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Association Between Hepatitis C Virus Coinfection and Regional Adipose Tissue Volume in HIV-Infected Men and Women

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Abstract

Objective—Coinfection with hepatitis C virus (HCV) is reported to be associated with a higher prevalence of lipodystrophy than HIV infection alone. We examine the association between HCV and adipose tissue volume in HIV-infected men and women.

Methods—Cross-sectional analysis of HIV-infected subjects from the study of Fat Redistribution and Metabolic Change in HIV Infection. MRI measured regional adipose tissue volume. Detectable HCV RNA defined HCV infection.

Results—Twenty percent of 792 men and 26% of 329 women were HIV/HCV-coinfected. HIV/HCV-coinfected and HIV-monoinfected women had similar amounts of subcutaneous adipose tissue (SAT) in the leg, lower trunk, upper trunk, and arm and similar amounts of visceral adipose tissue (VAT). Similar findings were seen in men, except in the leg and VAT. After adjustment, HCV infection remained associated with more leg fat in men (12.2%, 95% confidence interval [CI]: 0.3 to 25.3; $P = 0.043$). Among those on stavudine, HIV-monoinfected men had less leg fat (−7% effect per year of stavudine use, 95% CI: −9 to −5; $P < 0.001$); a weaker association was seen in HIV/HCV-coinfected men (−2% effect, 95% CI: −7 to 3; $P = 0.45$). Indinavir was associated with less leg fat (−4% in HIV-monoinfected men, 95% CI: −6 to −1; $P = 0.002$; −5% in HIV/HCV-coinfected men, 95% CI: −11 to 2; $P = 0.14$).

Conclusions—Our findings suggest that HIV/HCV coinfection is not associated with less SAT in men and women. HCV infection seems to mitigate the loss of leg fat seen in HIV-infected men on stavudine.

Keywords

adipose tissue volume; fat distribution; hepatitis C virus; HIV; lipodystrophy

Fat distribution changes, including peripheral fat loss and central fat gain, in HIV infection were first described as a “lipodystrophy syndrome.”¹ Subsequent studies suggested that concurrent infection with the hepatitis C virus (HCV) may be associated with a higher prevalence of clinical lipodystrophy, particularly lipoatrophy, than in those with HIV infection alone.^{2–4} These findings are of concern because approximately one third of HIV-infected individuals in the United States are concurrently infected with HCV⁵ and fat changes in HIV infection have been associated with decreased quality of life and potentially compromised adherence to otherwise effective antiretroviral therapy.⁶ Effective antiretroviral therapy has been shown to slow down the progression of HCV-associated liver disease.^{7–9}

Published studies that have investigated the association between concurrent HCV infection and lipodystrophy have been small and have defined lipodystrophy using subjective criteria of self-report confirmed by examination. The presence of facial or limb fat loss with or without central fat gain defined lipodystrophy in one study.³ Two other studies^{2,4} defined lipodystrophy as having lipoatrophy alone, lipohypertrophy alone, or a combination of lipoatrophy and lipohypertrophy. Furthermore, these studies included mainly men and may not be generalizable to women. Peripheral and central fat loss seems to predominate in HIV-infected men when measured using magnetic resonance imaging (MRI) and compared with control men.¹⁰ In HIV-infected women, peripheral fat loss also seems to predominate, but some women may have more upper trunk fat and visceral fat than control women.¹¹

We present our findings on the association of HCV infection confirmed by HCV RNA testing with MRI-measured regional adipose tissue volume in a large cohort of HIV-infected men and women from the study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM).

METHODS

Between June 2000 and September 2002, 1183 HIV-infected persons were enrolled in the FRAM study. HIV-infected participants were selected from coded lists of patients seen in 16 HIV or infectious disease clinics or cohorts during 1999 that were randomly ordered. Of the 1183 HIV-infected participants, 30% (or 350) were women. The recruitment and data collection procedures for the entire cohort have been described elsewhere.¹² Institutional review boards at all participating sites approved the study protocol and consent process.

