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GENDER-AFFIRMING HORMONE THERAPY DECREASES D-DIMER BUT WORSENS INSULIN SENSITIVITY IN TRANSGENDER WOMEN

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Abstract

Objectives: Gender-affirming hormonal therapies (GAHT) and HIV increase cardiovascular risk for transgender women (TW), yet little data quantifying cardiometabolic changes following GAHT initiation exists, particularly among TW with HIV.

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Conflicts of interest

JEL receives research support from Gilead Sciences, and serves as a consultant to Theratechnologies, unrelated to the work. JLC receives research support from Gilead Sciences, unrelated to the work. KHM has received unrestricted research grants from Gilead Sciences and Merck unrelated to this work, and has served on scientific advisory boards for Gilead and Merck unrelated to this work. NF has served as a consultant for Gilead, unrelated to this work. For the remaining authors none were declared.

Methods: The Féminas study enrolled TW from October 2016-March 2017 in Lima, Peru. Participants reported sexual activity that was high risk for HIV acquisition or transmission. All received HIV/STI testing and access to GAHT (estradiol valerate and spironolactone), HIV pre-exposure prophylaxis (PrEP) or antiretroviral therapy (ART) for 12 months. Biomarker measurement occurred on stored serum; fasting glucose and lipids were measured in real time.

Results: 170 TW (32 with HIV, 138 without HIV) had median age 27 years and 70% prior GAHT use. At baseline, PCSK9, sCD14, sCD163, IL-6, sTNFRI/II, CRP and EN-RAGE levels were significantly higher in TW with HIV vs TW without HIV. HDL and total cholesterol were lower and insulin and glucose parameters were similar. All TW with HIV started ART, but only 5 achieved virologic suppression at any time. No TW without HIV initiated PrEP. Over 6 months, all participants initiated GAHT and had worsening insulin, glucose and HOMA-IR. Large d-dimer decreases also occurred. Similar changes occurred in TW with and without HIV.

Conclusions: In this unique cohort of TW, GAHT decreased d-dimer but worsened insulin sensitivity. Because PrEP uptake and ART adherence were very low, observed effects are primarily attributed to GAHT use. Further study is needed to better understand cardiometabolic changes in TW by HIV serostatus.

Keywords

Transgender women; feminizing hormone therapy; cardiovascular disease; HIV; insulin resistance

Introduction

Gender-affirming hormonal therapies (GAHT) can be critical to harmonizing gender identity and expression with the desired bodily phenotype for transgender women (TW). However, GAHT (estrogen ± anti-androgen therapy) modulates inflammatory and coagulation pathways, causes fat gain and lean mass loss, and may increase metabolic disease risk.[1] Similarly, HIV and antiretroviral therapy (ART) use are associated with altered body composition and cardiometabolic disturbances.[2] Chronic HIV is also characterized by persistent inflammation, immune activation, and coagulation pathway abnormalities.[3]

The intersections of HIV−, ART− and GAHT-induced immuno-metabolic alterations and their effects on cardiometabolic risk in TW are poorly understood yet could profoundly affect the health of this population, and may also affect TW taking ART for HIV pre-exposure prophylaxis (PrEP). We assessed changes in cardiometabolic and inflammatory biomarker profiles among TW enrolled in the Féminas study following GAHT initiation, by HIV serostatus, and with ART or PrEP initiation.

Methods

Study Population

This is a secondary, post hoc analysis of stored samples from the Féminas study, which evaluated a gender-affirming medical care strategy for TW that integrated HIV and sexually transmitted infection (STI) prevention, testing, and treatment services with GAHT and peer health navigation between October 2016-March 2017 in Lima, Peru. Participants were:

≥18 years of age; assigned male sex at birth; currently identifying as a TW or on the trans-feminine continuum; with or without HIV but not engaged in care, or of HIV unknown serostatus; and engaged in ≥1 of the following: no condom use during the last anal sex encounter, >5 sex partners in the last 6 months, self-identified as a sex worker, had an STI diagnosis in the last 6 months, or had a current sexual partner living with HIV.

