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Decreased physical activity and prolonged sitting time are associated with liver steatosis in people with HIV

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Brief report

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Running head: Physical activity and liver steatosis

Abstract

Background: Physical activity (PA) regulates intrahepatic storage of fat and reduces the risk of liver steatosis. Given our limited understanding of the pathogenesis of metabolic complications in people with HIV (PWH), it remains unclear if evidence from the general population can be extrapolated to PWH. We investigated the association between PA and liver steatosis in a single site of the Swiss HIV Cohort Study (SHCS).

Methods: We screened consecutive SHCS participants using vibration controlled transient elastography and defined liver steatosis as CAP ≥248dB/m. PA was measured using the International Physical Activity Questionnaire. We evaluated the association of three different measures of PA with liver steatosis in separate multivariable logistic regression models.

Results: Of 466 participants, 127 (27.3%) were female, median age was 52 years (interquartile range 43-59) and 244 (52.4%) were overweight (BMI ≥25 kg/m^2). Liver steatosis was present in 235 (50.4%) individuals. In multivariable analysis, PA below the recommendations of the European Association for the Study of the Liver was associated with steatosis (adjusted odds ratio (aOR), 2.34; 95% confidence interval (CI), 1.44-3.85). Using alternative scales of PA, including metabolic equivalents task (MET) minutes (min) per week (aOR 0.76, 95% CI 0.60-0.94) and sitting hours per day (aOR, 1.16; 1.07-1.26), yielded comparable results and associations were similar when we restricted analyses to lean (BMI<25 kg/m^2) subjects.

Conclusion: Insufficient PA and prolonged sitting time were both associated with liver steatosis among PWH, independent of BMI. Our results support the importance of promoting PA to prevent liver steatosis in PWH.

Key words: Liver steatosis, people with HIV, physical activity, sedentary time

Introduction

Liver steatosis is a major cause of liver disease in people with HIV (PWH), affecting between 30% and 50% of individuals [1, 2]. Its clinical presentation and disease course is influenced by multiple elements, including genetics, metabolic comorbidities, and environmental factors [3]. PWH are at risk of developing liver steatosis due to the persistent immune activation, exposure to hepatotoxic antiretroviral therapy (ART) agents, as well as the high co-occurrence of metabolic comorbidities [4].

Physical activity (PA) plays an important role in the pathogenesis of liver steatosis, as it strongly regulates intrahepatic storage of fat and effectively reduces steatosis, independent of changes in body mass [5]. Several randomized controlled trials have shown that PA exerts a protective effect on steatosis, regardless of weight loss in the general population [6-8]. As there are currently no approved pharmacological therapies, lifestyle modifications remain the

cornerstone for preventing liver steatosis. The European association for the study of the liver (EASL) recommends 150-200 min of moderate intensity aerobic PA or ≥75min vigorous PA per week [9]. The World Health Organization (WHO) recommends a similar PA intensity to reduce the risk of chronic diseases [10].

Although guidelines encourage the implementation of lifestyle changes for prevention and treatment of steatosis, few data are available on the effect of exercise on steatosis in PWH [11]. Considering that PWH tend to develop steatosis at lower BMIs compared to individuals without HIV, it is crucial to understand the effect of PA on steatosis in this subpopulation [12, 13]. We evaluated the association between PA and liver steatosis among PWH in a single center of the Swiss HIV Cohort Study (SHCS).

Materials and methods

Study design and population

The SHCS (www.shcs.ch) is a nationally representative prospective cohort study including nearly 80% of PWH receiving ART in Switzerland [14]. Sociodemographic, clinical and laboratory data, as well as changes in ART and co-medications are recorded at registration, and every 6 months thereafter. All centers' local ethical committees approved the study, and participants provided written informed consent. For the present analysis, we included participants at Bern University Hospital who underwent screening for liver steatosis by vibration controlled transient elastography (VCTE) between November 2019 and March 2023. Participants with active or past viral hepatitis co-infection, defined as having a positive hepatitis C virus (HCV) antibody test or positive hepatitis B virus (HBV) surface antigen, as well as pregnant women were excluded from the study.

Study measurements

We obtained information on PA using the validated International Physical Activity Questionnaire (IPAQ SF) [15]. Participants were asked how much time (days, hours, minutes)

they had spent engaging in vigorous PA, such as heavy lifting, aerobics or fast cycling, as well as moderate PA like carrying light loads or cycling at a regular pace during the seven days prior to their visit. They were also asked about the amount of time (days, hours, minutes) they spent walking and sitting on typical weekdays (hours, minutes). The IPAQ interviews were conducted on the same day as the VCTE.

