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Adipocyte Dysfunction Despite Reduced Adipose Inflammation in Diabetics with HIV

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BACKGROUND

- Persons with HIV (PWH) are at risk for diabetes mellitus even in absence of traditional risk factors.
- Recent studies have shown profound changes to adipose tissue adaptive immune cell populations in HIV.
- Our group has previously shown that **adipose pro-inflammatory CD4⁺ T cells co-expressing CD57, GPR56, and CX_3CR1 (CGC⁺)** are associated with insulin resistance in PWH.
- We hypothesized that diabetes in PWH would be associated with altered adipose tissue expression of genes related to inflammation, macrophage activation, and energy handling as compared with non-diabetics.

METHODS

Vanderbilt Comprehensive Care Clinic
- Antiretroviral therapy for ≥ 18 months
- Serum HIV-1 RNA < 50 copies/mL for ≥ 12 months
- CD4⁺ T cell count > 350 cell/μL for ≥ 12 months

Non-diabetics (N = 30) | **Diabetics (N = 20)**

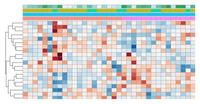
Subcutaneous Adipose Tissue Biopsy



- 5 grams of tissue
- Snap-frozen in liquid nitrogen

NanoString Gene Expression
- Immune response panel: 249 genes
- Adipocyte energy handling custom panel: 77 genes

DESeq2 Modeling
- Adjusted for batch, age, sex, body mass index
- Benjamini-Hochberg procedure for multiple comparisons



RESULTS

Table 1. Clinical characteristics by diabetes status.

	Non-Diabetic[a] (N = 30)	Diabetic[b] (N = 20)	P value
Age, median years	45.0 (31.8, 49.8)	55.0 (49.0, 58.0)	**0.002**
Female (%)	6 (20)	4 (20)	1.00
Race, Caucasian (%)	17 (57)	11 (55)	1.00
BMI, kg/m²	30.4 (28.4, 34.1)	33.1 (30.7, 37.4)	0.05
Waist circumference, cm	106 (94, 109)	113 (109, 120)	**0.001**
INSTI-based regimen (%)	20 (67)	16 (80)	0.48
Older NRTI exposure (%)	5 (17)	5 (25)	0.49
Hemoglobin A1c, %	5.3 (5.0, 5.4)	7.4 (6.6, 9.1)	**< 0.001**
Fasting glucose, mg/dL	88 (81, 92)	178 (139, 236)	**< 0.001**
CD4⁺ count at enrollment, cells/μL	824 (690, 1004)	992 (726, 1172)	0.21

Continuous variables are shown as median value with interquartile range (parentheses).
[a]Non-diabetics: hemoglobin A1c < 5.7% and fasting blood sugar < 100 mg/dL
[a]Diabetics: hemoglobin A1c ≥ 6.5% or fasting blood sugar ≥ 126 mg/dL or antidiabetic agent
BMI = body mass index; INSTI = integrase strand transfer inhibitor; NRTI = nucleoside reverse transcriptase inhibitor

Figure 1. Volcano plot showing adjusted log_2 fold change (diabetic vs. non-diabetic) vs. -log_{10}(p-value) for the immune response (A) and adipocyte energy handling (B) panels. Genes with adjusted p < 0.05 are shown in red (higher expression) and blue (lower expression). The fold change expression was notably lower in immune response genes compared with adipocyte energy handling genes.

