FEMINIZING HORMONAL THERAPIES WORSEN CARDIOMETABOLIC PROFILES IN TRANSGENDER WOMEN

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Background

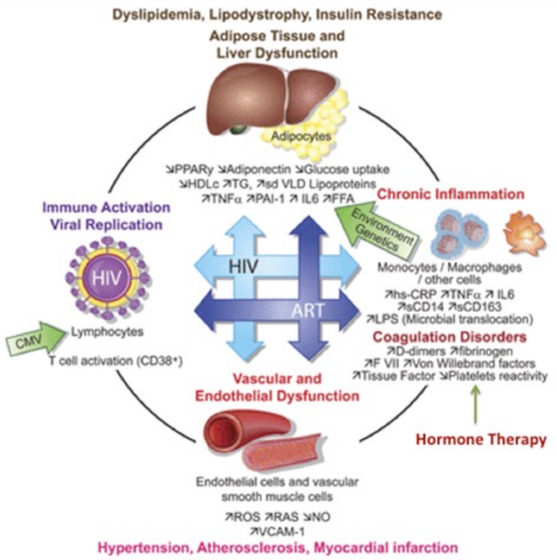


Fig. 1: Contributions of HIV and FHT to metabolic and inflammatory disease. Adapted from Hemkens and Bucher. *Eur Heart J. 2014*

- Transgender women (TW) are disproportionally affected by HIV and have a high prevalence of modifiable cardiovascular disease (CVD) risk factors[1,2]
- Feminizing hormonal therapy (FHT) and HIV potentially alter CVD risk in TW[3]
- We assessed relationships between sex hormone concentrations, body composition and inflammatory biomarkers among TW and matched cisgender men (CM)

Methods

Study Population:
- Adult TW on FHT were recruited from Houston, TX and Baltimore, MD
- Matched, control CM were selected from participants enrolled in The Multicenter AIDS Cohort Study (MACS) Cardiovascular Sub-studies 2 or 3

Inclusion Criteria:
- Self-identification as a TW
- 40-70 years of age
- On FHT for ≥3 months
- If living with HIV, on ART with HIV-1 RNA <50 copies/mL at screening

Exclusion Criteria:
- History of coronary artery bypass grafting, heart valve surgery, coronary angioplasty or atrial fibrillation
- Estimated glomerular filtration rate <60 mL/min
- History of contrast nephropathy

Study Design:
- Observational, cross-sectional study (2018-2020)
- CM from the MACS Cardiovascular 2 or 3 sub-studies were matched 2:1 to TW on HIV serostatus, age within 5 years, race/ethnicity, BMI category and ART type (latter where possible)

Analysis:
- Body composition was measured by a non-contrast, computed tomography (CT) cardiac imaging and single slice scans of the abdomen at the level of the umbilicus and at the level of the mid-thigh
- Sex hormones and inflammatory biomarker concentrations were measured centrally at end of study
- Wilcoxon rank-sum and Pearson χ^2 tests were used to compare continuous and categorical variables, respectively, between groups
- Due to limited number of participants without HIV, results are not stratified by HIV serostatus

