Subcutaneous Adipose Tissue Myofibroblasts are Associated with the Lipidome

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BACKGROUND

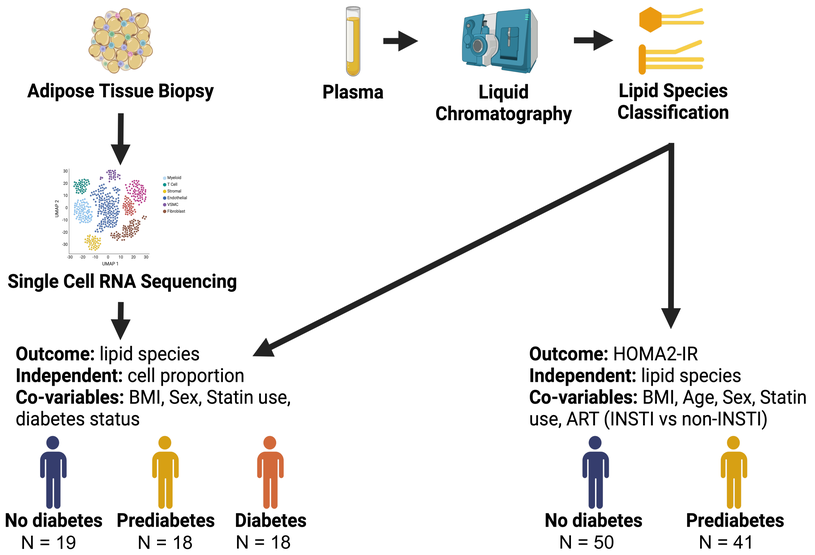
- Dyslipidemia is common in persons with HIV (PWH) and linked to the development of insulin resistance.
- Subcutaneous adipose tissue (SAT) regulates lipid homeostasis and is frequently altered in PWH on long-term antiretroviral therapy.
- Higher plasma triacylglycerols (TG) and lower sphingomyelin (SM) and phosphatidylcholine (PC) species are associated with risk of diabetes.

HYPOTHESIS

Greater fasting TG and lower SM and PC circulating concentrations will be associated with greater SAT inflammatory macrophages and pro-fibrotic myofibroblasts.

METHODS

- We performed untargeted liquid chromatography-high resolution mass spectrometry on fasting plasma and single-cell RNA sequencing on SAT samples (**Figure 1**).
- HOMA2-IR was calculated from fasting glucose and insulin.
- HOMA2-IR (non- and prediabetes only) was log_2-transformed and fit to a linear model with normalized lipid species (independent variable) and adjusted for age, sex, ART class (integrase strand transfer inhibitor [INSTI] vs non-INSTI), body mass index (BMI), and statin use.
- Partial Spearman was used to determine the association of SAT cell-type proportion and major lipid class adjusted for sex, BMI, statin use, and diabetes status.



RESULTS

- Median age was 44 years, BMI 31.3 kg/m^2, and 80% male (**Table 1**).
- HOMA2-IR was associated with higher TG, diacylglycerols (DG), phosphatidylinositol (PI), and oxidized TG species, and inversely associated with PC, lyso-PC, plasmenyl-phosphatidylethanolamines (plasmenyl-PE), and SM species (**Figure 2**).
- Higher proportion of myofibroblasts was associated with greater concentration of TG and oxidized TG, and inversely related to SM and plasmenyl-PE (**Figure 3).** The proportion of intermediate macrophages (IM) were inversely related to plasmenyl-PE concentration (**Figure 3**).

