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Racial Differences in the Association between Adiposity Measures and the Risk of Hepatitis C-related Liver Disease

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Abstract

Background—African-Americans have lower reported likelihood of HCV-related cirrhosis than Whites. It is unknown if relative differences in the distribution of adipose tissue, lean mass, and other anthropometric measurements may explain these observed interethnic differences in disease risk.

Aim—To evaluate the association between anthropometric measurements and advanced liver disease in a cross-sectional study of African-American and White male veterans.

Methods—We used the validated FibroSURE-ActiTest to assess hepatic pathology, and direct segmental multichannel bioelectric impedance analysis for anthropometric measurements. Race-stratified logistic regression was employed to evaluate risk of high fibrosis progression rate (FPR) and advanced inflammation (A2-A3).

Results—Among 330 eligible males (59% African-American), there were 43 White and 57 African American males with high FPR, and 70 African American and 59 White with advanced inflammation. % body fat (%BF) was a stronger predictor of high FPR risk than was a high BMI in African-Americans ($OR_{adj}=2.08$, 95% CI= 0.83–5.23 for highest %BF vs. lowest tertile and. $OR_{adj}=1.50$, 95% CI=0.60–3.75 for obese vs. normal BMI, respectively), but not in Whites. Highest lean leg mass was associated with a non-significant increased risk of both high FPR and advanced inflammation in African-Americans ($OR_{highFPRadj}=1.73$, 95% CI 0.73–4.10;

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Conflict of Interest Statement:

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OR_{AdvancedInflammationAdj}=1.65, 95% CI 0.76–3.56) vs. a decreased risk of both in Whites (OR_{highFPRadj}=0.62, 95% CI 0.21–1.79; OR_{AdvancedInflammationAdj}=0.58, 95% CI 0.22–1.48).

Conclusions—Interethnic differences in non-traditional anthropometric measurements like %BF suggests their potential role in understanding interethnic differences in HCV-related liver disease risk in males.

MeSH Keywords

epidemiology; veterans; infectious diseases; anthropometry; insulin resistance; cirrhosis; obesity; hepatology

Introduction

The prevalence of HCV is higher in African-Americans than Caucasians (3.2% vs. 1.5%, respectively), with African-Americans comprising approximately 22% of all HCV cases in the United States.¹ The progression of liver disease among HCV-infected patients may also differ among various ethnic groups. Several^{2–7} though not all^{3,8–10} studies reported that HCV-infected non-African American groups have significantly higher prevalence of cirrhosis or higher fibrosis progression rates than are reported in African-Americans. The reasons for these interethnic differences are unclear.

Greater abdominal or visceral adiposity is considered deleterious, and is thought to exert its adverse effect on the liver at least partly through associated increases in insulin resistance and hepatic steatosis, which is closely correlated with hepatic fibrosis. Several studies have examined ethnic differences in the association between adiposity assessed as BMI and HCV-related liver disease risk,^{3,5,9,11,12} most frequently risk of steatosis. Similar to results observed for NAFLD,¹³ hepatic steatosis in HCV-infected patients was more prevalent in Hispanics and non-Hispanic Whites than in African-Americans even after accounting for differences in BMI or other aspects of the metabolic syndrome in most studies. However, race-stratified estimates for the association between BMI-based adiposity and fibrotic or inflammatory activity are not as widely reported.

Although BMI-based categorizations are the most commonly employed measures of adiposity, they do not provide information on fat distribution including on relative abdominal or visceral adiposity, may erroneously suggest increased adiposity in those with increased muscle or skeletal mass, and have been shown to be unreliable or biased predictors or discriminators of adiposity in some populations.^{3,14,15} Body fatness or percent (%) body fat has been shown to be an independent, and in some instances also a much better, predictor of disease risk than BMI including for NAFLD risk in Japanese men.¹⁶ However, it has not been systematically evaluated in most HCV studies. Another widely used anthropometric measurement, waist circumference and the related waist-to-hip ratio (WHR) has been shown in some studies to better predict interethnic differences in disease risk including cardiovascular risk than BMI.¹⁷ However, several recent studies suggest there are potentially important differences in waist circumference cut-offs indicative of adiposity among ethnic groups.^{17–19} Waist circumference and WHR have been less examined than BMI in the context of HCV-related liver disease,^{3,20,21} with race-stratified estimates not generally reported.

