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BRIEF REPORT

Increased Prevalence of Hepatic Steatosis in Young Adults With Lifelong HIV

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Little is known about the effects of lifelong human immunodeficiency virus (HIV) or antiretroviral therapy on hepatic steatosis and fibrosis. Using transient elastography, we evaluated 46 young adults with lifelong HIV and 20 matched HIV-negative controls. Steatosis was present in 33% of persons with HIV and only 10% of controls ($P = .04$). Hepatic fibrosis scores were not elevated and did not differ between groups. Metabolic parameters, particularly increased waist circumference, and not HIV-specific factors, were significantly associated with steatosis. While this finding should be examined in larger cohorts, modifiable metabolic disturbances may be important targets to optimize liver health in this population.

Keywords. HIV; AIDS; hepatic steatosis; nonalcoholic fatty liver disease; young adults.

Chronic liver disease is a leading cause of morbidity and mortality that disproportionately affects persons with human immunodeficiency virus (PWH). High rates of coinfection with viral hepatitis partially account for this burden; however, liver disease unrelated to viral hepatitis or alcohol intake continues to be of major health concern. Nonalcoholic fatty liver disease (NAFLD), a condition characterized by the accumulation of lipid droplets within hepatocytes, has emerged as an important and incompletely understood contributor. NAFLD encompasses simple hepatic steatosis, nonalcohol steatohepatitis, and in more advanced forms may lead to liver cirrhosis and hepatocellular carcinoma (HCC) [1]. NAFLD has been increasingly observed in the context of human immunodeficiency virus (HIV) [2]. The interplay between HIV-specific risk factors, such as antiretroviral therapy (ART) toxicity and inherent immune activation, and traditional risk factors, such as obesity and dyslipidemia, may contribute to an elevated incidence of NAFLD in patients with HIV [2]. There is mounting evidence that simple hepatic steatosis, a world-wide epidemic prevalent in an estimated 25% of the general population [3] and 35% of PWH [2], can progress to advanced fibrosis and an increased risk of HCC [4], thus highlighting the need for early detection and prevention.

Individuals who acquired HIV in early life represent the first generation of young adults growing up with lifelong exposure to HIV and ART. Living with HIV since birth or early childhood may exacerbate the relationship between HIV and hepatic steatosis through prolonged exposure to ART, metabolic syndrome, and chronic inflammation; however, little is known about the prevalence and risk factors for hepatic steatosis in this unique population. Using transient elastography, a noninvasive liver ultrasound technology, we characterize hepatic steatosis and fibrosis in a cohort of PWH since early life and assess the relationships between these observations and metabolic and HIV-specific clinical characteristics.

METHODS

Forty-six PWH since birth or early childhood (ie, perinatal or transfusion acquired) and 20 age-, race-, and sex-matched HIV-negative controls were prospectively recruited as part of a convenience sample from a natural history study exploring the physical and psychological impact of lifelong HIV infection (Clinical Trials.gov NCT number 01656564). Recruitment of controls occurred to satisfy a 2:1 ratio. Clinical and demographic data were collected including body mass index (BMI), waist and hip circumference, blood pressure, prevalence of lipid lowering agents, current alcohol and tobacco use, and laboratory determinations, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), glucose, total and high-density lipoprotein (HDL) cholesterol, triglycerides, calculated homeostatic model to assess insulin resistance (HOMA IR), C-reactive protein (CRP), and D-dimer. HIV-related clinical data included detailed ART medication history, HIV viral load, and CD4 and CD8 T-cell counts. Participants with known diabetes or active hepatitis C or B virus, and those who were pregnant or were unable to complete transient elastography due to implantable metal devices were excluded from the study. Controls were required to be healthy adults ≥18 years of age, without HIV or known serious medical conditions. The investigation was approved by an NIH Institutional Review Board and all participants provided written informed consent prior to participation. Data were collected from March 2016 to August 2018.

