrogen"	Spironolactone		38.2		25.5
Mueller et al (2010)	Germany	NR	TF	84	oestradiol-17B valerate (10 mg, IM, q10days)	Goserelin Acetate (3.8 mg, SQ, q4wks)	24	36.3	100% NHW	22.3
Schönauer et al	Italy	2015–2018	TM	15	Testosterone Enthanate (250 mg, IM, q3wks)	"Sexual Reassignment Surgery"	24	NR	NR	23.45
				8	Testosterone Enthanate (250 mg, IM, q3wks)	None				28.07
Berra et al	Italy	NR	TM	16	testo-viron depot (100 mg Testosterone Enanthate + 25 mg Testosterone propionate, IM, q10days)	None	6	30.4	NR	21.8
Becerra et al	Spain	NR	TM	30	Testosterone Gel (50 mg, TD, qd); Testosterone Undecanoate (1000 mg, IM, q3mo)	None	36	28.8	NR	NR
Liu et al	Taiwan	2011–2019	TF	45	Conjugated Estrogen (PO, bid)	Cyproterone Acetate (PO, qd)	12	26	NR	20.6
			TM	65	Testosterone Cypionate (IM, q2wks)	None		27.9		22.6
Fernandez et al	USA	2008–2014	TF	33	50 % Estrogen (oral), 22 % Estrogen (TD), 22 % Estrogen (IM)	Spironolactone (100 mg, PO, qd)	12	31	NR	28.8
			TM	19	Testosterone (11 mg/day, IM, q2wks)	None		27		28.1
Abdala et al	Argentina	NR	TM	30	Testosterone Undecanoate (1000 mg, IM, q3mo); Testosterone Enanthate (250 mg, IM, q3wks); Testosterone Gel (1 %, TD, qd)	None	12	27	NR	NR
Chan et al	USA	2009–2016	TM	34	Testosterone Cypionate (max 125 mg, IM/SQ, qwk); Testosterone Enanthate (max 125 mg, IM/SQ, qwk)	None	72	33	NR	NR
Becerra-Fernández et al	Spain	2007–2009	TF	74	Estradiol Valerate (1 mg, PO,qd); Estradiol (8–16 mg,TD,qwk); Conjugated Estrogens (2.5–3.75 mg, PO, qd)	Cyproterone Acetate (100 mg, PO, qd)	12	30	NR	23.2
			TM	36	Testosterone Gel (50 mg, TD,qd), Testosterone Undecanoate (1000 mg,IM, q3mo), Testosterone	None		32		23.5

(*continued on next page*)

Table 1 (*continued*)

Study	Location	Study Period	Gender	Sample (n)	GAHT Regimen (Dose(s), Routes of Administration, Dose Frequency)	Co-Intervention(s)	Follow-up (months)	Mean/ Median Age (years)	Race/ Ethnicity	Body Mass Index (kg/ m^2)
					Cypionate (250 mg,IM,biw)					
Asscheman et al	Netherlands	1987–1989	TM	10	Testosterone Undecanoate (160 mg, PO,qd)	None	6	31	NR	NR
Colizzi et al	Italy	2008–2013	TF	79	Estradiol Gel (2.12 ± 0.57 mg, TD, qd)	Cyproterone Acetate (100 mg, PO, qd)	24	30.24	NR	21.76
			TM	43	Testosterone Ester Depot (250 mg, IM, q3wks)	None	24	28.77		21.03
Dittrich et al	Germany	NR	TF	60	oestradiol-17B valerate (6 mg, PO, qd)	Goserelin Acetate (3.8 mg, SQ, q4wks)	24	38.37	NR	24.19
Prior et al	Canada	1980–1985	TF	23	Conjugated Estrogen (Premarin,0.625 mg initially then 2.5 mg, PO, BID (3/4 wks))	Medroxyprogesterone (10 mg, PO, q4wks), Spironolactone (100–200 mg, PO,qd)	24	30.7	NR	NR
Iannantuoni et al	Spain	NR	TM	157	Testosterone Undecanoate (1000 mg, IM, q3mo);	None	3	26.2	NR	23.4
Lethin et al	Sweden	NR	TM	10	Testosterone Undecanoate (1000 mg, IM, q3mo);	None	12	NR	NR	NR
Korpaisarn et al	Thailand	2015–2019	TM	39	Testosterone Enanthate (250 mg, IM, q4wks)	None	24	27.8	NR	23.6
Yaish et al	Israel	2021–2022	TF	22	Estradiol hemihydrate (2 mg, PO, qd) or Estradiol (0.5 mg, sublingual, q6hrs)	Cyproterone Acetate (10 mg, PO, qd) for PO estradiol patients only	6	26.3 (sublingual group); 20.1 (PO group)	NR	25.1 (sublingual group); 22.5 (PO group)