Féminas Study Conduct

Institutional Review Board approval was obtained prior to recruitment and written informed consent obtained prior to study procedures. Participants underwent HIV, STI and tuberculosis testing, medical history collection, physical exam, basic biochemical profiling and storage of blood for future use.

All Féminas participants were offered GAHT consisting of spironolactone (50mg daily, increased by 50mg monthly until 200mg daily) and estradiol valerate (2mg po daily for 4 weeks, then 4mg daily). TW without HIV were offered PrEP consisting of emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) co-formulated as Truvada™. TW living with HIV were provided ART consisting of co-formulated FTC/TDF + efavirenz (EFV), with alternatives for safety/tolerability as per 2014 Peruvian Ministry of Health guidelines. Follow-up visits occurred at months 1, 3, 6, 9 and 12.

Blood for Biomarker Measurement

Blood was collected, processed, and immediately stored on site (≤−70°C). For this secondary analysis, cryopreserved serum and plasma were shipped overnight on dry ice to Dr. Funderburg (The Ohio State University, Columbus, OH) for batched analysis at end of study. Standard Funderburg lab cryopreservation protocols for plasma/serum collection and storage were adhered to ensure no temperature excursions occurred prior to analysis. Biomarkers of generalized inflammation (tumor necrosis factor [TNF]-α, interleukin [IL]-6, IL-8), metabolism (insulin, adiponectin, oxidized low-density lipoprotein [LDL], proprotein convertase subtilisin/kexin type 9 serine protease [PCSK9], fatty acid binding protein [FABP]-4), monocyte activation (soluble [s] CD14, sCD163), coagulation (d-dimer, plasminogen activator inhibitor [PAI]-1, von Willebrand factor [vWF]) and vascular health/activation (endothelin [ET]-1, vascular cell adhesion molecule [VCAM]-1, extracellular newly-identified receptor for advanced glycation end-products [EN-RAGE], sTNF receptor [sTNFR] II, CX3CL1) were measured by ELISA/EIA according to manufacturer specifications. Fasting glucose was obtained from parent study data, and the homeostatic model assessment of insulin resistance (HOMA-IR) value was calculated as (insulin [μU/L] x glucose [mmol/L])/22.5.

Statistical Analysis

Secondary descriptive analyses were generated for the cohort overall at baseline, and for the subset with paired samples through month 12. Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR), and data stratified by HIV serostatus. Wilcoxon rank-sum and Pearson χ^2 tests compared continuous and categorical variables, respectively, between groups. All tests were 2-sided (α=0.05), without correction for multiple testing given that all analyses were exploratory.

Although our sample size was fixed by the parent Féminas study, known biomarker distributions among TW and people living with HIV (PLWH) suggest sufficient power to observe between-group differences and baseline, and within-group differences longitudinally. Based on our preliminary data, seven TW per group provided 80% power to observe a similar effect by GAHT use status, and 100% power to see similar between-group differences by HIV serostatus. Additionally, in PLWH a 0.07 $\log_{10}$ sCD14 (SD 0.09) between-arm difference is associated with a clinically significant, 25% lower odds of a non-AIDS event or non-accidental death. [4] Thirty TW per group provided 85% power to detect a 0.07 $\log_{10}$ sCD14 difference between any two groups (two-sided α=0.05).

Results

Study Population

A total of 220 participants enrolled in the parent study. Of 170 TW (32 with HIV, 138 without HIV) with stored samples for analysis at baseline, there was a 77% 12-month retention and no differential dropout by HIV serostatus. Median age was 27 years, 69% had history of prior GAHT use, 100% identified as Latina. Only 13% of TW living with HIV were on ART at study entry. Comorbid disease and abnormal labs were infrequent, including no known viral hepatitis. All participants initiated GAHT. All TW living with HIV started ART, but only 5 (15.6%) achieved undetectable HIV-1 RNA at any time on study. Five TW without HIV (3.6%) became HIV+ during follow-up. No TW without HIV initiated PrEP.

