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Hepatic steatosis associated with increased central body fat by dual-energy X-ray absorptiometry and uncontrolled HIV in HIV/hepatitis C co-infected persons

Todd T. Brown^a, Shruti H. Mehta^b, Catherine Sutcliffe^b, Yvonne Higgins^a, Michael S. Torbenson^a, Richard D. Moore^{a,b}, David L. Thomas^a, and Mark S. Sulkowski^a

^aJohns Hopkins School of Medicine, Baltimore, Maryland, USA.

^bJohns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA.

Abstract

Objective—To evaluate the relationship between regional body composition and liver disease (fibrosis or steatosis) in HIV/HCV co-infected individuals.

Methods—Whole body dual-energy X-ray absorptiometry (DXA) was performed in 173 HIV/HCV co-infected persons within 12 months of a liver biopsy. Significant fibrosis was defined as a METAVIR stage greater than 1. Steatosis was graded as: 0, none; 1, steatosis involving less than 5% of hepatocytes; 2, 5–29%; 3, 30–60%; 4 greater than 60%, and was defined as more than 0. Poisson regression with robust variance was used to estimate prevalence ratios of the outcome measures.

Results—The population was 62% male and 84% black with a median body mass index of 25.2 kg/m² (interquartile range 22.5, 29.3 kg/m²). No differences in regional body fat or fat distribution were observed in 42 patients with significant fibrosis compared to others with less fibrosis. However, the 77 individuals (45%) with steatosis had greater central fat than those without steatosis [prevalence ratio 1.04 per kg trunk fat; 95% confidence interval (CI) 1.04, 1.11], after adjusting for hepatic fibrosis (prevalence ratio 1.77; 95% CI 1.29, 2.42), uncontrolled HIV replication (viral load >400 copies/ml) (prevalence ratio 1.57; 95% CI 1.12, 2.22), age, sex, race and diabetes mellitus.

Conclusions—In HIV/HCV co-infected individuals, measures of regional body fat or fat distribution were not associated with hepatic fibrosis. In contrast, increased central adiposity by DXA, as well as concomitant fibrosis and uncontrolled HIV, were associated with hepatic steatosis. The extent to which weight loss and effective antiretroviral therapy can reduce the risk of steatosis deserves further investigation.

Keywords

body composition; hepatic fibrosis; hepatitis C; HIV; steatosis

Introduction

End-stage liver disease (ESLD) is a major source of morbidity and mortality among HIV-infected patients and is in large part attributable to chronic co-infection with hepatitis C

virus (HCV) [1]. However, only a subset of HIV/HCV patients will progress to ESLD [2] and the risk factors associated with disease progression are not fully understood.

Body composition is one potential risk factor for disease progression. Excess adiposity is closely associated with hepatic steatosis, which is common in HIV/HCV co-infected patients and correlates with hepatic fibrosis [3–5]. In HCV mono-infected patients, steatosis is a risk factor for liver disease progression [6], and higher body mass index (BMI) has also been associated with hepatic fibrosis [7]. In addition, adiposity is related to a poorer response to hepatitis C therapy [8]. Taken together, these findings suggest that reducing excess adiposity may reduce the risk of liver disease progression and improve HCV treatment response.

Many previous studies which have evaluated the relationship between body composition and histologic liver outcomes in HIV/HCV co-infected patients have used BMI as a measure of adiposity [3–5,7]. BMI, however, does not account for differences in regional adiposity. Because of central fat accumulation and subcutaneous fat wasting among HIV-infected patients receiving potent antiretroviral therapy (ART) [9], BMI may underestimate visceral adiposity in this population [10,11]. In addition, BMI does not reflect fat distribution, which may be an independent predictor of steatosis [3].

Sophisticated measurements of body composition can be used to address some of these limitations. Dual-energy X-ray absorptiometry (DXA) is a widely used technique that can accurately quantify regional adiposity, as well as provide a precise measurement of fat distribution.