Although there are several gold-standard methods like DEXA and MRI that could be used to assess other potentially important aspects of adiposity including % body fat and lean trunk mass and the risk of advanced HCV-related liver disease, their cost and accessibility limit their use in large-scale epidemiological research. Recent advancements in bioimpedance analysis (BIA) technology along with validation data against DEXA in diverse populations

including adolescents²², Hispanic diabetics,²³ general population adults,^{24,25} and morbidly obese bariatric surgery candidates²⁶ support use of BIA in epidemiological research. The reliability of BIA-based measurements in individuals with cirrhosis prior to development of ascites has also been demonstrated.²⁷ However, only two small studies have employed newer BIA technology in the background of HCV, with each reporting only a few measures.^{28,29} No study that employed BIA in HCV-infected population also specifically accounted for or reported on either ethnicity- or gender-based differences in results.

In this study, we have examined the association between the severity of hepatic inflammation and fibrosis as determined by the validated FibroSURE-ActiTest and several indicators of BIA-assessed adiposity, and compared these associations between African-American and Caucasian males with chronic HCV infection.

Methods

Study design and Population

We performed a cross-sectional study at the Michael E. DeBakey VA Medical Center (MEDVAMC) in Houston, Texas. All consecutive veterans eligible for study participation were prospectively recruited at their scheduled appointments at the dedicated Hepatitis C primary care clinic between May 1, 2009 and March 31, 2011. The study population and procedures were previously described.³⁰

Eligibility criteria

Electronic medical records for all veterans with scheduled visits at the HCV clinic were reviewed by trained research assistants to ascertain potential study eligibility employing the following criteria: 1) presence of 1 diagnostic code or laboratory report finding suggestive of HCV, 2) between ages 18 and 70 years, 4) no history of co-infection with HBV or HIV, of liver transplant, of decompensated liver disease defined based on presence of ascites, bleeding esophageal varices, encephalopathy, or hepatocellular carcinoma (HCC), or of psychosis or dementia. For purposes of assuring internal validity, our current analysis was further restricted to veterans who self-identified as either African-American or White and not of Hispanic ethnicity (e.g., White, non-Hispanic and African-American, non-Hispanic) and who also met the following additional criteria: 1) male gender as males represent >97% of our eligible HCV+ veterans, 2) serologically confirmed presence of chronic infection and absence of HIV and hepatitis B surface antigen based upon confirmatory blood draw performed after initial study recruitment; 3) never had gastric bypass surgery; and 4) completed all study measures by June 1, 2011.

This study was jointly approved by the Institutional Review Boards for Baylor College of Medicine and the Michael E. DeBakey VA Medical Center.

Data Collection and Study Measures

Surveys—Research assistants (RAs) administered a computerized risk factor and medical history survey. It interrogated information on potential mode(s) and timing of biologically plausible exposures for HCV transmission utilizing questions employed in previous VA research in a national sample of HCV+ veterans,^{31–33} and on lifetime history of chronic medical conditions including diabetes. We used self-reported survey responses to estimate the maximum potential duration of infection as the difference in participant age at study enrollment and at first self-reported exposure to the most likely known HCV transmission risk factor based on current epidemiological and biological data, with injection drug use (IDU) and blood transfusions pre-1992 given precedence over other risk factors like intranasal cocaine use, tattoos, and high risk sexual behaviors. Self-reported data was also

obtained on lifetime history of alcohol use by interrogating average consumption of all individual types of alcohol (e.g., wine, beer, mixed drinks) over all age ranges in patient's life (e.g., 20s, 30s and 40s, etc.) using questions previously employed in population-based GI research.³⁴ We classified patients as having a positive history of chronic alcohol abuse if they self-reported drinking more than the recommended maximum 2 drinks per day for a period of 10 consecutive years. The survey also enquired on participant's body weight at fixed time intervals including at 1 and 5 years ago, with participants classified as overweight/obese at each time if calculated BMI was ≥ 25 , and on parental history of increased adiposity, with a positive history defined as either biological parent ever overweight or obese as adults.