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Transient elastography measurements, using Echosens FibroScan 502, were performed to evaluate liver fibrosis and steatosis. All measurements were performed by trained operators as described previously [5]. Evaluations with at least 10 valid measurements, a kPa interquartile range <30% of the median, and a successful acquisition rate of ≥60% were included in analysis. Hepatic steatosis of grade 1 or greater was defined as ≥248 dB/m and grade 2 or greater as ≥268 dB/m as per optimal controlled attenuation parameter (CAP) cut offs [6]. Clinical fibrosis was defined as a median kPa value of ≥7.1 [7, 8]. All participants were instructed to fast. In addition to fibroscan kPa values, AST-to-platelet ratio index (APRI) was calculated to assess fibrosis. An APRI cut off value of >0.5 was used to define stage F1 or greater [9].

Cross-sectional statistical comparisons between groups were completed using *t* tests and $\chi 2$ likelihood ratio tests as indicated. Using univariate linear regression, associations between CAP score and clinical characteristics were determined. Variables identified as significant on univariate regression were entered into a multivariate regression model to identify independent predictors of steatosis as measured by CAP score. Further, subgroup analyses were calculated for PWH and control groups separately. For statistical comparisons, nonnormally distributed variables (eg, HOMA IR, triglycerides, CRP, and D-dimer) were log-transformed to approximate a normal distribution. All statistical analyses were completed using JMP software (version 13.0; SAS Institute Inc., Cary, NC).

RESULTS

PWH participants were 61% female, 72% virally suppressed (HIV RNA <40 copies/mL), with a mean age of 28 years, mean CD4 T-cell count 605 cells/μL, and had an average of 19 years of ART exposure.

PWH participants did not differ significantly from HIV-negative controls in age, race, ethnicity, sex, BMI, overweight/obesity prevalence, diastolic blood pressure, total cholesterol, or social history, including current tobacco use, history of illicit drug use, or current lipid-lowering treatment (Table 1). No participant had a history of alcohol use disorder. However, PWH participants had significantly higher levels of several metabolic and inflammatory laboratory indices (Table 2). Compared to controls, PWH had lower HDL cholesterol and higher levels of triglyceride, glucose, HOMA IR, CRP, and D-dimer, as well as higher waist circumference and waist-to-hip ratio. PWH also had significantly lower CD4 T-cell and CD4/CD8 ratios compared to control subjects.

Compared to HIV-negative controls, PWH had significantly elevated transaminase levels; however, these differences were based on low-grade elevations or levels that were within the normal range. Transient elastrography and APRI evaluations demonstrated no significant differences between PWH and controls with respect to estimates of fibrosis. Using categorical cut off values for fibrosis and steatosis, there was no difference in fibrosis stage F1 prevalence between groups (kPa $P = .12$; APRI $P = .42$); however, hepatic steatosis ≥grade 1 was present in 33% of young adults with HIV and 10% controls ($P = .04$). In addition, using a diagnostic cut off for hepatic steatosis of ≥grade 2, 28% of PWH met the criteria for grade 2 steatosis versus only 5% of controls ($P = .02$).

Using linear regression analyses, BMI ($r = 0.4$, P value = .0008), waist circumference ($r = 0.54$, P value = .0001), waist-hip ratio ($r = 0.35$, P value = .004), cholesterol ($r = 0.25$, P value = .04), triglycerides ($r = 0.25$, P value > .05), and HOMA IR ($r = 0.35$, P value = .005) were significantly positively associated with CAP score, whereas age, sex, social history, diastolic blood pressure, HDL cholesterol, glucose, AST, ALT, CRP, and D-dimer were not. These associations largely persisted when repeated in a subanalysis of only PWH. The relationship between CAP score and waist-hip ratio ($r = 0.28$, P value = .07) was no longer significant when analyzed in the HIV group alone. Among PWH, neither CAP score nor frequency of hepatic steatosis differed by current protease inhibitor, nonnucleoside reverse transcriptase inhibitor, or integrase inhibitor use, CD4 count, viral suppression, or years of ART exposure.