Our previous studies in HIV/HCV co-infected individuals have shown that increased body weight was associated with steatosis [5] and that those with fibrosis progression tended to have a higher BMI compared to those with stable liver disease [12]. In this analysis, we sought to expand upon these findings by using DXA to examine the relationship between regional body composition and the histologic presence of liver disease (i.e. steatosis or fibrosis).

Methods

Study population

Study participants were recruited from the Johns Hopkins University HIV Clinic or the Viral Hepatitis clinical practice into a prospective cohort whose primary aim is to characterize liver disease progression among HIV/HCV co-infected persons. Between February 2005 and November 2007, 173 individuals enrolled in the cohort underwent body composition analysis with DXA within 1 year of a liver biopsy. The median time between the liver biopsy and the DXA was –18 days [interquartile range (IQR) –139, 6 days].

For all patients, information on prescribed medications and laboratory parameters was obtained from clinical and laboratory databases. As described previously, data on patient demographics, social practices, clinical and laboratory parameters, and prescribed antiretroviral and other medications are abstracted from charts by trained personnel and transferred electronically from the laboratory database at enrollment and subsequent 6–12-month intervals [13]. The designation of injection drug use and alcohol abuse was based on physician diagnosis and self-reports via orally administered questionnaires and audio computer-assisted self-interview. The presence of diabetes mellitus was self-reported. The study was approved by the Johns Hopkins Institutional Review Board and written informed consent was obtained for all participants.

Laboratory evaluations

Patients had standard laboratory assessments performed by licensed clinical laboratories, including a complete blood cell count, serum chemistry panels, aspartate amino-transferase (AST) levels, CD4 cell count, and plasma HIV-RNA level (reverse transcriptase polymerase chain reaction). HCV genotype testing was performed using reverse transcriptase polymerase chain reaction.

Liver histology

A transcutaneous liver biopsy was performed using an 18-gauge needle. Liver tissue was then fixed in 10% formalin, and paraffin-embedded sections were stained with hematoxylin–eosin and trichrome stains. Slides were evaluated by a single pathologist (M.T.). For fibrosis stage, biopsies were evaluated according to the META-VIR system [0 (no fibrosis) to 4 (cirrhosis)] [14]. Hepatic steatosis was classified on a 5-point scale: 0, none; 1, steatosis involving less than 5% of hepatocytes; 2, 5–29%; 3, 30–60%; 4 greater than 60%. The median biopsy length was 13 mm (IQR 11, 15 mm).

Body composition

Body mass index was defined as weight (kilograms) divided by the height (meters) squared. A wall-mounted stadiometer was used to measure height. Each participant was weighed while wearing minimal clothing. Whole body DXA was performed to assess regional body composition (trunk fat, extremity fat). The ratio of trunk fat to lower extremity fat [i.e. trunk fat mass : lower extremity fat mass ratio (FMR)] was calculated as a measure of fat distribution [15]. Procedures were done using a Hologic 4500A machine with QDA4500A software version 9.03 (Hologic Inc, Waltham, Massachusetts, USA).

Statistical analysis

Body composition measurements were compared between those with and without steatosis (steatosis grade >0) and those with and without significant fibrosis (METAVIR stage >1) using Wilcoxon rank-sum tests. Univariable and multivariable Poisson regression with robust variance was used to estimate prevalence ratios of steatosis or fibrosis by various body composition measurements [16]. Logistic regression tends to overestimate the prevalence ratio when the outcome is not rare (>10%) as was the case in this analysis. By contrast, Poisson regression provides a direct estimate of the prevalence ratio [17]. For multivariable models, variables that were associated with each histologic liver outcome in univariate analysis with a *P* value less than 0.10 were considered. Age, sex, and race were included in all multivariable models regardless of statistical significance. HIV RNA was analyzed as whether or not the concentration of HIV RNA was less than 400 copies/ml within 1 year of the DXA (median duration 13 days, IQR –8, 58 days). Two-sided *P* values less than 0.05 were considered statistically significant. Analysis was performed using SAS, version 9.1 (Cary, North Carolina, USA).