Results

Table 1: Baseline Characteristics

	CM (N=60)	TW (N=32)	*P*-Value
Age	54 (48, 56)	52 (45, 59)	**
Black race	29 (48%)	17 (53%)	**
Hispanic ethnicity	13 (22%)	7 (22%)	**
BMI (kg/m²)	29.3 (24.6, 32.7)	30 (24.7-32.5)	**
Current smoker	16 (27%)	12 (38%)	0.28
Hypertension	27 (46%)	10 (32%)	0.22
Diabetes mellitus	10 (17%)	4 (12.5%)	0.57
Fasting glucose (mg/dL)	**98 (92, 106)**	**92 (86, 102)**	**0.038**
Hyperlipidemia*	**44 (75%)**	**15 (47%)**	**0.008**
Total Cholesterol (mg/dL)	182 (156, 203)	172 (156,195)	0.38
HDL Cholesterol (mg/dL)	45 (37, 55)	47 (41,60)	0.19
LDL Cholesterol (mg/dL)	112 (91, 128)	97 (84, 123)	0.27
Triglycerides (mg/dL)	125 (78, 163)	120 (75, 157)	0.88
% living with HIV	44 (73%)	25 (78%)	**
INSTI-based ART	**20 (33%)**	**24 (75%)**	**<0.001**
CD4⁺ T-Cell Count (cells/μL)	726 (579, 1051)	792 (582, 939)	0.68
On hormone therapy			
Estrogens (any form)	0	29 (91%)	
Androgen antagonists	0	21 (66%)	
Testosterone	5 (8%)	0	

Frequency or median (interquartile range) presented; TW=Transgender Women, CM=Cisgender Men, BMI=Body Mass Index, INSTI=Integrase strand transfer inhibitor, ART=antiretroviral therapy. *Hyperlipidemia was clinically diagnosed and/or participant was on lipid-lowering agents at screening. **=matching factor

Table 2: Body composition

	CM (N=60)	TW (N=32)	*P*-value
Abdominal Sub-Q Fat (cm²)	279 (153, 413)	345 (253, 450)	0.09
Abdominal Visceral Fat (cm²)	154 (106, 207)	137 (89, 196)	0.43
Thigh Muscle Fat (cm²)	**7 (4, 10)**	**16 (12, 27)**	**< 0.001**
Thigh Sub-Q Fat (cm²)	45 (27, 80)	53 (36, 82)	0.24
Epicardial Fat (cm²)	70 (44, 96)	59 (46, 70)	0.1
Intrathoracic Fat (cm²)	**141 (83, 214)**	**77 (55, 89)**	**< 0.001**
Thoracic Peri-Aortic Fat (cm²)	**19.7 (11.1, 32.4)**	**7.1 (6.3, 10.2)**	**< 0.001**
Liver-Spleen Attenuation Ratio	1.24 (1.10, 1.34)	1.30 (1.16, 1.35)	0.25
Hepatic Steatosis (Liver-Spleen Ratio < 1.0)	5 (9%)	1 (6%)	0.61

Median (interquartile range) presented; TW=transgender women, CM= cisgender men, Sub-Q= subcutaneous

Table 3: Hormone Concentrations

	CM (N=60)	TW (N=32)	*P*-value
Cortisol (ug/dL)	8.4 (7.1, 10.8)	9.1 (7.2, 12.4)	0.38
Estradiol (pg/mL)	**23.1 (17.5, 28.1)**	**84.5 (31.7, 120.0)**	**< 0.001**
Total Testosterone (ng/dL)	441 (341, 571)	325 (17, 674)	0.11
Total Testosterone < 50 ng/ml	**0**	**9 (31%)**	**< 0.001**
Free Testosterone (ng/dL)	**13.2 (10.4-16.2)**	**7.13 (0.78, 15.2)**	**0.006**
SHBG (nmol/L)	**33.4 (27.9, 44.7)**	**72.8 (42.2, 104.4)**	**< 0.001**