The FRAM participants were asked about their physical activity, alcohol intake, smoking, illicit drug use, and adequacy of food intake using standardized instruments.^{13–16} Medical history was also assessed. Women who reported at least 12 months of amenorrhea attributable to natural menopause or a history of bilateral oophorectomy were categorized as being menopausal. Research associates interviewed HIV-infected participants and reviewed medical charts to determine the dates of use of individual antiretroviral medications.

Height and weight were measured. Body composition was measured by MRI using a standardized protocol.^{10,17,18} MRI scans were segmented using image analysis software (Tomovision, Montreal, Quebec, Canada). The volume of each tissue for the space between 2 consecutive slices was calculated by means of a mathematic algorithm.¹⁹ Using these methods, we quantified adipose tissue volume in the leg, lower trunk (abdomen and back), upper trunk (chest and back), arm, and abdominal viscera. Blood was drawn and sent to

Covance Labs (Indianapolis, IN) for determination of CD4 cell counts and HIV RNA levels by polymerase chain reaction (PCR).

Stored serum samples were tested centrally for HCV RNA level by branched DNA (bDNA) using the Bayer Versant HCV RNA 3.0 assay (Bayer HealthCare-Diagnostics, Tarrytown, NY) on all FRAM participants. Among the FRAM participants, 810 HIV-infected men and 341 HIV-infected women with stored serum samples available for testing were included in the study. Of these participants, 18 men and 12 women had an opportunistic infection or malignancy within the same or previous calendar month as the examination and were excluded because they may have had acute changes in fat. Therefore, 792 HIV-infected men and 329 HIV-infected women were included in the analysis.

Statistical Analysis

For prevalences, *P* values were calculated by the Fisher exact test. Numeric values were compared by the Mann-Whitney test.

Multivariate analysis was performed for adipose tissue volumes in each of the following 5 anatomic sites: visceral, legs, lower trunk, arms, and upper trunk. Methods were similar to those used in previous reports.^{10,11} For each anatomic site, comparisons were made of HIV-infected persons with HCV infection versus HIV-infected persons without HCV infection. These models were fitted to logarithmic transformations of MRI measures divided by height squared, analogous to body mass index (BMI); regression coefficients were back-transformed to produce estimated percentage effects on height-normalized quantity of adipose tissue. We note that controlling for BMI would not be appropriate, because BMI includes the outcomes being modeled as part of its definition.²⁰ Non-HIV-related variables controlled for in the models include the following: age, ethnicity, smoking, alcohol intake, type of illicit drug use (ie, crack/cocaine, marijuana, heroin, and speed were separately studied in the model), level of physical activity, and, for women, menopause. HIV-related variables controlled for in the models include HIV RNA level ($\log_{10}$) and CD4 cell count ($\log_2$) at the time of study visit.

In multivariate models controlling for these factors, we evaluated the total duration of each antiretroviral drug or antiretroviral drug class (nucleoside reverse transcriptase inhibitor [NRTI], nonnucleoside reverse transcriptase inhibitor [NNRTI], and protease inhibitor [PI]) and highly active antiretroviral therapy (HAART) that was ever used. HAART was defined by: (1) 2 or more NRTIs in combination with at least 1 PI or NNRTI; (2) 1 NRTI in combination with at least 1 PI and at least 1 NNRTI; (3) a regimen containing zidovudine and zalcitabine in combination with 1 NRTI and no NNRTIs; or (4) an abacavir-containing regimen of 3 or more NRTIs in the absence of PIs and NNRTIs. We checked linearity by fitting more complex models using linear splines, finding that linearity seemed reasonable in all cases. Duration of each antiretroviral drug, antiretroviral drug class, and HAART was added to the model in a forward-stepwise manner. We also checked for interactions in the model between HCV status and duration of antiretroviral drug use because both have been linked to mitochondrial toxicity, which, in turn, may affect adipose tissue. We found several statistically significant HCV/antiretroviral drug interactions in men in several depots, but results are limited to the leg because of a priori interest and because leg subcutaneous adipose tissue (SAT) was the only depot that seemed to be strongly associated with HCV infection. The models for HIV-infected men for leg SAT were therefore fit by including separate antiretroviral drug effects for HCV-infected men and HCV-infected men when warranted. We also examined the interaction between HCV and antiretroviral drugs graphically in the context of the multivariate model for leg SAT in men and women separately; residuals from this model were plotted against total stavudine duration, with separate regression lines shown for HCV-infected and HCV-infected subgroups. Individuals

with 0 antiretroviral drug duration were not displayed in the plot but were included in the residual and regression calculations.