Results

Description of study population

The demographic and clinical characteristics of the study population (*n* = 173) are presented in Table 1. The median age was 47.7 years; 61% were male; 84% were black; 71% had a history of injection drug use and 38% had a history of clinician-diagnosed alcohol abuse or alcoholism; 94% were infected with HCV genotype 1. The median CD4 cell count was 428 cells/μl with HIV RNA level less than or equal to 400 copies/ml in 70%. Of the 50 patients with uncontrolled HIV replication, 56% were receiving potent ART within a year of the DXA, 6% had previously received ART but not within a year of the DXA, and 38% had

never received ART. For patients who were ART-experienced, cumulative ART exposure was 6.3 years, cumulative exposure to protease inhibitor (PI) was 4.1 years and stavudine exposure was minimal (median 0 years, IQR 0, 2.0).

Significant hepatic fibrosis (METAVIR stage >1) was observed in 24%, whereas hepatic steatosis was found in 45%. Of those with steatosis ($n = 77$), the majority (66%) had minimal steatosis (grade 1, fat in <5% of hepatocytes). Among all participants, the median BMI was 25.1 kg/m² and 21% had BMI greater than 30 kg/m² consistent with obesity. The median trunk : lower extremity FMR by whole body DXA was 1.5 (IQR 1.1, 2.2) and the median trunk fat was 8.5 kg (IQR 5.7, 13.6 kg).

Body composition stratified by steatosis and fibrosis on liver biopsy

Participants with steatosis ($n = 77$) had a higher median BMI, more trunk fat, and more extremity fat and tended to have a higher trunk/lower extremity FMR compared to those without steatosis ($n = 96$) (Table 2). The most significant differences were observed for trunk fat, which tended to increase with higher steatosis grade (Fig. 1). Participants with and without significant fibrosis were not significantly different with respect to BMI, trunk fat, and extremity fat.

Correlates of hepatic steatosis and fibrosis

The presence of steatosis was associated with BMI and trunk fat in univariate analysis (Table 3). Other variables associated with steatosis included diabetes mellitus, hepatic fibrosis, and uncontrolled HIV replication (HIV RNA level >400 copies/ml). Notably, age, sex, race, current or nadir CD4 cell count, clinical diagnosis of alcohol abuse, or ART use, including current, ever, or cumulative exposure to PIs, non-nucleoside reverse transcriptase inhibitors (NNRTIs), stavudine, or zidovudine (data not shown), was not associated with steatosis. Because of their close correlations ($r > 0.8$), we chose only one of the body composition variables, trunk fat, to be carried forward in the multivariable analysis, since it had the strongest association with steatosis. In the multivariable analysis (model 1), independent predictors of steatosis included uncontrolled HIV replication, fibrosis, and higher trunk fat. Similar results were obtained when steatosis was defined as liver fat greater than 5% (i.e. grade 2 vs. grade 0) (data not shown). In a second multivariable analysis (model 2), we further assessed the relationship between steatosis and relative fat distribution, using trunk/lower extremity FMR which has been proposed as a measure of mixed lipodystrophy [15]. Trunk fat was, therefore, removed from model 1 and replaced with BMI and trunk/lower extremity FMR. Both BMI and the trunk/lower extremity FMR were independently associated with steatosis (Table 2, model 2).

In univariable analysis, the presence of significant fibrosis (METAVIR stage >1) was not associated with BMI [prevalence ratio 1.01; 95% confidence interval (CI) 0.97, 1.06, $P = 0.7$], extremity fat (prevalence ratio 0.99, 95% CI 0.94, 1.05, $P = 0.79$), trunk fat (prevalence ratio 1.00; 95% CI 0.96, 1.04, $P = 0.97$), or trunk/lower extremity FMR (prevalence ratio 1.75; 95% CI 0.90, 3.41, $P = 0.10$). The association between fibrosis and trunk/lower extremity FMR was not statistically significant after adjustment for other confounders including age, sex, race, PI use at DXA, steatosis, and AST (data not shown). Similar results were obtained for both models 1 and 2 when the sample was restricted to the 145 African-American participants (data not shown).