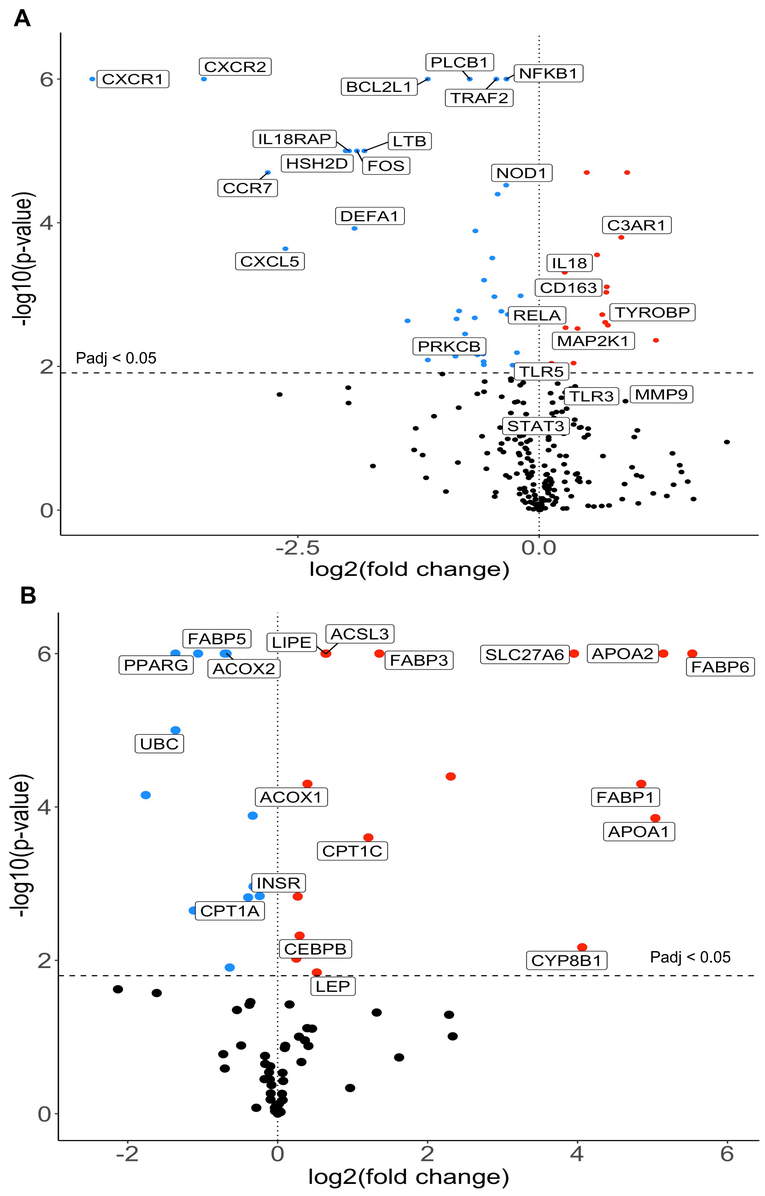
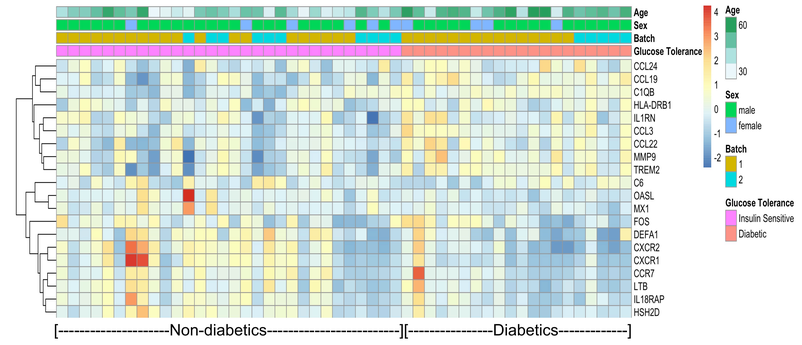


Table 2. Top gene ontology pathways for differentially expressed immune genes with adjusted P < 0.1 in diabetics vs. non-diabetics. Not all genes below are labeled in **Figure 1** due to space constraints.

Gene Ontology Pathway	Genes
Pathways with gene expression significantly increased in diabetics	
Macrophage Differentiation	CSF1, CDC42, **MMP9**
Regulation of Protein Activation Cascade	C1QB, C3, C1QA, C5, C1S, **C3AR1**, C2
Inflammatory Response	PTGER4, PTGFR, CCL24, RIPK2, IL10RB, TOLLIP, PTGER3, **C3AR1**, **IL18**, **RELA**
Pathways with gene expression significantly decreased in diabetics	
Dendritic Cell Chemotaxis	CCR1, **CXCR1**, CCL5, **CXCR2**, CXCR4, **CCR7**
Regulation of Nuclease Activity	OAS2, HMGB2, OASL
Cellular Response to Type I Interferon	IRF3, OAS2, STAT1, IRF1, MX2, MX1, IRF7, IFIT3, OASL, IFIT2
Positive Regulation of IL-12	**CCR7**, **LTB**, MAPK14, **PLCB1**, AGER
Positive Regulation of Vascular Endothelial Growth Factor	FLT1, **PRKCB**, IL1B

Figure 2. Heatmap of 20 most highly variable genes in the immune response panel. Genes with reduced expression in diabetics (blue) include CXCR1, CXCR2, CCR7, LTB, and HSH2D.



Columns represent individual participants

Conclusions

- In PWH, adipose tissue of diabetics is characterized by large differences in expression of adipocyte energy handling genes compared with non-diabetics**, but less difference in whole tissue immune response genes**.
- Given the profound changes to adipose tissue T cell populations in PWH, bulk tissue gene expression may not capture adaptive immune cell responses that have an important influence on adipocyte function.
- We are performing single T cell RNA sequencing on adipose tissue to further investigate changes that accompany HIV and diabetes.

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