Impact of HIV Infection on Adipose Tissue Fibrosis and Its Association With Insulin Resistance

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Diana L. Alba[1], Moon Kyung Choi[1], Alaa Abdellatif [1], Stephen Brown Mayfield[1], Thuy A. Pham[4], David Berrios[1], Antonio Rodriguez[1], Marin Ewing[1], Tony Figueroa[1], Dawei Bu[2], Philipp Scherer[2], Suneil K. Koliwad[1], Peter W. Hunt[1]

[1]University of California, San Francisco, San Francisco, CA, USA,· [2]Touchstone Diabetes Center, University of Texas Southwestern Medical Center, Dallas, TX, USA

BACKGROUND

People with HIV (PWH) are at increased risk for type 2 diabetes (T2D), driven by both obesity and HIV-specific factors, including chronic inflammation and antiretroviral therapy (ART).

Subcutaneous adipose tissue (SAT) fibrosis, which reduces adipose tissue flexibility, is implicated in insulin resistance (IR), a key driver of T2D, yet its role in PWH remains poorly understood.

This study evaluates SAT fibrosis and its association with insulin resistance in PWH, identifying unique molecular features distinct from obesity-related fibrosis in people without HIV (PWoH). Understanding these mechanisms is essential to addressing HIV-associated metabolic dysfunction.

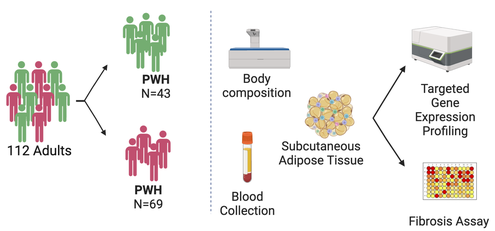
METHODS

Participants were recruited from two UCSF cohorts: IDEO (PWoH from local clinics) and SCOPE (PWH on ART ≥1 year with viral suppression). All participants were 18–75 years old and excluded if they had a diagnosis of T2D.

SAT fibrosis-associated gene expression was analyzed using the NanoString fibrosis panel. Participants were stratified by HIV status and body fat percentage (%BF) for subgroup comparisons.

SAT fibrosis was measured by hydroxyproline (HP) levels, IR by HOMA-IR, and plasma endotrophin (a profibrotic collagen VIα3 cleavage product) by ELISA.

We performed correlation analysis between hydroxyproline levels, anthropometric measures, insulin resistance, and plasma endotrophin levels.



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PWH have increased SAT fibrosis, independent of obesity, which is linked to IR. COL14A1 is a potential HIV-specific driver of fibrotic remodeling, while plasma endotrophin serves as a noninvasive marker of fibrosis and metabolic impairment, highlighting new biomarkers and therapeutic targets for metabolic dysfunction in PWH.

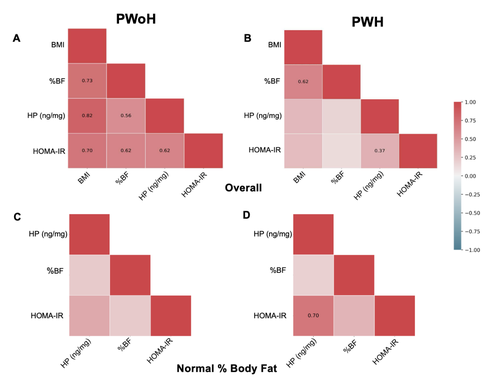
RESULTS

Characteristics of Study Participants

	PWoH (n=69)	PWH (n=43)	p-value
Age (years)	46 ± 13	54 ± 10	<0.01
Sex at birth			
Female	33	10	0.02
Male	36	33	
Race/Ethnicity			
White	28	15	
Hispanic	11	8	
Asian	27	1	<0.01
Black	3	16	
Other*	0	3	
BMI (kg/m²)	28.6 ± 7.9	29.2 ± 7.3	0.26
Body Fat Percentage (%)	31.3 ± 8.5	29.3 ± 7.5	0.13
VAT mass/total mass (%)	0.6 ± 0.3	0.8 ± 0.3	0.03
Fasting glucose (mg/dL)	94.0 (87.0, 104.0)	91.0 (85.5, 104.0)	0.54
Fasting insulin (mU/L)	9.75 (5.7, 17.4)	10.0 (7.5, 16.7)	0.66
HOMA-IR	2.2 (1.3, 4.3)	2.7 (1.6, 4.2)	0.84
HbA1c (%)	5.8 ± 1.2	5.4 ± 0.9	0.18
Duration of HIV (years)	-	13 ± 7	-
Duration of ART use (years)	-	10 ± 4	-
CD4⁺ cell count at enrollment	-	669 (560, 947)	-
Hydroxyproline (ng/mg fat)	193.5 (59.6, 689.8)	537.7 (301.7, 899.5)	<0.01

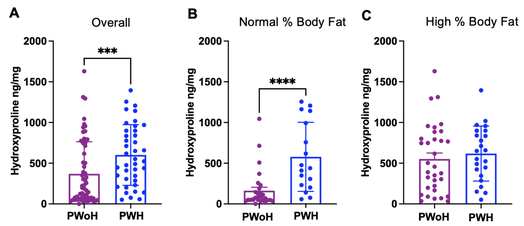
VAT: visceral adipose tissue. *Other category: includes American Indian, Pacific islander or Hawaiian or more than one race.