Abbreviations: NR, Not Reported **Location**: USA, United States of America; Gender: TM, Transmasculine; TF, Transfeminine; Dose: mg, milligrams; ug, micrograms; **Routes of Administration:** TD, Transdermal; IM, Intramuscular; PO, Per Os (Oral); SQ, Subcutaneous; **Frequency**: qd, daily; qwk, weekly; qXdays, every X days; qXmo, every X months;
qXwks, every X weeks; biw, twice per week; bid, twice per day; **Race/Ethnicity:** NHW, Non-Hispanic White; NHB, Non-Hispanic Black; H, Hispanic; A, Asian; O, OtherIf dose, route of administration, or dosing frequency is not included in GAHT Regimen or Co-Intervention(s) columns, then it was not reported in the manuscript

intervention[25,26,33,35,45,49,51], and 3 reported results using spironolactone as a co-intervention.[40,46,53] Among studies of masculinizing regimens, 8 reported results for patients taking short-acting testosterone[22,26,28,31,32,42,45,48] and 8 did so for long-acting testosterone (testosterone undecanoate).[25,31,32,34,36,38,39,55]. Only 2 studies reported results of TD testosterone gel, preventing a meaningful *meta*-analysis.[28,31].

Overall Meta-Analysis results

As shown in Table 2 and Fig. 2, among TGD persons receiving masculinizing GAHT there was a statistically significant increase in LDL-C levels starting six months following GAHT initiation (MDM: 7.6mg/dL; 95% CI: 3.9, 11.2; I^2: 0%). This difference progressively increased through 60 months post-GAHT with MDM reaching 26.2mg/dL (95% CI: 23.3, 29.0; I^2: 0%). By contrast, HDL-C decreased starting at 3 months (MDM: −7.5mg/dL; 95% CI: −10.5, −4.5; I^2: 32%), a change that remained relatively stable through 60 months post-GAHT (MDM: −9.4mg/dL; 95% CI: −12.0, −6.7; I^2: 0%). Total cholesterol appeared to continuously increase starting at 12 months post-GAHT through 60 months post-GAHT with MDM (95% CI) estimates of 7.7 (1.4, 14.0) and 26.1 (22.8, 29.4) mg/dL, and I^2 values of 86% and 0%, respectively. Triglycerides showed an increase starting at six months (MDM: 5.1mg/dL; 95% CI: 0.7, 9.4; I^2: 0%), followed by variable changes between 18 and 36 months post-GAHT and a more pronounced increase by 60 months post-GAHT reaching an MDM of 30.7mg/dL (95% CI: 6.9, 54.6; I^2: 35%).

Among TF populations there were no notable changes from baseline by 60 months post-GAHT for HDL-C (MDM: 5.3mg/dL; 95% CI: −1.7, 12.4; I^2: 54%) or triglycerides (MDM: 4.7mg/dL; 95% CI: −21.3, 30.6; I^2: 52%). The corresponding results for the remaining two measures were inconsistent during the majority of follow up; however, there was an overall increase by 60 months post-GAHT with MDM of 13.8mg/dL (95% CI: 2.6, 25.0; I^2: 5 %) for total cholesterol and 6.6mg/dL (95 % CI: 2.4, 10.8; I^2: 0%) for LDL-C. The results for feminizing GAHT demonstrated variable heterogeneity with I^2 values at 60 months ranging from 0% to 90% (Table 2, Fig. 2).

Results of Sub-Analyses

Due to the small number of relevant studies, the sub-analyses by GAHT regimen, route of administration, and GAHT co-intervention are limited to the 12-month timepoint. The results of these sub-analyses are presented in Table 3a and Table 3b. supplemental material Figures S5-S7 present data for individual studies contributing to these subanalyses.

The analyses restricted to patients receiving intramuscular or

Table 2
Meta-analysis of changes in blood lipids from baseline by timepoint and GAHT.