Confidence intervals (CIs) were determined using the bias-corrected accelerated bootstrap method,²¹ with *P* values defined as the one minus the highest confidence level that still excluded 0. This was necessary because many outcome measures seemed to be non-Gaussian, even after log transformation.

RESULTS

Demographic and Clinical Characteristics by Hepatitis C Virus Status

One fifth (or 160) of 792 HIV-infected men and 26% (or 87) of 329 HIV-infected women had chronic HCV infection as determined by detectable HCV RNA. Among men and women, those with HCV infection were older, more often African American, and more likely to have a history of injection drug use (Table 1). Men with HCV infection had higher HIV RNA levels and lower CD4 cell counts than men without HCV infection. There seemed to be little difference in the HIV RNA level and CD4 cell count between women with and without HCV infection. Nadir CD4 cell count was similar between those with and without HCV infection in men (median: 141 cells/ μ L vs. 153 cells/ μ L; *P* = 0.44) and women (median: 169 cells/ μ L vs. 150 cells/ μ L; *P* = 0.29).

Regional Adipose Tissue Volume by Hepatitis C Virus Status

HIV/HCV-coinfected men had more leg fat and less visceral adipose tissue (VAT) than HIV-monoinfected men (Table 2). There was no statistically significant difference in the amount of SAT in the lower trunk, arm, and upper trunk between HIV/HCV-coinfected and HIV-monoinfected men. There was no statistically significant difference in SAT in any body depot or in VAT between HIV/HCV-coinfected and HIV-monoinfected women. Use of statins, which was recently reported to be associated with some recovery in limb fat, was less often used in HIV/HCV-coinfected than in HIV-monoinfected subjects (2% vs. 16% for men; *P* < 0.001 and 2% vs. 11% for women; *P* < 0.021). Use of thiazolidinedione agents was rare in our cohort.

After multivariate adjustment, HCV infection remained associated with more leg fat in HIV-infected men, but it no longer seemed to be associated with more VAT (Fig. 1). In women, VAT seemed higher in those with HCV infection, but this had a wide CI.

Association of Antiretroviral Drug Exposure With Leg Subcutaneous Adipose Tissue by Hepatitis C Virus Status

In men, the effects of the antiretroviral drugs (individually and by class) on leg SAT were estimated separately by HCV status, because significant interactions between HCV and antiretroviral drugs were identified when investigating the association with leg SAT. Use of the nucleoside analogue stavudine was associated with less leg SAT in HIV-monoinfected men (−7.0% effect per year of use, 95% CI: −9.2 to −4.8; *P* < 0.001) and was more weakly associated in HIV/HCV-coinfected men (−2.4% effect, 95% CI: −7.4 to 3.3; *P* = 0.45; HCV/stavudine interaction, *P* = 0.043). Two nucleoside analogues, didanosine and abacavir, were also associated with less leg SAT in HIV-monoinfected men (−3.6% effect per year of didanosine use, 95% CI: −7.1 to −0.4; *P* = 0.022 and −5.9% effect per year of abacavir use, 95% CI: −10.4 to −1.3; *P* = 0.012). An association between didanosine and abacavir was not found in HIV/HCV-coinfected men (1.4% effect, 95% CI: −4.0 to 8.9; *P* = 0.55; HCV/didanosine interaction, *P* = 0.024 and 8.3% effect, 95% CI: −3.1 to 21.8; *P* = 0.13; HCV/abacavir interaction, *P* = 0.035, respectively), however.