Relationships among BMI, %BF, IR and hydroxyproline (HP)



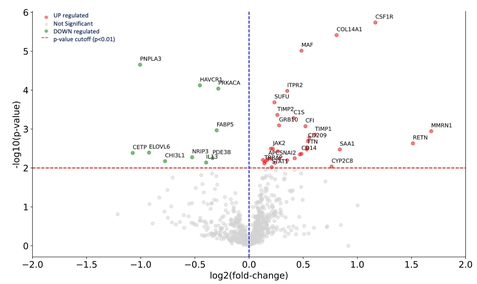
Top panels: (A) PWoH (n = 62) and (B) PWH (n = 40) for the overall group. Lower panels: (C) PWoH with normal %BF (n = 29) and (D) PWH with normal %BF (n = 17). Spearman's rank-order correlations were adjusted for sex, age, and race; only significant correlations (p < 0.05) are shown.

PWH exhibit greater adipose tissue fibrosis than PWoH, particularly in those with normal %BF

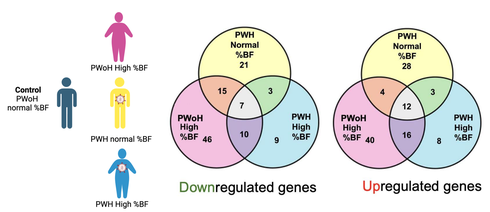


(A) Hydroxyproline levels in PWoH (n = 62) and PWH (n = 40). (B) Subgroup analysis for normal %BF (**<25% males, <35% females**) in PWoH (n = 29) and PWH (n = 17). (C) High %BF (**≥25% males, ≥35% females**) in PWoH (n = 33) and PWH (n = 23). ***p < 0.001.

PWH have a distinct transcriptional pattern of fibrosis-associated gene expression in the SAT

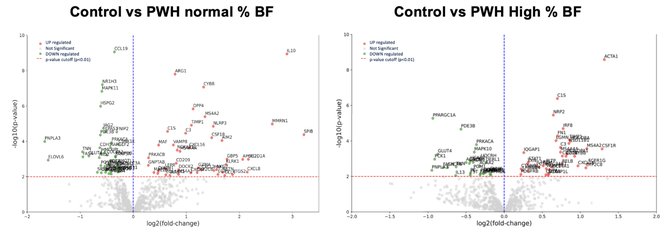


Differentially expressed genes in adipose tissue from PWH (n = 37) vs. PWoH (n = 38). Dashed lines indicate log2 fold change (blue) and p < 0.01 (red). Expression analysis used generalized linear models (negative binomial), adjusted for age, sex, race/ethnicity, %BF, and batch.

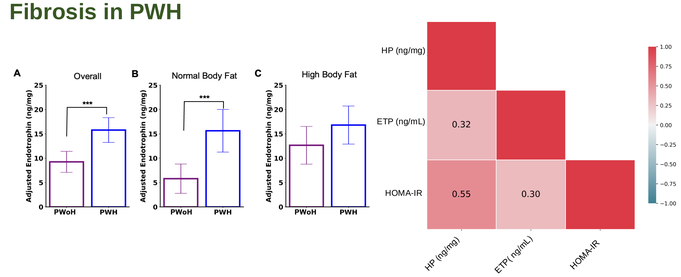


Stratified analysis of SAT transcriptional data to distinguish HIV-specific effects on fibrosis-related gene expression from adiposity-driven changes

Identifying a fibrosis-related transcriptional signature unique to HIV infection and independent of adiposity



Endotrophin is an adiposity-independent mediator of SAT Fibrosis in PWH



Adjusted Endotrophin levels (ETP). A) Overall group (PWoH n = 43, PWH n = 25). (B) Normal %BF (PWoH n = 19, PWH n = 9). (C) High %BF (PWoH n = 24, PWH n = 16). Model adjusted for sex, age, and race/ethnicity. *p < 0.05. Right panel: correlation between ETP, IR and Fibrosis in PWH.

CONCLUSIONS

- PWH exhibit increased SAT fibrosis independent of obesity, with fibrosis strongly linked to IR, while BMI and %BF are not reliable predictors of metabolic dysfunction in this population.
- Upregulation of *COL14A1* in PWH may play a pivotal role in promoting SAT fibrosis and associated metabolic dysfunction
- Overlapping pathways between HIV and obesity suggest shared mechanisms contributing to IR and T2D risk in PWH, warranting further exploration of their cellular origins and functional relevance.
- Plasma endotrophin is a potential noninvasive marker of SAT fibrosis; future studies should assess its prognostic and therapeutic potential in PWH.

ACKNOWLEDGEMENTS

We are grateful to all study participants. This research is supported by R01DK112304, K08DK124679, Harold Amos Medical Faculty Development Program, UCSF NORC grant, UCSF-Bay Area Center for AIDS Research, UCSF Clinical & Translational Science Institute.

Author Contact Information:
Email: Diana.Alba@ucsf.edu