VCTE (Fibroscan 530, Echosens, Paris, France) provided results for liver stiffness measurement (LSM) and controlled attenuation parameter (CAP). A minimum of 10 valid measurements with >60% success rate was required [16]. In overweight individuals with a skin-capsular distance of >25mm, we used the XL probe instead of the M probe. Liver steatosis was defined as follows: using the M probe, S1 (mild steatosis) if CAP 248-267dB/m, S2 (moderate steatosis) if CAP 268-279dB/m, and S3 (severe steatosis) if CAP ≥280dB/m or; using the XL probe, S1 if 242-266dB/m; S2 if 267-285dB/m; S3 if ≥286dB/m [17-19]. Liver fibrosis was categorized according to Metavir-equivalent stages: F0-1 (no or mild fibrosis) if LSM <7.1kPa, F2-3 (significant fibrosis) if LSM 7.1-11kPa, and F4 (cirrhosis) if LSM ≥11.1kPa, as established previously [20]. In addition, we calculated the Fibroscan-AST (FAST) score which is based on LSM, CAP and AST. A FAST score >0.67 indicates steatohepatitis with significant fibrosis [21].

Outcomes and definitions

Our primary outcome was the presence of liver steatosis, defined as CAP ≥248dB/m using the M probe and CAP ≥242 dB/m using the XL probe. The exposure included three different measures of PA: (1) Metabolic equivalents task (MET) minutes (min) per week, by assigning standardized MET values of 3.3 for walking, 4 for moderate, and 8 for vigorous intensity [22]; (2) performance of ≥200 min/week moderate or ≥75min/week vigorous activity [9, 23]; and (3) sitting hours/day. We categorized participants as lean if BMI was <24.9 kg/m^2 and overweight/obese if the BMI was ≥25 kg/m^2. Arterial hypertension was defined as two measurements ≥140/90 mmHg within one year prior to VCTE or current antihypertensive

treatment; diabetes mellitus as HbA1c ≥6.5% or current treatment with antidiabetic medication; and dyslipidaemia as total cholesterol to high density lipoprotein (HDL) ratio > 5 and/or currently receiving lipid lowering therapy. Hazardous alcohol consumption was defined as an AUDIT-c >4 for men and >3 for women [24].

Statistical analysis

We used multivariable logistic regression to evaluate the association between liver steatosis and PA measures among lean and overweight participants. We evaluated covariates of clinical significance, including sex, age (<50 vs ≥50 years), ethnicity (European vs other origin), HIV transmission (men who have sex with men [MSM] vs other), CD4 nadir (<350 vs ≥350 cells/μL), BMI (<25 vs ≥25 kg/m2), diabetes, dyslipidaemia, arterial hypertension, and hazardous alcohol consumption. Covariates that were significantly associated with liver steatosis in univariable analyses (P<0.05) were included in multivariable models. In addition, all models were adjusted for exposure to tenofovir alafenamide (TAF) and integrase-strand transfer inhibitors (InSTI). Statistical analyses were performed using STATA 16.0 (StataCorp, College Station, TX, USA) and R (version 4.3).

Results

Study population

During the study period, 484 SHCS participants followed at Bern University Hospital underwent screening for liver steatosis and fibrosis by VCTE. We excluded 18 PWH without data on PA. Of 466 individuals included in our analyses, 127 (27.3%) were female, 339 (72.7%) were Caucasian, and 244 (52.4%) were overweight/obese. The median age was 52 years (interquartile range [IQR] 43-59) and the median CD4+ count was 723 cells/μl (IQR 545-953). EASL recommendations for PA were met by 148 individuals (31.8%) (Table 1). Cardio-metabolic risk factors were more frequent in the group who did not meet the EASL recommendations: 56.6% vs. 43.2% were overweight, 41.5% vs 31.1% had dyslipidemia,

33.0% vs. 25.7% arterial hypertension, and 13.5% vs. 6.8% diabetes mellitus. The proportion of individuals exposed to TAF was 60.1% in the group who did not meet the EASL recommendations, and 46.6% in the other group. A similar proportion of participants was exposed to InSTI in both groups (70.4% and 78.4%, respectively).