Time Intervals	Studies of Masculinizing GAHT					Studies of Feminizing GAHT				
	N	n	MDM (95% CI)◆	p-value	I^2	N	n	MDM (95% CI)	p-value	I^2
LDL-C (mg/dl)										
Baseline*	25	1,281	105.2 (99.6, 110.8)	NA	86%	13	1,063	102.4 (98.5, 106.3)	NA	55%
3 months	6	422	4.3 (−3.7, 12.3)	0.22	41%	4	293	−2.0 (−5.1, 1.1)	0.15	0%
6 months	8	298	7.6 (3.9, 11.2)	0.001	0%	4	209	−4.6 (−11.5, 2.4)	0.37	0%
12 months	19	998	10.1 (7.8, 12.5)	<0.001	0%	11	1,025	−1.2 (−6.6, 4.1)	0.63	69%
18 months	4	165	11.2 (−1.1, 23.5)	0.07	0%	Too few studies				
24 months	10	587	14.4 (6.8, 22.0)	<0.001	52%	5	522	4.2 (−11.0, 19.5)	0.50	90%
36 months	5	222	13.1 (−0.9, 27.1)	<0.001	56%	Too few studies				
60 months	4	255	26.2 (23.3, 29.0)	<0.001	0%	3	265	6.6 (2.4, 10.8)	0.01	0%
HDL-C (mg/dl)										
Baseline*	25	1,281	56.2 (53.9, 58.5)	NA	83%	16	1,171	51.0 (48.3, 53.7)	NA	87%
3 months	6	422	−7.5 (−10.5, −4.5)	<0.001	32%	4	293	1.3 (−4.6, 7.2)	0.58	60%
6 months	8	298	−6.5 (−9.4, −3.6)	<0.001	0%	5	239	2.1 (−3.8, 8.0)	0.40	37%
12 months	19	998	−8.3 (−10.5, −6.0)	<0.001	63%	13	1,103	0.1 (−2.9, 2.9)	0.96	84%
18 months	4	165	−6.3 (−14.2, 1.6)	<0.001	72%	Too few studies				
24 months	10	587	−7.6 (−10.8, −4.3)	<0.001	65%	5	522	−0.2 (−9.1, 8.8)	0.96	90%
36 months	5	222	−6.8 (−10.8, −2.7)	<0.001	22%	Too few studies				
60 months	4	255	−9.4 (−12.1, −6.7)	<0.001	0%	4	320	5.3 (−1.7, 12.4)	0.11	54%
Total cholesterol (mg/dl)										
Baseline*	24	1,260	176.1 (170.4, 181.8)	NA	81%	18	1,305	178.6 (171.9, 185.3)	NA	89%
3 months	7	458	3.5 (−8.9, 15.9)	0.51	88%	5	367	−1.1 (−5.1, 2.9)	0.51	0%
6 months	7	275	0.7 (−2.5, 3.8)	0.62	0%	5	239	5.9 (−12.9, 24.7)	0.46	79%
12 months	18	977	7.7 (1.4, 14.0)	<0.001	86%	15	1,237	−2.9 (−9.1, 3.3)	0.34	81%
24 months	8	530	8.2 (−5.6, 21.9)	0.21	79%	6	582	6.5 (−8.0, 21.0)	0.31	88%
36 months	4	188	9.1 (−9.7, 27.8)	0.25	54%	Too few studies				
60 months	3	221	26.1 (22.8, 29.4)	<0.001	0%	4	320	13.8 (2.6, 25.0)	0.02	5%
Triglycerides (mg/dl)										
Baseline*	23	1,247	87.3 (77.2, 97.4)	NA	95%	17	1,249	107.2 (93.0, 121.5)	NA	99%
3 months	7	458	6.5 (−10.3, 23.2)	0.38	73%	5	367	−7.7 (−17.9, 2.5)	0.11	0%
6 months	7	275	5.1 (0.7, 9.4)	0.030	0%	5	239	2.1 (−10.8, 14.9)	0.75	80%
12 months	18	994	14.9 (7.3, 22.5)	18	71%	13	1,162	1.6 (−9.1, 12.4)	0.34	81%
18 months	3	142	3.7 (−13.9, 21.2)	0.46	0%	Too few studies				
24 months	9	564	21.6 (10.9, 32.4)	<0.001	62%	7	601	12.5 (−7.8, 32.9)	0.19	74%
36 months	4	192	20.6 (−15.6, 56.8)	0.19	76%	Too few studies				
60 months	3	221	30.7 (6.9, 54.6)	0.03	35%	3	265	4.7 (−21.3, 30.6)	0.64	52%