The PI indinavir was associated with less leg SAT in HIV-monoinfected men (-3.5% effect, 95% CI: -5.7 to -1.2 ; $P = 0.002$) and seemed to have a similar effect in HIV/HCV-coinfected men (-5.0% effect, 95% CI: -10.9 to 1.6 ; $P = 0.14$). Conversely, the nonnucleoside analogue nevirapine was associated with more leg SAT in HIV/HCV-coinfected men (15.5% effect, 95% CI: 0.5 to 29.5 ; $P = 0.044$) but not in HIV-monoinfected men (-2.8% effect, 95% CI: -6.7 to 1.3 ; $P = 0.16$; HCV/nevirapine interaction, $P = 0.011$).

Antiretroviral drug effects on leg SAT seemed similar in HIV/HCV-coinfected and HIV-monoinfected women, and interactions between HCV and antiretroviral drugs did not reach statistical significance. Similar to findings previously presented,¹¹ use of stavudine was associated with less leg fat (-9.2% effect, 95% CI: -12.7 to -5.1 ; $P < 0.001$), as was use of the antiretroviral drug class NNRTI (-6.2% effect, 95% CI: -11.9 to -0.5 ; $P = 0.034$).

Because stavudine was associated with less leg SAT in men and women, this relation was examined graphically by HCV status for men (Fig. 2A) and women (see Fig. 2B) by plotting residuals from the multivariate model against stavudine duration. HIV/HCV-coinfected men demonstrated little leg fat loss with increasing duration on stavudine, whereas HIV-monoinfected men showed a loss with increasing duration on stavudine. HIV/HCV-coinfected women seemed to have smaller decreases in leg fat with increasing duration on stavudine compared with HIV-monoinfected women, but the difference was less pronounced than in men.

DISCUSSION

In our large multicenter study using MRI-measured regional adipose tissue volume, we found that HIV/HCV coinfection was not associated with less fat when compared with HIV-monoinfected men and women. Our findings are contrary to those of previous studies, which reported an association between HIV/HCV coinfection and peripheral fat loss when compared with HIV-monoinfected individuals. Furthermore, previous studies have not addressed the association of HCV infection with fat changes in HIV-infected women.

We found that HIV/HCV-coinfected women had similar amounts of regional fat when compared with HIV-monoinfected women. HIV/HCV-coinfected men also had similar amounts of regional fat, except in the leg. On average, HIV/HCV-coinfected men had more leg fat than HIV-monoinfected men. The findings of more leg fat in HIV/HCV-coinfected men than in HIV-monoinfected men must be tempered by the fact that the amount of leg fat in HIV/HCV-coinfected men was still less than that in FRAM controls, however.¹⁰

When we investigated the association between antiretroviral drugs and leg fat by HCV status, our findings were again contrary to what has been proposed, that the presence of HCV infection and HIV nucleoside analogues may further worsen lipoatrophy. HIV nucleoside analogues, particularly stavudine, have been associated with lipoatrophy, and the proposed mechanism has been thought to be attributable to nucleoside analogue-induced mitochondrial toxicity. HCV has been shown to induce mitochondrial toxicity in the liver.²² Because it is thought that HIV-infected patients usually acquire their HCV infection before HIV infection, it is possible that the mitochondrial toxicity already established as a result of HCV infection does not allow for further toxic effects as a result of HIV infection and NRTIs.

We found that stavudine use was less associated with reduced leg fat in HIV/HCV-coinfected men when compared with HIV-monoinfected men. HIV/HCV-coinfected men demonstrated approximately a 2% loss of leg fat per year of stavudine use (which might imply a loss of approximately 0.08 L [or 70 g] of leg fat in the first year of use for someone starting with 3.29 L [or 2.96 kg] of leg fat; overall mean shown in Table 2), whereas HIV-

monoinfected men demonstrated approximately a 7% loss per year of stavudine use (which might imply a loss of approximately 0.2 L [or 180 g] of leg fat for someone starting with 2.8 L [or 2.53 kg] of leg fat). From a clinical perspective, the amount of leg fat lost per year in either group would most likely not be associated with visibly noticeable changes. HIV/HCV-coinfected women also seemed to have slightly smaller decreases in leg fat with increasing duration of stavudine use when compared with HIV-monoinfected women. These data suggest that the presence of HCV infection may, in fact, mitigate the leg fat loss that occurs as a result of HIV infection and stavudine use.