In a multivariate regression including HIV status and variables identified as significantly associated with CAP score on univariate analyses, waist circumference was the only variable identified as significantly associated with CAP score (P

Table 1. Clinical Demographics of the Cohort

Clinical Variable	PWH (n = 46)	Controls (n = 20)	*P* Value
Age, years, mean (SD)	27 (3.1)	28 (4.7)	.44
Race, n (%)			
Black	25 (54)	15 (75)	.32
White	15 (33)	4 (20)	
Mixed/other	6 (13)	1 (5)	
Hispanic ethnicity, n (%)	8 (17)	2 (10)	.43
Sex, n (%)			
Male	18 (39)	8 (40)	.95
Female	28 (61)	12 (60)	
Current tobacco use, n (%)	4 (9)	0 (0)	.08
History of illicit drug use, n (%)	10 (21)	6 (30)	.47
Current lipid-lowering treatment, n (%)	1(2)	0 (0)	.40
CD4 T-cell count, cells/mm^3, mean (SD)	605 (400)	775 (213)	.01
CD4/CD8 ratio, mean (SD)	0.91 (0.60)	1.77 (0.55)	.0001
HIV viral suppression, n (%)	33 (72)		
ART exposure, mean, y	19		
Current ART use, n (%)			
NRTI	41 (89)		
NNRTI	16 (35)		
PI	23 (50)		
INSTI	32 (70)		

P values represent results of *t* test and $\chi 2$ statistical comparisons between groups.

Abbreviations: ART, antiretroviral therapy; INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PWH, persons with human immunodeficiency virus.

Table 2. Transient Elastography, and Metabolic and Inflammatory Parameters

Measurement	PWH (n = 46)	Controls (n = 20)	*P* Value
CAP, dB/m	224 (62)	198 (48)	.08
Steatosis ≥S1, n (%)	15 (33)	2 (10)	.04
Steatosis ≥S2, n (%)	13 (28)	1 (5)	.02
Fibrosis score, kPa	5.1 (1.12)	5.0 (1.9)	.86
Fibrosis ≥ 7.1 kPa, n (%)	3 (7)	4 (20)	.12
APRI score	0.22 (0.2)	0.19 (0.09)	.08
APRI > 0.5, n (%)	5 (11)	1 (5)	.42
Metabolic and inflammatory parameters			
BMI, kg/m^2	27 (7)	26 (4.6)	.31
Overweight/obese, n (%)	27 (59)	11 (55)	.78
Waist/hip ratio	0.93 (0.08)	0.84 (0.05)	.0001
Waist circumference, cm	92 (15)	85 (8.6)	.03
Diastolic blood pressure, mmHg	70 (9)	71 (8)	.8
Total cholesterol, mg/dL	165 (41)	158 (31)	.44
HDL cholesterol, mg/dL	50 (14)	62 (14)	.004
Triglycerides, mg/dL	109 (73)	60 (33)	.0004
Glucose, mg/dL	93 (10)	89 (7)	.04
HOMA IR	6.3 (10)	2.4 (1)	.009
AST, IU/L	25 (12)	18 (4)	.001
ALT, IU/L	23 (16)	15 (6)	.002
CRP, mg/L	5.2 (12)	0.9 (0.8)	.02
D-dimer, µg/mL	0.46 (0.5)	0.30 (0.07)	<.05

Data represent mean (SD) unless otherwise noted. *P* values represent results of *t* test and $\chi 2$ statistical comparisons between groups.

Abbreviations: ALT, alanine transaminase; APRI, AST-to-platelet ratio index; AST, aspartate transaminase; BMI, body mass index; CAP, controlled attenuation parameter; CRP, C-reactive protein; HDL, high-density lipoprotein; HOMA IR, homeostatic model to assess insulin resistance; PWH, persons with human immunodeficiency virus.

value = .03). The addition of sex to this model did not alter the significance. HIV status was not significantly associated with increased steatosis score in either multivariable analysis.

DISCUSSION

In this study, we demonstrated that hepatic steatosis is highly prevalent (33%) in PWH who have been infected since birth or early childhood. Categorical cut offs for grade 1 (CAP ≥ 248 dB/m) and grade 2 (CAP ≥ 268 dB/m) steatosis revealed a significantly higher prevalence of hepatic steatosis in PWH compared to matched HIV-negative controls. These results are of concern, particularly as they were observed in young adult patients without diabetes or HCV, known risk factors for NAFLD.

