Effect of Obesity on Response to Antiretroviral Therapy in SIV-infected Rhesus Macaques

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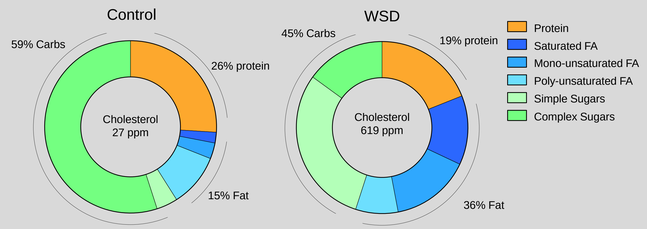
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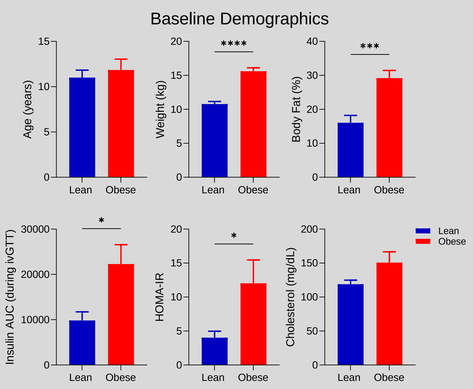
INTRODUCTION

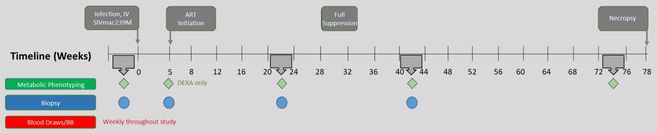
Modern antiretroviral therapy (ART) regimens are associated with increased risk of weight gain and associated metabolic disease. Adipokines play a role in adipose tissue dysfunction and are indicators of cardiometabolic disease risk. A reduced adiponectin:leptin ratio (ALR) is a predictive biomarker that correlates with a number of metabolic risk factors, as well as with markers of chronic inflammation. We employed the rhesus macaque model of SIV infection to determine if a modern ART regimen would elicit metabolic dysfunction with a corresponding decrease in the ALR, and if this effect was exacerbated by pre-existing obesity.

METHODS



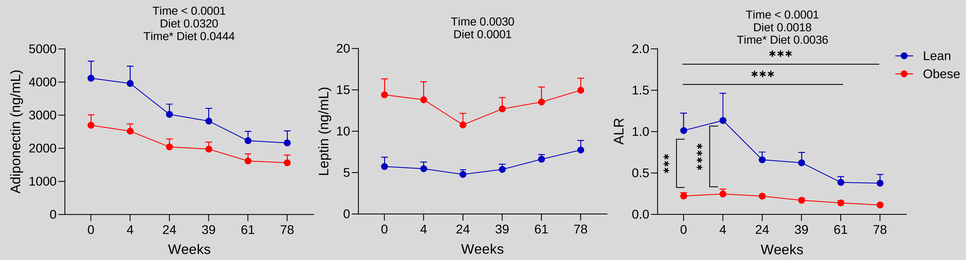
Lean, metabolically healthy (n=12) and western-style diet-induced obese (n=10) adult male macaques were infected intravenously (iv) with 10,000 IU of SIVmac239 and ART (consisting of the tenofovir prodrug tenofovir disoproxil fumarate (TDF), emtricitabine (FTC), and dolutegravir (DTG)) was initiated at 5 weeks post-infection (PI) and continued for 16 months. Baseline and longitudinal assessments of plasma, adipose tissue morphology, and systemic measures of metabolism such as dual x-ray absorptiometry (DEXA) and iv glucose tolerance tests (GTT) were obtained.



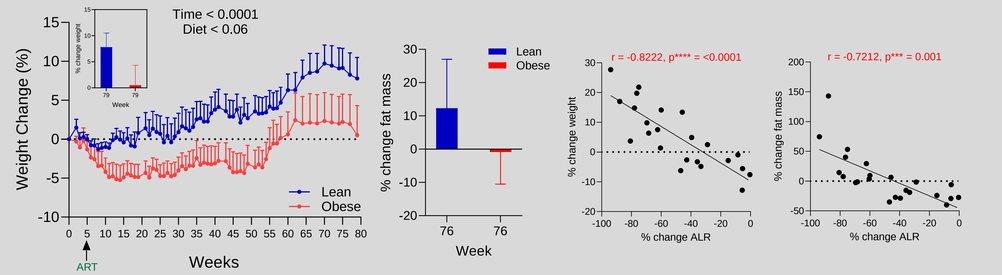


RESULTS

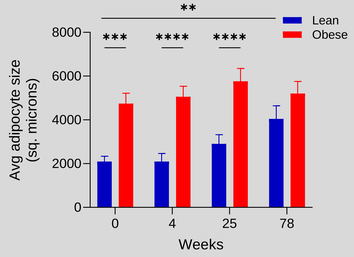
- Unsurprisingly, the obese cohort exhibited a significantly lower ALR at baseline compared to the lean cohort (Obese 0.22±0.04 vs Lean 1.01±0.21, p=0.0004). The ALR in the lean group progressively decreased throughout the time course of infection, ART initiation (5 weeks PI), and full suppression of viremia (~32 weeks PI), that was principally driven by a decrease in adiponectin, and that became significant at 61 weeks PI (Lean average 0.39±0.07).