Discussion

In this cohort of HIV/HCV co-infected patients who underwent DXA and histologic evaluation of contemporaneous liver biopsy specimens, hepatic steatosis was significantly

associated with increased central fat, whether measured in absolute or relative terms, whereas hepatic fibrosis was not correlated with any measure of body composition. We also found that steatosis was associated with uncontrolled HIV replication rather than the use of ART or specific antiretroviral drugs. These findings confirm the importance of central adiposity and central fat distribution as a potentially modifiable risk factor for hepatic steatosis and suggest that current antiretroviral regimens, without stavudine, may attenuate rather than promote liver fat accumulation.

To our knowledge, this is one of the only studies in HIV/HCV co-infected patients which employs the best available measures of both body composition and steatosis. Most previous studies have relied on BMI or body weight as a measure of adiposity [3–5,18] or have used noninvasive surrogate measures for steatosis (e.g. magnetic resonance imaging or ultrasound techniques) [19]. Using DXA, we also quantified the regional distribution of adipose tissue and found the expected association between central fat and hepatic steatosis.

There are important physiologic differences in various adipose tissue depots. Central fat has a major role in the pathogenesis of steatosis, likely through increased insulin resistance [20], elaboration of free fatty acids [21], and adipocytokine production [22]. In contrast, subcutaneous fat of the lower extremities may protect against metabolic derangement, including steatosis, by serving as a triglyceride storage depot [21]. In the FRAM cohort, for example, hypertriglyceridemia and elevated alanine transaminase (ALT), suggestive of steatosis, were associated with both increased visceral fat and lower amounts of subcutaneous fat [19,23]. As a result, in HIV-infected patients, measures of fat distribution, such as the ratio of central fat to lower extremity fat may be particularly relevant in identifying those at increased risk of metabolic abnormalities [15]. Similarly, we found that this DXA-derived measure of fat distribution was associated with steatosis, independent of BMI.

Another important finding in our study was that uncontrolled HIV replication was independently related to the presence of hepatic steatosis. This observation is similar to that from a recent large case–control study which observed that a higher plasma HIV viral load was associated with severe hepatic steatosis as determined by ultrasonography [24]. Although it is not possible to determine a causal relationship from cross-sectional data, uncontrolled HIV replication may contribute to the pathogenesis of steatosis through increased insulin resistance and inflammation. In the Multicenter AIDS Cohort Study, all groups of HIV-infected men, including those not receiving ART, were more insulin-resistant compared to HIV-uninfected men [25]. Moreover, in a large cohort of ART-naïve patients, insulin resistance was associated with higher viral load and lower CD4 cell count [26], which may be mediated by the increased expression of proinflammatory cytokines, including TNF- α [27,28] and IL-6 [29], thereby promoting steatosis. The extent to which effective antiretroviral therapy can decrease the risk of steatosis deserves further investigation.

In contrast to previous studies, including our own [5,30], we did not observe a relationship between specific antiretroviral agents and steatosis. In older studies, stavudine exposure has been most closely associated with steatosis, through its effect on mitochondrial function [30,31]. However, stavudine usage is now very uncommon in our cohort and, in those who were previously exposed, the effects of stavudine on hepatic steatosis may have reversed with discontinuation.

In this study, most patients did not have more than 5% steatosis. Nonetheless, as in previous studies of HIV/HCV co-infected patients [3–5,18,30], hepatic steatosis was associated with concomitant liver fibrosis. Ectopic fat accumulation in the liver can lead to hepatic necrosis

and apoptosis through the generation of oxidative stress and inflammation [32]. In a previous longitudinal study [12], we did not find an association between baseline steatosis and fibrosis progression, but this important issue deserves further attention.