Abbreviations: GAHT = gender affirming hormone therapy; CI = confidence interval; LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; MDM = meta- difference of means; N = number of studies, n = total sample size across studies.
◆units = mg/dL; *The MDM column here represents *meta*-means (95 % CI) at baseline in mg/dL.

subcutaneous (i.e. injectable) testosterone showed an increase in LDL-C (MDM: 8.8mg/dL; 95% CI: 5.3, 12.3; I^2: 0%), decrease in HDL-C (MDM: −9.1mg/dL; 95% CI: −11.2, −7.2; I^2: 26%), increase in total cholesterol (MDM: 5.1mg/dL, 95% CI: 0.4, 9.8; I^2: 6%), and increase in triglycerides (MDM: 13.1mg/dL, 95% CI: 5.8, 20.4; I^2: 44%). The direction and magnitude of these associations were similar to the associations observed for all studies combined. The corresponding meta-analysis restricted to TGD people receiving transdermal testosterone was not possible as only two studies provided the relevant data.

The results for short and long-acting testosterones were similar for LDL-C and HDL-C, but different for the remaining two measures under investigation. In the analysis of total cholesterol, the MDM (95% CI; I^2) estimates were 1.4mg/dL (−1.6, 4.3; 0%) for short-acting testosterone and 9.1mg/dL (0.4, 17.8; 22%) for testosterone undecanoate, while the corresponding MDM (95% CI; I^2) estimates in the analysis of triglycerides were 11.0mg/dL (1.9, 20.2; 27%) and 17.5mg/dL (4.8, 30.2; 58%).

When the analyses of feminizing GAHT were restricted to modern regimens (after excluding data for oral ethinyl estradiol and Premarin; one study was excluded), the results were generally similar to the corresponding results for all studies combined with all MDM estimates close to the null value. When data on PO estradiol (4 studies) was compared to TD estradiol (4 studies) the respective MDM estimates were different for LDL-C (−6.3mg/dL; 95% CI: −9.3, −3.4; I^2: 0% vs. 3.4mg/dL; 95% CI: −12.2, 19.0; I^2: 89%), HDL-C (1.30mg/dL; 95% CI: −5.9, 8.4; I^2: 86% vs. −5.4mg/dL; 95% CI: −8.3, −2.5; I^2: 35%) and total cholesterol (−7.4mg/dL; 95% CI: −16.5, 1.8; I^2: 54% vs. −0.7mg/dL; 95% CI: −21.5, 20.2; I^2: 93%). The results for triglycerides did not differ by route of administration (7.9mg/dL; 95% CI: −11.3, 27.2; I^2: 68% vs. 7.4mg/dL; 95% CI: −14.5, 29.3; 88%) but were quite different from the results for all studies combined (1.6mg/dL; 95% CI: −9.1, 12.4; I^2: 81%).

Analyses restricted to feminizing GAHT with either CPA (6 studies) or spironolactone (3 studies) as a co-intervention showed similar results without significant change from baseline at 12 months post-GAHT initiation for total cholesterol and triglycerides. In the analysis of HDL-C, the MDM (95% CI; I^2) estimates were −2.1mg/dL (−7.2,3.1; 75%) for CPA and 4.2mg/dL (0.5,7.8; 0%) for spironolactone. For LDL-C, there was no statistically significant change from baseline in the CPA group, whereas the data on spironolactone were too sparse to permit a meta-analysis.

Discussion

In this systematic review and meta-analysis, we observed an overall worsening of blood lipid profiles following the initiation of masculinizing GAHT, with changes especially evident 5 years since the start of testosterone therapy. By contrast, studies of TF populations receiving estrogen-containing GAHT on balance demonstrated relatively stable lipid profiles.

Subgroup analyses among TM populations showed similar changes associated with intramuscular and subcutaneous testosterone. A corresponding comparison of short-acting (testosterone enanthate and cypionate) and long-acting (testosterone undecanoate) formulations also demonstrated no notable differences except for total cholesterol, which appeared to increase only in response to long-acting testosterone undecanoate.

