

Metabolic dysfunction-associated steatotic liver disease in people with HIV is associated with lower BMI and more liver fibrosis compared to the uninfected population

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Aim: People with HIV (PWH) are at high risk of metabolic dysfunction-associated steatotic liver disease (MASLD), defined by the presence of hepatic steatosis plus any among overweight, diabetes, hypertension, or dyslipidemia. There are limited data whether MASLD in PWH differs in clinical presentation from MASLD in the uninfected population. **Aim:** to compare the severity of metabolic and hepatic dysfunction between MASLD patients with and without HIV.

Methods: 212 consecutive HIV mono-infected patients with MASLD at McGill University in Montreal were compared to a sex and age matched MASLD HIV negative control group at Policlinico Hospital in Milan. Fibroscan with controlled attenuation parameter (CAP) was used to define MASLD (CAP \geq 248 dB/m), severe MASLD (CAP $>$ 280 dB/m), and significant liver fibrosis (liver stiffness measurement $>$ 7.0 kPa).

Results: PWH with MASLD presented lower median BMI (28[25-31] vs 29[27-32] Kg/m², p=0.002) and lower prevalence of obesity (26% vs 44%, p<0.001) compared to MASLD uninfected patients, along with a lower prevalence of hypertension (21% vs 38%, p<0.001). The prevalence of dyslipidemia (41% vs 26%, p<0.001), hypertriglyceridemia (26% vs 9%, p<0.001) and low HDL cholesterol (34% vs 15%, p<0.001) was higher in MASLD patients with vs without HIV. No difference in

cardiovascular events and diabetes prevalence was observed between the two groups. Regarding liver disease, PWH with MASLD had lower prevalence of severe MASLD (54% vs 74% p<0.001) but higher prevalence of significant liver fibrosis (15 vs 7%, p=0.03) compared to MASLD uninfected patients. After adjustment, HIV positivity was an independent factor associated with significant liver fibrosis (figure).

Conclusions: Despite having lower BMI, PWH with MASLD have a more severe hepatic presentation and atherogenic lipid profile than MASLD uninfected patients. HIV positivity seems to be independently associated with significant liver fibrosis. Screening and follow-up for MASLD and liver fibrosis is recommended in PWH, even if they are lean.

The aging of neutrophils is actively involved in the metabolic consequences of high fat diet

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Aim: The epigenetic modifications induced by High Fat Diets (HFDs) in long-living hematopoietic cells have been well described, but whether they affect the “aging” of neutrophils, characterized by far shorter half-life, is less clear. Neutrophils “age” through a reciprocal regulation of CXCR4, promoting a “fresh” status when leaving the BM, and CXCR2, accelerating their aging in the circulation. We study whether derailed aging exacerbates the metabolic and inflammatory consequences of HFD.

Methods: We immunophenotyped neutrophils and characterized the metabolic responses in physiology (wild-type mice, WT) and in mice with either constitutively aged neutrophils (MRP8 driven conditional deletion of CXCR4; herein CXCR4fl/flCre+) or with constitutively fresh neutrophils (MRP8 driven conditional deletion of CXCR2; CXCR2fl/flCre+), following 20 weeks of HFD feeding (45% Kcal from fat).

Results: CXCR4fl/flCre+ mice display higher plasma triglycerides levels versus WT, despite comparable glucose levels, when monitored during standard feeding. This metabolic difference was exacerbated by feeding mice a HFD for 20 weeks. Indeed, despite a comparable gluco-metabolic profile between CXCR4fl/flCre+ and WT mice, liver damage was increased in CXCR4fl/flCre+, linked to the higher accumulation of CXCR4fl/flCre+ neutrophils in the liver after 20 weeks and two hours after intragastric gavage with olive oil versus fasting. As this finding was not observed after 20 weeks of standard fat diet, these results suggest that HFD feeding redirects aged neutrophil to the liver, resulting in enriched oxidative metabolism and NETosis- and inflammation-related pathways in the liver of CXCR4fl/flCre+ mice. Conversely, CXCR2fl/flCre+ mice were protected from obesity and insulin resistance, exhibiting a proresolutive phenotype.

In humans, increased plasma levels of Cxcl1 (ligand of CXCR2) correlated with visceral obesity and metabolic syndrome.

Conclusions: Neutrophil aging might contribute to the cardio-metabolic consequences of HFD. This aging could represent a new therapeutic target beyond the current anti-inflammatory therapies approved for the treatment of cardiovascular diseases.

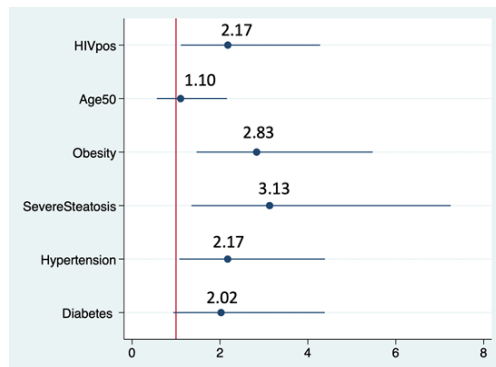


Figure
Multivariable regression analysis of factors associated with significant liver fibrosis (adjusted OR with 95% CI).