In contrast to findings in HCV mono-infected patients [7], we did not find an association between adiposity and the presence of hepatic fibrosis. This lack of association was also observed in another cohort of HCV/HIV co-infected patients and, in that study, was attributed to the relatively low BMI (mean ~ 25 kg/m²) and the presence of other contributing factors, such as low CD4 cell count [7]. We did observe a nonsignificant trend towards a higher trunk/extremity fat mass ratio in those with fibrosis. Longitudinal studies are required to assess the contribution of central fat distribution to fibrosis progression.

Our study had several limitations. First, 94% of our cohort was infected with genotype 1 and most are African-American; thus, it is unclear whether our findings are generalizable to populations with other genotypes or different racial composition. Genotype 3 virus, in particular, is thought to cause steatosis through direct viral mechanisms, and steatosis is likely a more important problem in countries, such as Spain, with higher genotype 3 HCV prevalence [33]. Second, although well correlated with other measurement techniques, such as magnetic resonance imaging [34], DXA does not distinguish subcutaneous from visceral fat, which would be helpful in understanding the contributions of various fat depots to steatosis risk. It is also impossible to ascertain whether the association between unsuppressed HIV RNA and steatosis reflects HIV replication or other factors like unacknowledged alcohol use that might be associated with both steatosis and incomplete antiretroviral adherence.

In conclusion, the relative and absolute amount of central fat was correlated with hepatic steatosis. These findings underscore the potential of weight loss to improve hepatic outcomes in HIV/HCV co-infected patients. In addition, the independent association of uncontrolled HIV infection and hepatic steatosis suggests that effective HIV therapy may be an important tool to reduce the burden of liver disease in HIV-infected patients.

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Fig. 1.
The distribution of trunk fat by dual energy X-ray absorptiometry stratified by steatosis grade in 173 HIV/HCV co-infected patients (+ represent median value in category).

Table 1Characteristics of HIV/HCV co-infected cohort ($n = 173$).

		<i>N</i>
Age [years, median (IQR)]	47.7 (43.3–52.3)	173
Sex (% male, <i>n</i>)	61, 106	173
Race (% black, <i>n</i>)	84, 145	173
BMI [kg/m ² , median (IQR)]	25.1 (22.7–29.1)	173
AST [mg/dl, median (IQR)]	44 (33–69)	173
History of injection drug use (% , <i>n</i>)	71, 123	173
History of alcohol abuse	38, 65	173
History of diabetes mellitus	10, 18	173
Significant liver fibrosis (metavir >1) (% , <i>n</i>)	24, 41	173
Fibrosis grade (% , <i>n</i>)		173
0	26, 45	
1	50, 87	
2	10, 17	
3	6, 11	
4	8, 13	
Steatosis (% , <i>n</i>)	45, 77	173
Steatosis grade (% , <i>n</i>)		173
0	55, 96	
1	30, 52	
2	9, 16	
3	3, 6	
4	2, 3	
HCV genotype (% , <i>n</i>)		
1	94, 161	171
2	3, 5	
3	2, 3	
4	1, 2	
HCV viral load (IU/ml)	1 690 000 (439 000–5 570 000)	150 ^a
History of prior HCV treatment (% , <i>n</i>)	26, 45	173
CD4 cell count [cells/μl, median (IQR)]	428 (248–585)	169
Nadir CD4 cell count [cells/μl, median (IQR)]	150 (36–264)	173
HIV RNA (% <400 copies/ml)	70, 119	169
History of potent ART use (% , <i>n</i>)	74, 128	173
Potent ART within 1 year (% , <i>n</i>)	68, 118	173
PI within 1 year (% , <i>n</i>)	53, 91	173
d4T within 1 year (% , <i>n</i>)	3, 6	173
ZDV within 1 year (% , <i>n</i>)	28, 48	173
Cumulative potent ART exposure [years, median (IQR)]	4.15 (0–8.41)	173
Cumulative PI exposure [years, median (IQR)]	1.21 (0–7.99)	173

		<i>N</i>
Cumulative d4T exposure [years, median (IQR)]	0 (0–2.01)	173
Cumulative ZDV exposure [years, median (IQR)]	2.30 (0–6.40)	173
BMI [kg/m ² , median (IQR)]	25.1 (22.7–29.1)	173
Extremity fat [kg, median (IQR)]	7.9 (4.6–11.4)	173
Trunk fat [kg, median (IQR)]	8.4 (5.7–13.6)	173
Trunk fat/extremity fat [median (IQR)]	1.5 (1.1–2.1)	173

ART, antiretroviral therapy; AST, aspartate aminotransferase; d4T, stavudine; HCV, hepatitis C virus; IQR, interquartile range; ZDV, zidovudine.