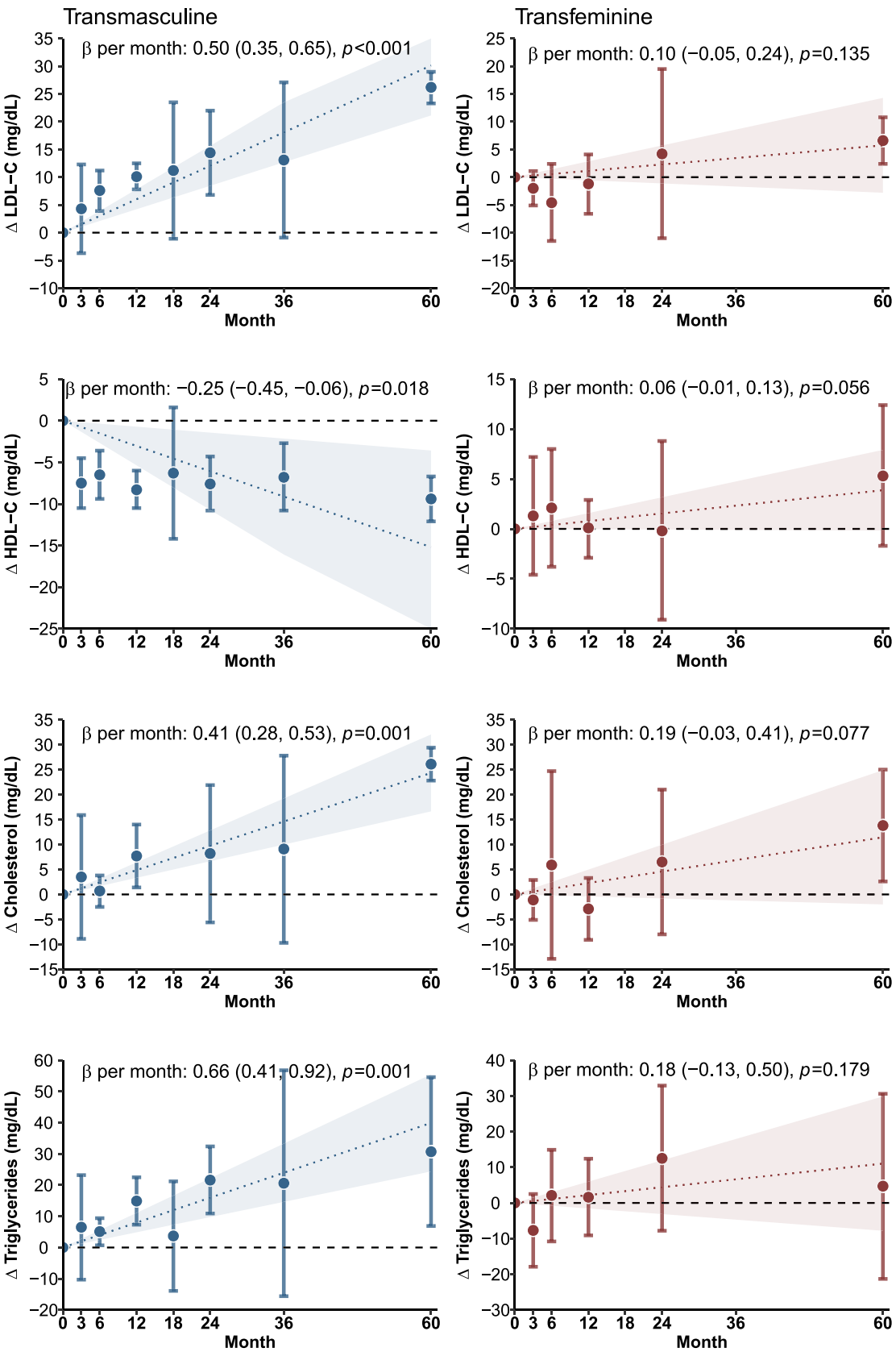

Fig. 2. Longitudinal absolute changes in lipid values from baseline. Longitudinal absolute changes in lipid values from baseline for transmasculine (left panel) and transfeminine (right panel) patients. Shaded region of each graph reflects *meta*-regression results with the change in value on a monthly basis displayed at the top of each graph.

Table 3a
Subgroup Analyses at Baseline and 12-Month Timepoint Compared to All Studies (LDL-C & HDL-C).