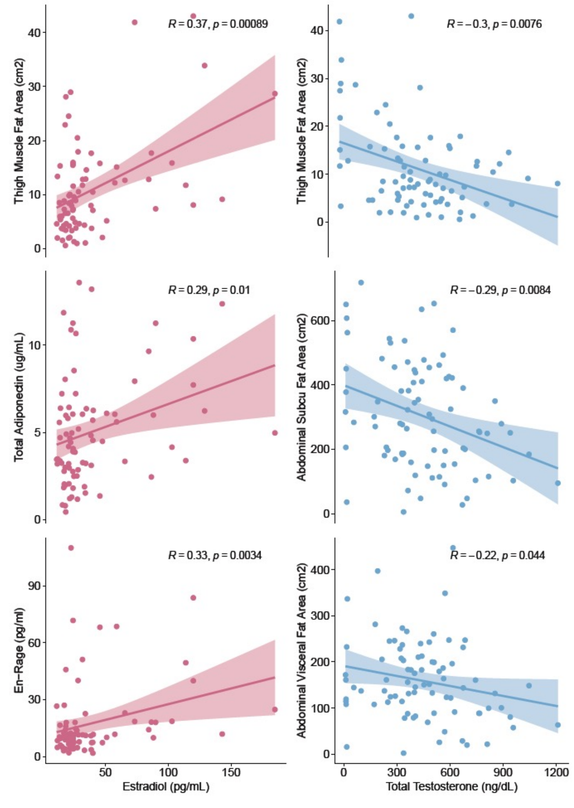
Frequency or median (interquartile range) presented; TW=transgender women, CM= cisgender men

Table 4: Biomarker Concentrations

	CM (N=60)	TW (N=32)	*P*-value
Total Adiponectin (μg/mL)	**3.86 (2.48, 5.92)**	**5.60 (3.45, 6.36)**	**0.04**
Human EN-RAGE (pg/mL)	**9.1 (4.8, 11.4)**	**23.0 (14.2, 51.1)**	**<0.001**
Endothelin (pg/mL)	**1.50 (1.24, 1.95)**	**3.14 (1.95, 4.85)**	**<0.001**
sCD14 (μg/mL)	1.63 (1.41, 1.82)	1.49 (1.33, 1.65)	0.11
sCD163 (ng/mL)	550 (442, 659)	548 (451, 663)	0.73
TNFRii/TNFRi (pg/mL)	2930 (2250, 3649)	3079 (2507, 3494)	0.71
VCAM-1 (ng/mL)	601 (506, 806)	552 (441, 672)	0.11
HOMA-IR	1.88 (1.49, 3.40)	1.72 (1.22, 3.07)	0.43
HOMA-B	74 (58, 129)	108 (70, 149)	0.08
FABP-4 (pg/mL)	23493 (16739, 31547)	24414 (16867, 34133)	0.47
IL-6 (pg/mL)	1.56 (0.87, 2.80)	1.69 (1.29, 2.86)	0.23
IL-8 (pg/mL)	4.1 (1.0, 4.1)	3.4 (1.3, 4.1)	0.72
PAI-1 (pg/mL)	23779 (15849, 41706)	17768 (10867, 24856)	0.07

Median (interquartile range) presented; TW=transgender women, CM=cisgender men

Fig. 2: Correlation Between Biomarkers Concentrations and Body Composition vs. Hormone Concentrations



-Higher estradiol and lower total testosterone concentrations correlated with greater thigh muscle fat area

-Lower total testosterone concentrations correlated with greater abdominal subcutaneous and visceral fat area.

-Higher estradiol correlated with higher adiponectin and EN-RAGE concentrations.

-After removing four participants with estradiol concentrations deemed as outliers, correlation coefficients and *p*-values shown remained similar.
-When including outliers, higher estradiol concentrations correlated with higher endothelin concentrations (r=0.22, *p*= 0.046).

Summary & Conclusions

- **In this group of older TW on FHT, higher estradiol and lower total testosterone concentrations were associated with worse body composition and mixed effects on select cardiometabolic biomarkers.**
- **Specifically, greater visceral fat and fatty muscle infiltration and higher endothelin-1 and EN-RAGE concentrations have been associated with increased cardiovascular risk in the general population, though higher adiponectin is generally thought to be beneficial.**
- **More nuanced understanding of the relationships between FHT and cardiometabolic risk in TW is needed.**

References and Acknowledgements

[1]*Lancet Infect Dis* 2013;13(3):214-22 [2]*Arch Sex Behav*. 2005;34:679-90 [3]*Clin Endocrinol.* 2010; 72(1):1-10

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