Association of PA measures with liver steatosis

Overall, 235 (50.4%) participants had liver steatosis, and 157 (33.7%) had severe steatosis. Among individuals with liver steatosis, 9 (3.8%) had a LSM compatible with significant fibrosis (F2-F3), 4 (1.7%) had a measurement compatible with cirrhosis (F4), and 3 (1.3%) participants had a FAST score compatible with steatohepatitis with significant fibrosis. One patient had an autoimmune hepatitis without signs of activity or fibrosis, and one patient had a hemochromatosis with significant fibrosis (F2-3). The proportion of individuals with liver steatosis was 34.3% in participants who met the EASL PA recommendations and 56.3% in individuals who did not. In multivariable analyses, individuals who reported PA below EASL recommendations had an increased risk for steatosis compared to the others (adjusted odds ratio [aOR] 2.34, 95% confidence interval [CI] 1.44-3.85, Figure 1 Panel A). Additional risk factors for liver steatosis included age ≥50 years, BMI≥25 kg/m^2, diabetes mellitus, being Caucasian, and exposure to TAF. Using alternative scales of PA yielded similar results: PA measured in MET-min/week was inversely associated with the risk of liver steatosis (aOR 0.76 per increase of 5000 MET-min per week, 95% CI 0.60-0.94, Figure 1, Panel B), whereas the risk of steatosis was associated with increased daily sitting time (aOR, 1.16 per additional hour, 95% CI 1.07-1.26, Figure 1 Panel C). The association between daily sitting time and liver steatosis remained significant in people who did not meet the EASL PA recommendations (aOR 1.19; 95%CI 1.07-1.26).

Association of PA measures with liver steatosis in analyses stratified by BMI category

Among 222 lean individuals, 65 (29.3%) had liver steatosis and 2 (0.9%) had fibrosis or cirrhosis. The inverse association between MET-min/week and liver steatosis remained

similar when we restricted the analyses to lean subjects (aOR 0.58, 95% CI 0.38-0.86, Figure 1 Panel B). In addition, the association and effect size between sitting time and liver steatosis was similar in the lean subpopulation (aOR 1.14, 95% CI 1.02-1.29, Figure 1 Panel C). However, we found no evidence for an independent association between PA below EASL recommendations and steatosis among lean individuals (aOR 1.63, 95% CI 0.83-3.25, Figure 1 Panel A). Among 244 overweight participants, 170 (69.7%) had liver steatosis, and 11 (4.5%) had liver fibrosis or cirrhosis. In this subgroup we did not find a significant association between MET-min/week and the presence of liver steatosis (aOR 0.89, 95% CI 0.67-1.18, Figure 1 Panel B), but overweight individuals who did not met the EASL recommendations had a higher risk of liver steatosis (aOR 3.32, 95% CI 1.63-6.90, Figure 1 Panel A). Increased sitting hours (aOR 1.17, 95% CI 1.04-1.32), remained significantly associated with liver steatosis in overweight subjects (Figure 1 Panel C).

Discussion

In our single site study of consecutive PWH undergoing systematic screening for liver steatosis, participants with physical activity below EASL recommendations were more than twice as likely to have liver steatosis compared with more active individuals. We observed similar results when using other measures of physical activity, including MET-min/week or sitting time, and most associations remained significant when we constrained the analyses to lean subjects. Taken together, our results highlight the importance of promoting PA and reducing sitting time to prevent liver steatosis among PWH.

In line with studies among populations without HIV, we found a strong association between PA below EASL recommendations of ≥200 min/week of moderate or ≥75min/week vigorous activity and liver steatosis, after adjusting for steatosis risk factors and ART components linked to weight increases, such as INSTIs and TAF. Our association between MET-min/week and liver steatosis contributes to the available evidence that a combined effect of

different PA intensities is associated with a lower risk of liver steatosis in PWH. MET-min are used to estimate the energy expenditure for PA, and thereby present an objective measurement. In line with previous studies in the general population, we showed a significant dose-response effect of PA measured by MET-min/week on the risk of liver steatosis [25]. This finding is especially relevant for participants who cannot reach the recommended amount of PA and indicates that increasing time spent walking or in lower intensity PA, may also be beneficial. As some studies among PWH showed no significant effect of PA interventions on weight, PA may have an independent effect on the development of liver steatosis, which could be driven by metabolic changes other than weight [26].