Baseline Biomarker Profiles

At baseline, PCSK9, sCD14, sCD163, IL-6, sTNFRI/II, hs-CRP and EN-RAGE levels were significantly ($p<0.05$) higher in TW with HIV vs. without HIV, whereas HDL and total cholesterol were lower, and insulin, glucose and d-dimer parameters were similar (data not shown).

Longitudinal Biomarker Changes

Over 6 months, TW on GAHT with and without HIV had increased insulin, glucose and HOMA-IR values that persisted at 12 months (Table 1), while the remaining biomarkers persisted clinically unchanged (data not shown). Large decreases in d-dimer also occurred, particularly for TW without HIV; notably, without virologic suppression, d-dimer could not be reasonably expected to decline among TW living with HIV. Therefore, the large observed effect in TW without HIV is believed to represent an GAHT effect. Though potentially clinically significant for individuals, variability was very high, preventing observation of statistical significance for the cohort. Similar changes in TW with and without HIV suggest that persistent viremia did not obscure GAHT effects.

Discussion

In this unique cohort of TW initiating GAHT, several important findings were observed. First, all 32 TW living with HIV initiated ART, but only five (16%) achieved virologic suppression at any time over the 12-month follow-up period. Second, no TW initiated PrEP.

Third, GAHT initiation was associated with worsening insulin, glucose and HOMA-IR values, but also large decreases in d-dimer.

Though a full description of contributors to engagement in care and ART or PrEP adherence among TW is beyond the scope of this report, lack of virologic suppression and PrEP uptake among Féminas study participants significantly influences biomarker data interpretation for this secondary analysis. Notably, low virologic suppression rates among this group of TW living with HIV limits ability to observe of biomarker changes on GAHT following virologic suppression. Lack of PrEP uptake, while worrisome in a population at high risk of HIV acquisition, actually allowed for observation of biomarker changes following GAHT initiation that were not confounded by PrEP effects. Finally, five TW seroconverted to become HIV+ during study follow-up, and required data censoring at the time of seroconversion.

D-dimer is a fibrin degradation product associated with increased risk of cardiovascular disease events and all-cause mortality in healthy populations.[5] Among persons assigned male sex at birth, d-dimer levels are: positively associated with serum testosterone levels, negatively associated with serum estradiol levels, and positively associated with testosterone:estradiol ratio.[6] Similarly, androgen deprivation therapy for prostate cancer with estradiol hemihydrate is associated with reduced d-dimer levels.[7] Though oral contraceptive use is associated with increased or stable d-dimer levels in persons assigned female sex at birth,[8] it has been associated with reduced d-dimer levels when used for the treatment of polycystic ovarian syndrome.[9] Together, these findings suggest that GAHT in TW might lower d-dimer through androgen deprivation. However, in one cross-sectional study of Japanese TW, d-dimer was not different between TW on GAHT vs GAHT-naïve TW.[10] Thus, to our knowledge, we are the first to report a reduction in d-dimer, and therefore possibly cardiovascular risk, in TW receiving estradiol valerate-based GAHT regardless of HIV serostatus. Because PrEP uptake and ART adherence were very low, and observed changes were similar for TW with and without HIV, these effects seem primarily due to GAHT use.

GAHT has previously been associated with reduced insulin sensitivity.[11,12] GAHT is associated with increased adipocyte size,[13] suggesting adipocyte hypertrophy rather than hyperplasia, a mechanism of fat gain associated with insulin resistance and diabetes.[13,14] Persons assigned male sex at birth have less ability to modulate adipocyte size compared to pre-menopausal, non-obese persons assigned female sex at birth, leading to predominantly detrimental responses to fat gain.[15] Therefore, insulin resistance in TW on GAHT may be a maladaptive response influenced by genetic sex. Indeed, though TW have lower android:gynoid fat mass ratios, android fat content correlates more strongly with the development of insulin resistance than gynoid fat.[16] Additionally, GAHT causes lean mass loss in TW. Though complex relationships between sarcopenia and insulin resistance have been documented in the general population, data in TW are lacking, and body composition was not measured by the parent study.