Anthropometric measurements—We obtained multiple anthropometric measurements for each study participant including BMI, % body fatness, total body water and lean body mass using the InBody520 Direct Segmental Multi-frequency Bioelectrical Impedance Analysis (DSM-BIA) scale which has 8 built-in surface electrodes (two for each foot and hand). It has reported 98% correlation with dual-energy X-ray absorptiometry (DEXA) and 99% reproducibility. Height in inches was obtained using a study-designated stadiometer. RAs obtained bioimpedance and height measurements with participant standing in bare feet.

A flexible tape measure was used to obtain waist circumference rounded down to nearest half inch at umbilicus level at the narrowest part of the waist. Hip circumference was measured over the participant's right side at greatest buttock protrusion. All measurements were taken in duplicate with heels together and arms at the side after normal comfortable exhalation, with the average measurement recorded.

Serology—A fasting blood draw was performed at study enrollment and was analyzed by MEDVAMC's CLIA-certified Central Laboratory Service for HCV antibodies using immunometric immunoassay (Ortho Clinical Diagnostics), HCV genotype using the InnoLiPA HCV II (Siemens), quantitative viral load using the COBAS TaqMan HCV Test (Roche), and for fasting insulin and glucose levels. We defined diabetes mellitus as present if the patient self-reported ever receiving a physician's diagnosis of diabetes, if fasting glucose was above 126 mg/dl, if non-fasting glucose was above 200 mg/dl, or if a fasting glucose test was not performed because of medical-record documented diabetes. We used participant's fasting glucose and insulin to calculate the Homeostasis Model of Assessment-Insulin Resistance (HOMA-IR) as $\text{fasting glucose (mg/dl)} \times \text{fasting insulin } (\mu\text{U/mL}) / 405$. We employed a cut-off value of HOMA-IR ≥ 3 to indicate presence of insulin resistance in HCV+ males without diagnosed diabetes.

FibroSURE-ActiTest (FibroSURE)—Severity of liver disease was determined using the FibroSURE-ActiTest, known in Europe as the FibroTEST-ActiTest (BioPredictive, France) which has been validated in multiple study populations including those with HCV^{31,37-41}. The test, hereafter referred to as FibroSURE, also classifies those scale scores into METAVIR biopsy-based equivalent hepatic fibrosis (F0, no fibrosis present – F4, cirrhosis) and inflammatory activity (A0, no inflammatory activity – A3, severe inflammatory activity).

FibroSURE-determined case and control status—We calculated an estimated Fibrosis Progression Rate (FPR) by adapting the formula proposed by Poynard et al⁴² to be the ratio FibroSURE-determined METAVIR numeric fibrosis stage (0–4) to the estimated maximum duration of HCV infection. The FPR assumes that fibrosis was absent prior to HCV infection as well as a constant rate of fibrosis progression. We classified study participants as either advanced fibrosis progression cases if their calculated FPR was in the

upper tertile using the distribution of the entire study sample to establish cut-points, or mild fibrosis progression rate controls if their FPR was in the lower two tertiles. We similarly classified participants as advanced inflammation cases if their FibroSURE test indicated METAVIR equivalent inflammatory grades between A2-A3 or mild/no inflammation controls (A0-A1/A2).

Analysis—All analyses were race-stratified or performed separately in African-American and White males unless otherwise reported to help assess if the magnitude of association between each individual anthropometric variable and liver disease risk was similar enough to support use of multivariate race-adjustment. First, we compared baseline sociodemographic, clinical and anthropometric variables within each racial subgroup using the chi-square test for categorical variables and ANOVA or Brown-Mood Median Test for normally and non-normally distributed continuous variables, respectively. Next, we assessed if there was an association between median FPR and increasing level of each anthropometric variable (e.g., tertile of % body fat) employing the non-parametric Jonckheere-Terpstra test for ordered alternatives. We also evaluated if there was an association between each anthropometric variable and risk of advanced inflammation (A2-A3) using binary logistic regression.