^a19 of 169 patients with available HCV RNA had levels greater than the upper limit of the assay (Cobas Amplicor HCV Monitor v2.0) are therefore not included.

Table 2

Body composition measurements in 173 HIV/hepatitis C co-infected patients, stratified by steatosis and fibrosis (METAVIR score >1) on liver biopsy.

	No steatosis	Steatosis	<i>P</i>	No fibrosis	Fibrosis	<i>P</i>
<i>N</i>	96	77		132	41	
BMI [kg/m ² , median (IQR)]	24.7 (22.3–27.8)	26.3 (23.0–31.1)	0.04	25.0 (22.6–29.0)	25.8 (22.8–29.6)	0.8
Extremity fat [kg, median (IQR)]	7.3 (4.2–10.5)	9.0 (5.3–12.1)	0.06	8.0 (4.6–11.5)	7.2 (4.1–10.7)	0.6
Trunk fat [kg, median (IQR)]	7.4 (5.0–11.7)	10.1 (6.1–14.4)	0.008	8.4 (5.7–13.8)	9.5 (5.7–11.9)	0.8
Trunk fat/extremity fat [median (IQR)]	1.4 (1.1–2.0)	1.5 (1.3–2.2)	0.1	1.4 (1.1–2.0)	1.6 (1.3–2.3)	0.2

Table 3Determinants of hepatic steatosis in HIV/hepatitis C virus co-infected patients ($n = 173$).

Variable	Univariate prevalence ratio (95% CI)	<i>P</i>	Multivariate model 1 (95% CI)	Multivariate model 2 (95% CI)
Age (per 5 years)	0.94 (0.84–1.05)	0.29	0.95 (0.83–1.09)	0.93 (0.81–1.07)
Sex [F vs. M (ref)]	1.07 (0.76, 1.49)	0.71	0.86 (0.60–1.25)	0.99 (0.69–1.43)
Race [black vs. white (ref)]	0.87 (0.57–1.32)	0.51	0.85 (0.55–1.32)	0.96 (0.57–1.61)
Alcohol abuse (yes or no)	1.06 (0.76–1.49)	0.73		
Diabetes (yes or no)	1.59 (1.09–2.31)	0.02	1.36 (0.91–2.01)	1.32 (0.89–1.97)
CD4 cell count (cell/ μ l) (200 vs. <200)	0.88 (0.58–1.33)	0.54		
Nadir CD4 cell count (continuous)	1.00 (1.00–1.00)	0.54		
HIV-RNA viral load (<400 vs. 400 copies/ml)	1.39 (1.00–1.93)	0.05	1.57 (1.12–2.22)	1.59 (1.13–2.24)
Ever ART (yes vs. no)	1.07 (0.73–1.59)	0.72		
Current ART (yes vs. no)	1.17 (0.80–1.70)	0.43		
Cumulative ART exposure (continuous)	0.97 (0.93–1.01)	0.18		
Fibrosis (yes vs. no)	1.64 (1.20–2.25)	0.002	1.77 (1.29–2.42)	1.69 (1.24–2.30)
BMI (continuous)	1.03 (1.01–1.06)	0.006		1.04 (1.01–1.06)
Trunk fat (continuous)	1.03 (1.01–1.06)	0.005	1.04 (1.02–1.07)	
Extremity fat (continuous)	1.02 (0.99–1.05)	0.23		
Trunk fat/extremity fat ratio (continuous)	1.14 (0.97–1.34)	0.12		1.21 (1.01–1.45)