There are several possible reasons why our findings differ from those of previous studies. First, our study is the largest to date to investigate the association of concurrent HCV infection (confirmed by HCV RNA testing) on fat changes in a representative cohort of HIV-infected individuals in medical care in the United States. Second, we used MRI measurement of regional adipose tissue volume, whereas other studies used subjective criteria to define lipodystrophy based on self-report and examination. Third, we adjusted for factors known to affect body composition, which had not been done previously in most other studies.

Similar to other published studies, our study is cross-sectional; therefore, we are unable to address fat changes prospectively, and thus to establish a causal relation between HCV infection and fat changes over time. Another limitation of our cross-sectional design is that we could not account for the possibility of survivor bias. The HIV/HCV-coinfected patients included in our study may have had slowly progressive HCV liver disease compared with those not included in our study (who may have died as a result of rapidly progressive HCV liver disease). We did not have histologic data to assess the degree of HCV-related liver disease and how it might be associated with body fat changes. Investigation of the association between regional fat and liver enzyme abnormalities in our cohort is underway.

In summary, our findings contradict previous reports of an association between HIV/HCV coinfection and peripheral fat loss compared with individuals with HIV monoinfection. We found an association between concurrent HCV infection and more leg fat in men compared with those without HCV infection and little apparent association between HIV/HCV coinfection and any regional adipose tissue volume in women. In the absence of direct measures of regional adipose tissue volume in a large cohort of HIV-infected individuals, the findings of other studies must be interpreted with caution. Furthermore, the mechanisms by which HIV, antiretroviral drugs, and HCV may affect fat changes may be more complex than previously hypothesized and warrant further investigation in men and women.

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APPENDIX

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Daniel Lee); Washington University (William Powderly and Kevin Yarasheski); Veterans Affairs Medical Center, Atlanta (David Rimland); University of California, Los Angeles (Judith Currier and Matthew Leibowitz); Veterans Affairs Medical Center, New York (Michael Simberkoff and Juan Bandres); Veterans Affairs Medical Center, Washington, DC (Cynthia Gibert and Fred Gordin); St. Luke's–Roosevelt Hospital Center (Donald Kotler and Ellen Engelson); University of California, San Francisco (Morris Schambelan and Kathleen Mulligan); Indiana University (Michael Dube); and Kaiser Permanente, Oakland (Stephen Sidney)

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FIGURE 1.

Point estimates and 95% CIs for the percent difference in regional adipose tissue volume in HIV/HCV-coinfected subjects compared with HIV-monoinfected subjects by gender. The model adjusts for HCV status, race, age, alcohol, smoking, physical activity, illicit drugs, CD4 cell count, and HIV viral load. Regional adipose tissue volume is defined by log (adipose tissue per height squared).

FIGURE 2.

A, Regression of leg SAT by duration of use of stavudine (d4T) in HIV/HCV-coinfected and HIV-monoinfected men. Individuals with 0 antiretroviral drug duration are not displayed in the plot but are included in the residual and regression calculations. B, Regression of leg SAT by duration of use of d4T in HIV/HCV-coinfected and HIV-monoinfected women. Individuals with 0 antiretroviral drug duration are not displayed in the plot but are included in the residual and regression calculations.