Although liver steatosis is closely linked to being overweight, a subset of PWH developed liver steatosis despite a normal BMI. In lean persons, genetics or the gut microbiota are well-recognized factors influencing the development of liver steatosis, and behavioural factors such as PA, diet or alcohol use may also contribute [27]. For instance, Mohammed et al. showed that PWH with liver steatosis had a lower BMI and were more physically active compared to controls[12]. In our cohort, nearly half of participants were lean and one third of them had steatosis. The magnitude of the association between MET-min/week or sitting time and liver steatosis remained similar to results from the main analysis, which confirms the importance of PA in non-obese populations as well. To improve our understanding of the link between PA and liver steatosis, prospective cohorts with subgroup analyses for distinct phenotypes are needed.

We investigated the association between PA and liver steatosis in a well-characterized cohort of consecutive PWH who underwent systematic assessments of several measures of PA and VCTE. Our results appear robust because the detailed demographic, clinical, laboratory and behavioural data, as well as the longitudinal information on ART regimens and co-medications allowed for an accurate adjustment for relevant confounders. However, given the cross-sectional nature of this study, the temporal relationship between liver steatosis and PA

remains unclear. Only a small number of participants had a LSM compatible with significant fibrosis or cirrhosis, thus we were unable to investigate the association of PA with advanced liver steatosis or NASH. Finally, we had a relatively low number of PWH of African origin in our study, so that our results may not be generalizable to other settings.

In conclusion, we show that decreased PA and prolonged sitting time are associated with liver steatosis among PWH, independent of BMI. These observations highlight the beneficial effect of physical activity and highlight the importance of incorporating counselling on PA in the management and prevention of liver steatosis.

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Authors' contributions: CR, AB, HF, AR and GW designed the study. CR and GW drafted the first version of the manuscript. C.R. and G.W. performed the statistical analyses. AB, BS, HFG and PET contributed to the conception of the study and revised the manuscript for substantial intellectual content. All authors read and approved the final manuscript.

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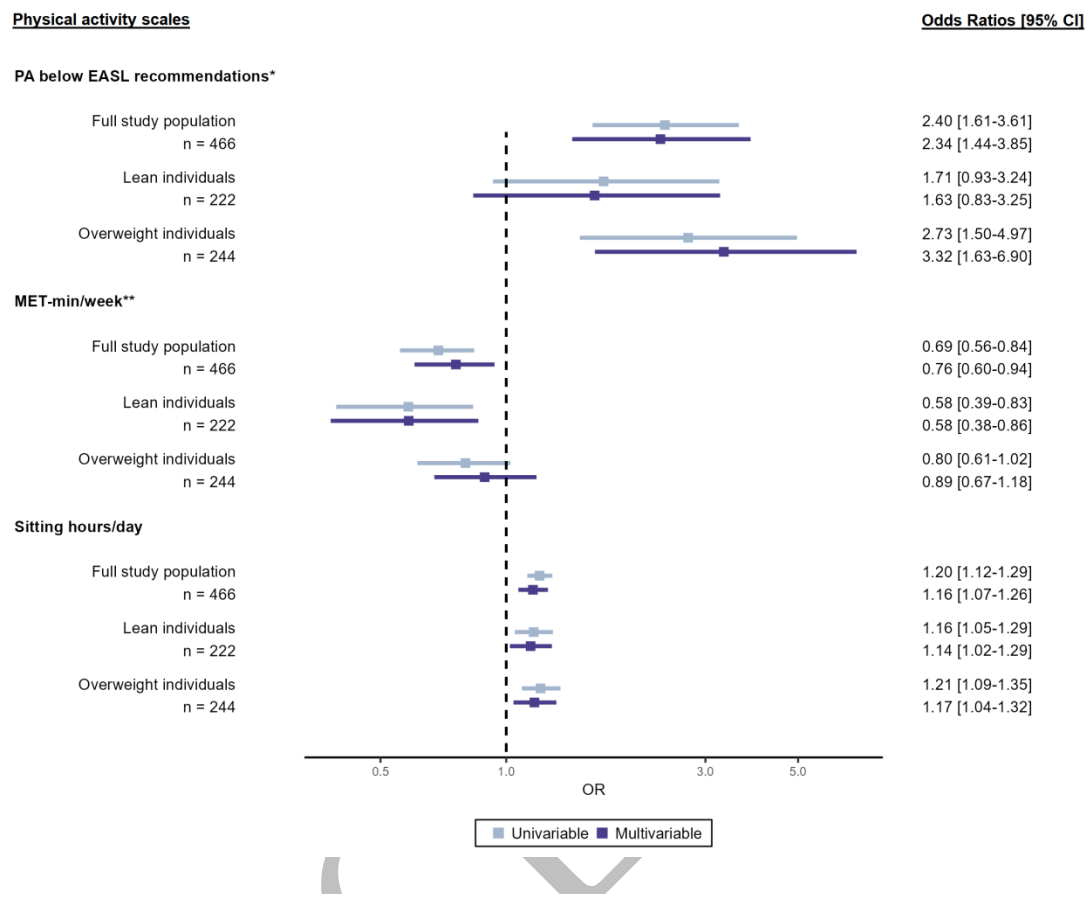
Figure 1. Forest plot of odds ratios among patient subgroups for the association between liver steatosis and three PA scales. Multivariable analyses were adjusted for age, sex, BMI,