Analysis category	LDL-C N	LDL-C n	LDL-C Baseline Meta-Mean (95% CI)◆	LDL-C I^2	LDL-C MDM (95% CI)◆	LDL-C I^2	HDL-C N	HDL-C n	HDL-C Baseline Meta-Mean (95% CI)◆	HDL-C I^2	HDL-C MDM (95% CI)◆	HDL-C I^2
Transmasculine Populations												
All Studies	19	998	105.2 (99.6, 110.8)	86 %	10.1 (7.8, 12.5)	0 %	19	998	56.2 (53.9, 58.5)	83 %	−8.3 (−10.5, −6.0)	63 %
Route												
IM/SQ	15	528	107.22(99.5,115.0)	84 %	8.8 (5.3, 12.3)	0 %	15	528	56.3(53.0,59.6)	77 %	−9.1(−11.1, −7.2)	26 %
Regimen												
Short-acting*	8	253	106.2(97.9,114.5)	76 %	8.5 (4.8, 12.2)	0 %	8	253	53.4(48.7,62.0)	85 %	−8.0 (−11.8, −4.3)	43 %
Long-acting°	8	256	110.9(94.0,127.82)	88 %	9.3 (1.6, 17.0)	34 %	8	256	57.6(53.9,61.30)	63 %	−10.5 (−12.8, −8.2)	0 %
Transfeminine Populations												
All Studies	11	1025	102.4 (98.5, 106.3)	55 %	−1.2 (−6.6, 4.1)	69 %	13	1103	51.0 (48.3, 53.7)	87 %	0.1 (−2.9, 2.9)	84 %
Modern GAHT⊥	10	1005	101.8(98.1,105.6)	62 %	−0.6 (−5.6, 4.3)	82 %	11	1060	53.1(50.5,55.6)	85 %	−2.3 (−4.7, 0.0)	82 %
Route+												
Oral	4	249	102.5(92.5,112.4)	58 %	−6.3 (−9.3, −3.4)	0 %	5	299	51.1(40.2,62.1)	94 %	1.3 (−5.9,8.4)	86 %
Transdermal	4	276	107.5(98.6,116.5)	65 %	3.4 (−12.2, 19.0)	89 %	4	276	54.5(52.5,56.5)	0 %	−5.4 (−8.3, −2.5)	35 %
Co-Intervention×												
CPA	6	402	106.0(100.0,112.0)	53 %	−0.4 (−11.2,10.5)	80 %	6	402	53.0(46.9,59.2)	90 %	−2.1 (−7.2,3.1)	75 %
Spironolactone	Too few studies						3	138	44.5(36.6,52.5)	73 %	4.2 (0.5,7.8)	0 %

Abbreviations: LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; MDM = meta- difference of means; IM/SQ = intramuscular/subcutaneous; CPA = Cyproterone Acetate N = number of studies, n = total sample size across studies.
◆ units = mg/dL.
* testosterone enanthate and cypionate.
° testosterone undecanoate.
⊥ excludes results for oral ethinyl estradiol and Premarin
+ Includes studies that reported results for a single route of administration. Studies reporting aggregate results excluded. Number of studies in "Route" row is different from the combination of oral and transdermal studies as some individual studies reported separately for both oral and transdermal regimens.
× Includes studies that reported results for a single co-intervention, either CPA or spironolactone. Studies reporting aggregate results excluded.
*The MDM column here represents *meta*-means (95 % CI) at baseline in mg/dL.

In the subgroup analyses comparing blood lipid changes following oral and transdermal estradiol therapy the only notable difference was observed for HDL-C where a pronounced change was apparent only for oral route of administration. When interpreting these results, it is important to keep in mind that many clinicians treating TGD patients, specifically at European centers participating in the ENIGI cohort, preferentially prescribe transdermal estrogen formulations to patients 45 years and older.[58] For this reason, it is unclear if the observed discrepancy between results for oral and transdermal estrogen is attributable to the route of administration or the difference in patient ages. A sensitivity analysis excluding estrogen formulations not regularly used in modern practice (Premarin, conjugated equine estrogen, and ethinyl estradiol) showed a similar pattern of results but with attenuation of point estimates towards the null (except for HDL-C). A sub-analysis restricted to studies with a co-intervention of spironolactone alongside estradiol showed a slight increase in HDL-C; however, these results are subject to considerable uncertainty because they were based on just 3 studies.

Three prior reviews evaluated the same or similar research questions.[10,59,60] The most recent of these studies[10] also reported an increase in LDL-C and triglyceride levels among TM. The differences observed in that study were similar in magnitude to MDM values in our meta-analysis in the interval prior to 24 months post-GAHT. After that time point, our results demonstrated a greater absolute change. A decrease in HDL-C levels was similar in both studies, however changes in total cholesterol in our analysis were more pronounced, especially at the 12-month timepoint.