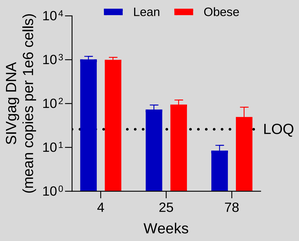
- The percent change in ALR was inversely correlated to percent change in body weight and fat mass (from baseline at week 0), where animals with the largest decrease in ALR also had the greatest percentage increase in weight and fat mass.



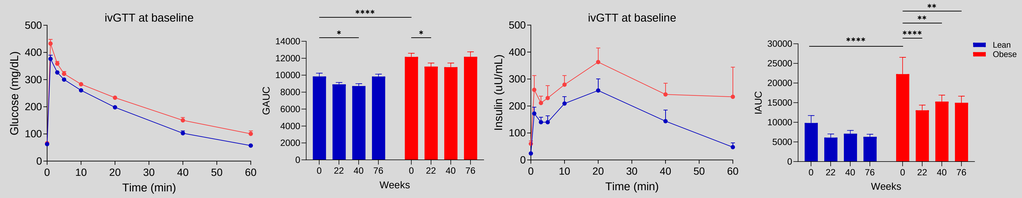
- Baseline adipocyte size in omental (OM) white adipose tissue (WAT) was significantly larger in the obese cohort. However, during ART treatment, lean adipocyte size significantly increased.



- Cell-associated viral load in OM WAT decreased in both cohorts after initiation of ART treatment. However, SIVgag DNA was still detectable at 78 weeks, approximately 46 weeks after full suppression, supporting a role for WAT as a latent viral reservoir.

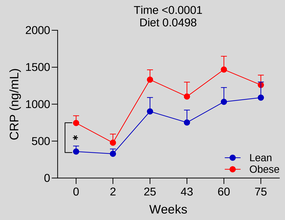


- Consistent with the distinct baseline phenotypes, glucose response between cohorts during pre-infection ivGTTs differed. Glucose area under the curve (GAUC) decreased in both groups during acute SIV infection but recovered to levels equal to baseline after full suppression with ART. Insulin AUC (IAUC) demonstrated no significant changes over time within in the lean cohort, whereas the obese cohort had improved IAUC PI that remained lower throughout the remainder of the time course, presumably due to PI weight loss.

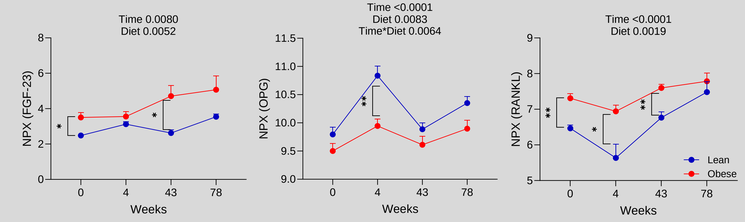


RESULTS

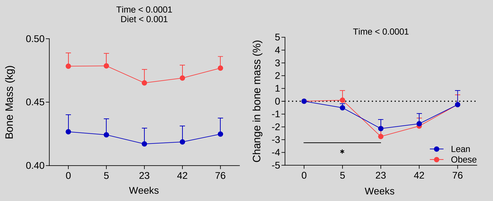
- The obese cohort exhibited elevated circulating c-reactive protein (CRP), indicating pre-existing inflammation at baseline. However, both cohorts exhibited increased inflammation PI that was not alleviated following ART suppression.



- Additionally, we preformed O-link cytokine profiling and examined biomarkers of bone health and glucose homeostasis, including fibroblast growth factor-23, osteoprotegerin (OPG), and receptor activator of nuclear factor-kappa B (NF-kappaB) ligand (RANKL). FGF-23 has been shown to be positively associated with visceral obesity and was significantly elevated in the obese cohort at baseline and continued to increase over the time course. The OPG-RANKL axis plays a role in pathogenesis of obesity and metabolic disease; OPG is a decoy receptor for RANKL and the two typically demonstrate a reciprocal relationship. RANKL was significantly elevated in the obese cohort at baseline, consistent with data from other animal models of obesity. Acute infection-associated changes in both OPG and RANKL were more severe in the lean cohort.



- Even though the magnitude of change between cohorts differed in both OPG and RANKL during peak viremia, both cohorts demonstrated a small but significant decrease in bone mineral content at 23 weeks PI.



CONCLUSIONS

- Obese NHPs had a significantly lower baseline ALR, consistent with metabolic dysfunction. SIV infection and subsequent ART preferentially decreased ALR in lean animals, indicating a trend toward an obese phenotype in initially lean animals.
- Decreased ALR correlated with increased weight and fat mass gain.
- Obese NHPs had significantly larger OM WAT adipocytes at baseline. However, full suppression with ART significantly increased adipocyte size in lean animals to levels similar to obese animals.
- There was a significant reduction in cell-associated SIVgag DNA in OM WAT by week 78. However, there was still detectable viral DNA at this final timepoint, indicating that WAT is a latent viral reservoir.
- Obese NHPs exhibited elevated baseline circulating CRP and both cohorts demonstrated further increases during ART treatment.
- Biomarkers for bone and glucose homeostasis were differentially expressed in lean versus obese animals and also demonstrated differential responses to SIV and subsequent ART.