ethnicity, diabetes, dyslipidemia, arterial hypertension, exposure to TAF and exposure to InSTI.



Abbreviations: EASL, European association for the study of the liver; PA, physical activity; MET-min/week, metabolic equivalents task minutes; OR, odds ratio; CI, confidence interval; TAF, tenofovir alafenamide; InSTI, integrase-strand transfer inhibitorsanalogues

*Performance of ≥200 min/week moderate or ≥75min/week vigorous activity
**per 5000 MET-min more per week

Table 1. Demographic and clinical characteristics of the study population at the time of transient elastography measurement and lifestyle assessment, stratified by physical activity (PA) recommendations by EASL

Characteristics	PA according to EASL recommendations* N= 148	PA below EASL recommendations* N= 318
Median age, years (IQR)	51 (42-59)	52 (44-59)
Female sex (%)	32 (21.6)	95 (29.9)
Region of origin (%)		
Europe	114 (77.0)	225 (70.8)
Africa	24 (16.2)	63 (19.8)
Asia	4 (2.7)	21 (6.6)
Other	6 (4.1)	9 (2.8)
HIV transmission group (%)		
MSM	89 (60.1)	142 (44.7)
Heterosexual	52 (35.1)	150 (47.2)
PWID	0 (0.0)	2 (0.6)
Other/unknown	7 (4.7)	24 (7.5)
Overweight or obese (%)	64 (43.2)	180 (56.6)
Arterial hypertension (%)	38 (25.7)	105 (33.0)
Diabetes (%)	10 (6.8)	43 (13.5)
Dyslipidemia (%)	46 (31.1)	132 (41.5)
History of cardiovascular disease (%)**	8 (5.4)	23 (7.2)
Median BMI, kg/m^2 (IQR)	24.4 (22.1-26.8)	25.8 (22.9-29.8)
Hazardous alcohol consumption (%)***	35 (25.6)	60 (20.8)

Smoking (%)	32 (21.8)	86 (26.8)
Median current CD4+ count, cells/µl (IQR)	695 (540-942)	734 (550-968)
Median CD4 nadir in cells/µl (IQR)	263 (128-379)	217 (118-330)
Median eGFR in mL/min (IQR)	87.5 (73.8-101.7)	86.3 (71.9-101.8)
ART duration, years (IQR)	11 (6-20)	12 (7-19)
Current ART regimen (%)		
3TC/ABC/DTG	41 (27.7)	59 (18.6)
FTC/TAF/BIC	28 (18.9)	55 (17.3)
FTC/TAF/DTG	15 (10.4)	47 (14.8)
3TC DTG	13 (8.8)	12 (3.8)
Other	49 (33.1)	139(43.7)
No treatment	2 (1.3)	6 (1.9)
Current exposure to TAF (%)	69 (46.6)	191 (60.1)
Current exposure to InSTI (%)	116 (78.4)	224 (70.4)
Current exposure to TDF (%)	6 (4.1)	12 (3.8)
Current exposure to EFV (%)	6 (4.1)	12 (3.8)
Median sitting hours on typical week-day (IQR)	5 (3-7)	5 (3-8)

*Performance of ≥200 min/week moderate or ≥75min/week vigorous activity

**A history of cardiovascular disease included the past occurrence of myocardial infarction, cerebral infarction, coronary angioplasty/stenting, coronary artery bypass grafting, or any procedure on peripheral arteries.

***Hazardous alcohol consumption was defined as an AUDIT-c >4 points for men and >3 points of women.