TABLE 1
Demographic and Clinical Characteristics of HIV-Infected Men and Women by HCV RNA Status

	HIV+ Men			HIV+ Women		
	HCV+	HCV-	P	HCV+	HCV-	P
n	160	632		87	242	
Age (y)						
Median	46.0	42.0	<0.0001	44.0	40.0	<0.0001
IQR	42.0–51.0	37.0–48.0		40.0–48.0	34.0–46.0	
Race*						
African American	54%	28%	<0.0001	68%	50%	0.015
White	31%	61%		24%	36%	
Hispanic	12%	9%		3%	11%	
Other	3%	2%		5%	3%	
Height (cm)						
Median	175.1	175.5	0.17	162.4	162.6	0.34
IQR	170.2–180.3	171.5–180.3		156.0–166.4	158.2–166.6	
Weight (kg)						
Median	74.3	75	0.42	66.9	71.5	0.067
IQR	66.3–83.2	68.2–83.6		58.7–76.3	59.2–83.2	
BMI (kg/m ²)						
Median	24.2	24.4	0.74	25.3	26.6	0.10
IQR	21.8–26.8	22.3–26.8		21.9–28.9	22.7–32.2	
Current smoker	59%	37%	<0.0001	69%	36%	<0.0001
Alcohol use (past year)	64%	78%	0.0002	52%	65%	0.029
Menopause	n/a	n/a		26%	18%	0.033
HBsAg ⁺	3%	9%	0.009	0	2%	0.33
Log ₁₀ HCV RNA						
Median	6.2	n/a		6.3	n/a	0.45 [†]
IQR	5.8–6.6			5.9–6.6		
HIV risk factors						

	HIV+ Men			HIV+ Women		
	HCV+	HCV-	P	HCV+	HCV-	P
IDU	59%	7%	<0.0001	71%	10%	<0.0001
MSM	22%	78%		n/a	n/a	
Heterosexual	10%	10%		20%	70%	
Other	9%	5%		9%	20%	
Duration of HIV (y)						
Median	8.8	7.7	0.052	9.7	7.6	0.001
IQR	5.6–12.4	4.8–11.9		6.5–12.0	5.7–10.1	
Log ₁₀ HIV RNA						
Median	2.8	2.6	0.020	2.9	2.6	0.48
IQR	2.6–4.3	2.6–3.9		2.6–4.3	2.6–4.1	
CD4 count (cells/ μ L)						
Median	272	382	<0.0001	351	358	0.86
IQR	162–412	238–558		225–503	192–568	
Total duration of HAART (y)						
Median	3.3	3.5	0.019	3.1	3.3	0.40
IQR	1.9–4.3	2.4–4.6		1.8–4.5	2.0–4.6	

* Test of proportion of whites versus African Americans.

[†]Test of men versus women for coinfecting subjects.

Participants with an opportunistic infection were excluded.

HBsAg indicates hepatitis B surface antigen; IQR, interquartile range; n/a, not applicable.

TABLE 2
Comparison of Adipose Tissue Volume* by MRI in HIV-Infected Men and Women by HCV RNA Status

Median (95% CI)	HIV+ Men			HIV+ Women		
	HCV+	HCV-	P	HCV+	HCV-	P
Leg SAT (L)	3.2 (2.9 to 3.7)	2.7 (2.6 to 2.9)	0.002	6.5 (6.1 to 7.9)	7.8 (7.1 to 8.7)	0.48
Lower trunk SAT (L)	3.5 (3.0 to 3.8)	3.3 (3.1 to 3.5)	0.14	9.0 (7.1 to 9.8)	9.9 (8.5 to 10.6)	0.15
Arm SAT (L)	1.0 (0.9 to 1.1)	1.0 (0.9 to 1.0)	0.47	1.8 (1.6 to 2.0)	1.9 (1.7 to 2.2)	0.52
Upper trunk SAT (L)	2.3 (2.1 to 2.7)	2.6 (2.4 to 2.7)	0.18	5.2 (4.1 to 6.0)	6.0 (5.5 to 6.7)	0.059
VAT (L)	1.3 (1.0 to 1.7)	1.9 (1.7 to 2.1)	0.0001	1.3 (1.0 to 1.6)	1.5 (1.2 to 1.7)	0.31

* Adipose tissue volume was divided by height squared, medians and confidence intervals were calculated, and these were then multiplied by the mean height squared.