Table 1. Cohort Characteristics

	Female (N = 18)	Male (N = 73)	P-value
Age, median years	49 (44, 57)	41 (35, 53)	0.04
BMI, kg/m^2	32.9 (29.5, 36.9)	30.7 (28.6, 34.7)	0.23
Race, White (%)	6 (33)	44 (60)	0.04
INSTI-based regimen (%)	9 (50)	46 (63)	0.31
Statin Therapy, Yes (%)	7 (39)	16 (22)	0.14
HOMA2-IR	1.97 (1.28, 3.71)	2.61 (1.61, 4.52)	0.52
Fasting glucose, mg/dL	97 (88, 113)	96 (88, 110)	0. 88
Total cholesterol, mg/dL	201 (181, 214)	170 (149, 193)	0. 006

Continuous variables are shown as median value with interquartile range (parentheses).
BMI = body mass index; INSTI = integrase strand transfer inhibitor

Figure 2. Volcano plot showing β coefficient (x-axis) and –log_{10} adjusted p value (y-axis). Linear model evaluating relationship of HOMA2-IR with lipid species. Lipid species with FDR p-value < 0.05 are shown in red (increased) and blue (decreased).

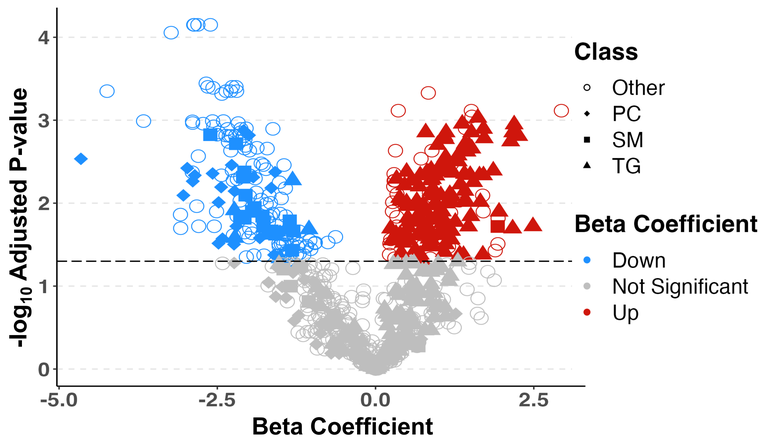
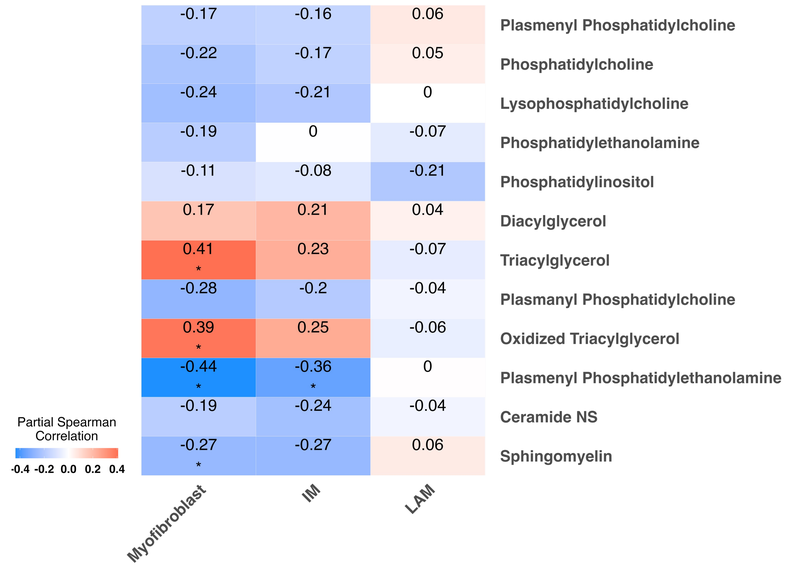


Figure 3. Heatmap of partial Spearman correlation between lipid classes and myofibroblast or macrophage proportion, adjusted for statin use, sex, body mass index, and diabetes status. For intermediate (IM) and lipid-associated macrophages (LAM), 50 individuals were included. * P < 0.05.



CONCLUSIONS

- HOMA2-IR is strongly associated with TG and inversely associated with SM and PC species in PWH on contemporary antiretroviral therapies.
- The proportion of SAT myofibroblasts was associated with TG and inversely associated with SM species but not PC species. The proportion of inflammatory macrophage populations were not associated with TG, SM, or PC species.
- These data suggest SAT cellular stromal composition may influence circulating lipidomics.
- Future studies evaluating circulating free fatty acids and mature adipocyte populations are needed to understand how SAT changes in PWH may promote dyslipidemia.

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