While the prevalence of hepatic steatosis in cohorts of adults with HIV infection varies, ranging from 29% to 43% [2], our results are consistent with large-scale studies utilizing transient elastrography. Pembroke et al [10] demonstrated a prevalence of hepatic steatosis of 36% (n = 541, CAP ≥ 248 dB/m) in a large Canadian cohort of adults with HIV infection. A study of 326 subjects in Spain reported a 37% prevalence (≥238 dB/m) [11], and, more recently, Perazzo et al [5] reported a similar prevalence of 35% (≥248 dB/m) in Brazil. Despite a younger average age, our cohort exhibited a prevalence on par with those of older, largely male populations. In contrast, our observed fibrosis prevalence of 7% (kPa ≥ 7.1) was lower than previously reported values, which range from 13% to 34%, a difference that could be attributed to the relatively young age of our cohort.

In the general population, there are well-established risk factors for NAFLD, including insulin resistance, central adiposity, and dyslipidemia, factors that parallel rising levels of obesity, diabetes mellitus 2, and metabolic syndrome [3]; however, less is known about the pathophysiology of NAFLD in HIV. Previous research indicates that combination ART, altered lipid metabolism, chronic immune activation, low CD4/CD8 T-cell ratio, and inflammation place HIV populations at increased risk for liver disease [12]. In a 2017 meta-analysis of NAFLD in individuals with HIV without HCV, hepatic steatosis was most closely related to metabolic parameters, including BMI, waist circumference, hypertension, dyslipidemia, and elevated fasting glucose [2]. Recently, both Pembroke et al [10] and Macias et al [11] found that upon multivariate analysis BMI remained the sole independent predictor of hepatic steatosis. Our results reinforce previously observed relationships between metabolic parameters and hepatic steatosis. We found hepatic steatosis was increased in those with HIV, and positively associated with BMI, waist circumference, cholesterol, and HOMA IR. Waist circumference emerged as the only independent risk factor for hepatic steatosis in this population. While modifiable, many of these risk factors disproportionately affect PWH due to the confluence of social, economic, and HIV-specific factors. For example, increased waist circumference may represent central adiposity associated with lipodystrophy and antiretroviral-specific effects on body fat distribution.

Simple hepatic steatosis is highly prevalent among young HIV populations, which is worrisome because hepatic steatosis may progress to more severe forms of liver disease. With rising rates of obesity and diabetes globally, and a disproportionate burden of NAFLD in PWH, early and effective detection of high-risk patients and subsequent preventative strategies are needed.

To our knowledge, this is the first study to evaluate the hepatic consequences of lifelong HIV in young adults using transient elastography and to use a well-matched HIV-negative comparison group. However, our study may have several limitations. Due to the relatively small sample size, we may not have been able to detect the role of HIV-specific factors, including ART regimen and duration, viral suppression, and CD4 count in hepatic steatosis; however, in larger adult studies, the relationship between HIV-specific factors and hepatic steatosis also remains unclear. Two studies in high-resource settings [10, 11] found no relationship between ART duration and hepatic steatosis prevalence. A recent study in Germany found that ART and control of HIV seem to play an indirect role in the development of hepatic steatosis through return to health effects [13]. Prior research linked exposure to thymidine analogues to hepatic steatosis [5], but in current US cohorts the use of these

agents is increasingly rare. None of our cohort were using a thymidine analogue during the study. An additional potential limitation is the cross-sectional design of our study that did not allow for the determination of a temporal relationship between hepatic steatosis and/or the possible development of liver fibrosis and cirrhosis. Lastly, we excluded individuals who were living with HCV and diabetes in order to isolate HIV-specific risk factors, which may limit the generalizability of our study to the broader population of PWH.

In conclusion, hepatic steatosis was common in our cohort of PWH since birth or early childhood, with prevalence on a par with that of older populations with HIV infection. We found metabolic parameters to be the largest contributors to hepatic steatosis, in particular waist circumference. However, future studies with larger sample sizes and longitudinal follow-up are needed to further elucidate the role of HIV and HIV-related risk factors in NAFLD and to assess the predictive abilities of transient elastography for future progression of liver disease in this setting.

Notes

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