A unique and important component of *Féminas* was the inclusion of TW living with HIV. Most studies describing metabolic and inflammatory changes following GAHT initiation

exclude TW with HIV or do not account for HIV serostatus. Given the significant metabolic and inflammatory perturbations associated with HIV and ART, data from TW on ART and GAHT are needed to understand the potential intersections of cardiometabolic risk. Future research in TW with HIV on suppressive ART who are initiating GAHT will help fill this knowledge gap. Strengths of this analysis include the relatively large sample size and the use of standardized GAHT with estradiol valerate instead of ethinyl estradiol. As ethinyl estradiol is no longer recommended for GAHT due to adverse event profiles, new data using contemporary GAHT regimens are needed to optimize care for TW.

The main limitations of this study include that it is a secondary data analysis and that rates of virologic suppression among TW living with HIV on ART were exceedingly low, as detailed above. Specifically, low rates of virologic suppression among TW living with HIV limited our ability to observe biomarker changes on GAHT following virologic suppression. The larger than expected variability in biomarker values also prevented demonstration of statistically significant differences between groups, though we report large, potentially clinically significant differences in d-dimer and insulin glucose homeostasis. Finally, serum hormone levels were not systematically obtained through routine care, and were not measured by the parent study, which prevented exploration of potential correlations between hormone and biomarker concentrations. Nonetheless, the strengths of this analysis outweigh the limitations and contribute to the existing body of literature.

Conclusions

In this unique cohort, GAHT initiation appeared to decrease d-dimer but worsen insulin sensitivity for both TW with and without HIV. Because PrEP uptake and ART adherence were very low, and observed changes were similar for TW with and without HIV, these effects seem primarily due to GAHT use. Further study is needed to better understand cardiometabolic changes in TW on GAHT and with ART and/or PrEP use.

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Table 1.

Longitudinal Biomarker Changes

	HIV−			HIV+		
	Month 0 N=138	**Month 6 N=124**	**Month 12 N=106**	**Month 0 N=32**	**Month 6 N=26**	**Month 12 N=25**
d-dimer (ng/mL)	170.6 (116.8, 338.4)	127.9 (83.7, 205.2)	126.2 (82.4, 187.1)	271.2 (140.1, 362.4)	160.2 (115.1, 229.8)	145.9 (109.1, 273.8)
Insulin (pmol/L)	26.8 (19.3, 42.9)	39.2 (28.0, 67.8)	36.2 (22.7, 69.3)	25.6 (19.4, 43.5)	38.8 (24.3, 53.4)	34.5 (23.4, 75.9)
Glucose (mg/dL)	87.7 (82.3, 92.7)	90.6 (86.1, 95.3)	89.5 (86.4, 95.0)	85.5 (81.7, 90.1)	92.7 (88.9, 95.8)	89.6 (85.5, 95.5)
HOMA-IR	0.8 (0.6, 1.4)	1.3 (0.9, 2.2)	1.1 (0.8, 2.3)	0.8 (0.6, 1.3)	1.2 (0.8, 1.7)	1.1 (0.8, 2.6)
	6-Month Changes *			**12-Month Changes** *		
	HIV−		**HIV+**	**HIV−**		**HIV+**
	Median (IQR)	%	Median (IQR) %	Median (IQR)	%	Median (IQR) %
d-dimer (ng/mL)	−36.5 (−157.4, 30.7)	−21	−5.5 (−285.8, 36.6) −2	−60.6 (−176.3, 10.1)	−36	−51.1 (−251.6, −0.9) −19
Insulin (pmol/L)	8.7 (−3.5, 30.8)	+32	5.7 (−8.1, 30.7) +22	6.5 (−3.1, 25.4)	+24	7.0 (−2.8, 32.8) +27
Glucose (mg/dL)	3.4 (−3.0, 9.5)	+4	5.0 (2.2, 12.5) +6	2.8 (−3.0, 9.1)	+3	2.8 (−1.9, 10.0) +3
HOMA-IR	0.3 (−0.1, 1.1)	+38	0.2 (−0.3, 1.1) +25	0.2 (−0.2, 1.2)	+25	0.3 (−0.1, 1.4) +38

* P >0.05; HOMA-IR: homeostatic model assessment of insulin resistance; IQR: interquartile range

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