Much of the prior literature assessing the effects of masculinizing and feminizing GAHT focused on acute cardiovascular events.[9,61–63] Studies have generally shown an increased risk of venous thromboembolism and ischemic stroke (to varying degrees) among TF populations compared to both cisgender men and women.[63] This is thought to be in part due to increased pro-coagulant profiles secondary to feminizing GAHT.[61] Similarly, an increased risk of myocardial infarction comparing TF to cisgender women has been shown while MI risk remains roughly equivalent to cisgender men.[9,62,63] No such differences in cardiovascular events have been seen among TM populations.[63,64] While understanding the risk of acute events such as myocardial infarction or stroke in TGD people is very important, an assessment of subclinical cardiometabolic effects of GAHT can inform primary prevention and early detection in this population

Most available studies on the relationship between endogenous and exogenous testosterone and lipid levels have largely focused on cisgender men. Lower endogenous testosterone levels in this population have been shown to correlate with higher total cholesterol and triglycerides, and lower HDL-C.[65–67] While the underlying mechanism is not clear, some hypotheses propose that lower testosterone levels may activate lipoprotein lipase, thereby increasing triglyceride uptake.[68] This runs counter to our findings pertaining to feminizing GAHT; however, it is possible that the anti-androgen therapy in TF populations does not produce sufficient reduction of testosterone levels to affect lipoprotein lipase activity. Among TM, reductions in HDL may be driven by increased reverse cholesterol transport; [67] however, this would not explain the rise in LDL-C and triglycerides in this population.

Table 3b
Subgroup Analyses at Baseline and 12-Month Timepoint Compared to All Studies (Total Cholesterol & Triglycerides).

Analysis category	Total cholesterol N	n	Baseline Meta-Mean (95% CI)◆	I^2	MDM (95% CI)◆	I^2	Triglycerides N	n	Baseline Meta-Mean (95% CI)◆	I^2	MDM (95% CI)◆	I^2
Transmasculine Populations												
All Studies	18	977	176.1 (170.4, 181.8)	81%	7.7 (1.4, 14.0)	86%	18	994	87.3 (77.2, 97.4)	95%	14.9 (7.3, 22.5)	71 %
Route												
IM/SQ	13	471	176.2(169.5,183.8)	70%	5.1 (0.4, 9.8)	6%	13	488	88.4(75.9,100.9)	88%	13.1 (5.8, 20.4)	44 %
Regimen												
Short-acting*	6	196	175.7(167.6,183.8)	45%	1.4 (−1.6, 4.3)	0%	6	213	71.6(54.2,88.9)	75%	11.0 (1.9, 20.2)	27 %
Long-acting°	8	256	179.2(163.7,194.8)	77%	9.1 (0.4, 17.8)	22%	8	256	99.5(82.0,116.9)	81%	17.5 (4.8, 30.2)	58 %
Transfeminine Populations												
All Studies	15	1237	178.6 (171.9, 185.3)	89%	−2.9 (−9.1, 3.3)	81%	13	1162	107.2 (93.0, 121.5)	99%	1.6 (−9.1, 12.4)	81 %
Modern GAHT⊥	13	1194	177.4(170.5,184.4)	91%	−4.1 (−10.5, 2.4)	86%	12	1139	101.5(85.9,117.1)	99%	0.8 (−8.9, 10.4)	89 %
Route+												
Oral	6	359	176.3(164.5,188.1)	77%	−7.4 (−16.5, 1.8)	54%	5	339	92.9(75.9,109.9)	72%	7.9 (−11.3, 27.2)	68 %
Transdermal	4	276	179.1(162.7,195.5)	89%	−0.7 (−21.5, 20.2)	93%	4	276	86.0(69.79,102.1)	77%	7.4 (−14.5, 29.3)	88 %
Co-Intervention×												
CPA	7	476	180.7(164.6,196.8)	95%	−3.7 (−15.0,7.7)	83%	6	456	107.9(68.4,147.4)	100%	3.1 (−19.2,25.5)	92 %
Spironolactone	3	138	175.3(139.5,211.2)	83%	2.4 (−37.8,42.5)	69%	3	138	113.1(73.4,152.9)	48%	1.6 (−55.0,58.1)	63 %

Abbreviations: LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; MDM = meta- difference of means; IM/SQ = intramuscular/subcutaneous; CPA = Cyproterone Acetate N = number of studies, n = total sample size across studies.
◆ units = mg/dL.
* testosterone enanthate and cypionate.
° testosterone undecanoate.
⊥ excludes results for oral ethinyl estradiol and Premarin
+ Includes studies that reported results for a single route of administration. Studies reporting aggregate results for multiple routes of administration excluded.
× Includes studies that reported results for a single co-intervention, either CPA or spironolactone. Studies reporting aggregate results excluded.
*The MDM column here represents *meta*-means (95 % CI) at baseline in mg/dL.

Conversely, testosterone supplementation in hypogonadal cisgender men has been shown to produce a reduction in HDL-C as well as a lowering of total cholesterol and LDL-C.[69] Notably, exogenous testosterone delivered transdermally to older, hypogonadal cisgender men did not show an impact on HDL-C levels.[66] Taken together these results indicate that findings from studies of cisgender men may not necessarily apply to TM populations.

Important distinguishing features of our analyses, compared to previous reviews, include a larger number of eligible studies, the ability to present sub-analyses by GAHT characteristics and co-interventions, and the availability of data at six different timepoints that allowed constructing meta-regression models to assess long-term trends. On the other hand, limitations of our review include the inability to complete all steps in duplicate. Specific steps not completed in duplicate included data extraction and risk of bias assessment.

Our review also identified several important knowledge gaps and limitations of the extant literature. For example, the sub-analyses for transdermal versus injectable testosterone were not possible due to sparse data. The relatively short duration of most studies also limits our ability to examine the long-term influence of GAHT on lipid profiles. Some studies did not explicitly indicate the sample size at each timepoint. This represents another limitation of the available data because the assumption of no loss to follow-up may not be valid. While this meta-analysis allowed presenting data by medication regimen, route of administration, and co-intervention, the lack of longitudinal follow-up data beyond one year for these sub-analyses remains a limitation. Only 12 of 35 studies specified that laboratory analyses were conducted using fasting samples.[22,25,26,28,29,33,39,43,45,46,51,57] Thus, inclusion of studies that did not mention fasting status may have affected the meta-analysis results particularly for triglycerides. Additionally, lipids can vary across the menstrual cycle; however, no studies identified in the present review addressed this issue in TM individuals.[70] The current analysis does not represent global experiences because most studies were conducted in the USA or in Western Europe. Care should be taken when generalizing results given the diversity of populations and GAHT regimens globally. Additional studies with extended follow-up are needed to compare long-term GAHT-induced lipid profile changes to those observed in cisgender populations. For example, useful information can be drawn by comparing TM people to hypogonadal cisgender men receiving testosterone supplementation.

Conclusion

In summary, despite important limitations of existing studies, the available low-to-fair quality evidence suggests that testosterone-based GAHT among TM individuals may worsen cardiometabolic profiles with increases in LDL-C, total cholesterol, and triglycerides and corresponding decreases in HDL-C. Studies evaluating the effects of feminizing GAHT on balance demonstrate no notable changes in HDL-C or triglycerides while the results for LDL-C and total cholesterol were inconsistent. Taken together these results appear somewhat reassuring for TF individuals on GAHT. The results also suggest that TM patients receiving testosterone may benefit from closer monitoring of lipid profiles or lifestyle interventions; however, the direct impact of masculinizing GAHT on cardiovascular disease risk is beyond the scope of the present review.

Other information

Registration and protocol

The protocol for this systematic review and meta-analysis was registered with PROSPERO on September 11, 2021 under registration number CRD42021267269.

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Competing interests

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CRediT authorship contribution statement

Bennett Gosiker: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Data curation, Conceptualization. **Jude Moutchia:** Methodology, Investigation, Formal analysis, Data curation. **Nghiem Nguyen:** Validation, Investigation. **Darios Getahun:** Writing – review & editing, Project administration, Methodology, Conceptualization. **Michael Goodman:** Writing – review & editing, Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Michael Goodman, Darios Getahun reports a relationship with Patient-Centered Outcomes Research Institute that includes: funding grants. Michael Goodman, Darios Getahun reports a relationship with National Institute of Child Health and Human Development that includes: funding grants. Michael Goodman, Darios Getahun reports a relationship with National Institute of Aging that includes: funding grants. Michael Goodman reports a relationship with Epidemiologic Research & Methods, LLC that includes: consulting or advisory. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.].

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcte.2024.100349.

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