We performed two sets of race-stratified multivariate analyses where we evaluated the association between each individual anthropometric variable and risk of advanced HCV-related liver disease defined as either high FPR (in the upper tertile) or advanced inflammatory activity (A2-A3) using binary logistic regression analysis. Each multivariate model adjusted for potential confounding by age and history of chronic alcohol abuse. Every model was assessed for goodness of fit with the Hosmer-Lemeshow test, with all multivariate estimates reported as odds ratios with associated 95% confidence intervals. We performed a sensitivity analysis where we evaluated the association between anthropometric variables and advanced fibrosis risk using an alternate definition with advanced disease cases defined as F3/F4-F4 instead of in upper tertile of FPR to evaluate robustness of observed associations. We also performed exploratory multivariate analyses that adjusted for race/ethnicity and obtained equivalent estimates of the associations between each individual anthropometric measurements and risk of advanced HCV-related liver disease to assess if the resulting race-adjusted estimates of effect for each ethnic group adequately reflected those obtained for them separately in race-stratified analyses.

Finally, to help assess if any observed differences in relative risk of advanced liver disease conveyed by individual BIA measurements may be explained by race-based differences in correlation with traditional anthropometric measurements, we calculated race-stratified correlations between each individual bioimpedance-based measurement and the traditional anthropometric measurements of BMI and WHR using the non-parametric Kendall's tau test. All analyses were performed with SPSS 18 (Somers, NY).

Results

Our study sample (89% consent rate) included 330 chronically HCV+ male veterans between ages 50 and 59 years old, with 59% of African American and 41% of non-Hispanic White race/ethnicity. (Table 1) Multiple medical and behavioral comorbidities were highly prevalent in this population including diabetes (26%) and obesity (31%). Almost all participants (93%) reported exposure to at least one known risk factor for HCV transmission as well as correspondent ages for exposure, with the most frequently reported risk factors injection drug use (58%), blood transfusion pre-1992 (9%), intranasal cocaine use (8%), and tattoos (12%). The estimated maximum median duration of HCV infection was 32.0 years. Prevalence of cirrhosis (F4) was non-significantly modestly higher in Whites compared to

African-Americans (29% vs. 35%, respectively). Only two participants (0.6%) were on antiviral therapy, with both study-confirmed viremic. Overall, <5% of our participants had ever been on HCV antiviral therapy, which was discontinued after several months because of non-response, side-effects, or non-compliance.

Unadjusted median fibrosis progression rates (FPR) across ordered levels of sociodemographic, clinical and anthropometric variables are presented separately for Whites and African-Americans in Supplementary Table 1. In White HCV+ males, increasing BMI category was associated with significant increased median FPR ($p_{\text{trend}}=0.03$). There were also suggestive but non-significant trends for increasing % body fat (FPR=0.077, 0.088, and 0.092 for lowest, middle, and highest tertile of % body fat, respectively, $p_{\text{trend}}=0.12$), and with increasing duration of overweight/obese or BMI ≥ 25 (FPR=0.066, 0.088, and 0.097 for never overweight/obese, overweight/obese for last year, and overweight/obese for at least the last five years, respectively, $p_{\text{trend}}=0.08$). In univariate analysis in African-American HCV+ males, there were also significant increases in median FPR across increasing levels of % body fat and duration of BMI ≥ 25 (overweight/obese) ($p_{\text{trend}}=0.04$ and 0.02 , respectively). However, in contrast to White males where median FPR was the same in non-diabetics regardless of whether they had IR or not, in African-Americans males the median FPR was significantly higher in non-diabetics with IR compared to non-diabetics without IR (FPR=0.100 vs. 0.077 for IR+ and IR-, respectively).

Multiple differences in risk of high FPR were also observed in race-stratified multivariate analyses that adjusted for age and chronic alcohol abuse. (Table 2) In HCV+ White males, there were no statistically significant associations between any individually assessed anthropometric measure and risk of high FPR. The single anthropometric measurement which approached significance was the 133% decreased high FPR risk in White males in the highest tertile of lean trunk mass ($OR_{\text{adj}}=0.43$, 95% CI 0.17–1.09, $p=0.08$). There was also increased high FPR risk with increased BMI ($OR_{\text{adj}}=1.48$ and 1.51 for overweight and obese in comparison to normal weight, respectively), and with increased % body fat ($OR_{\text{adj}}=1.27$ and 1.60 for those in middle and highest compared to those in the lowest tertile, respectively), though these effects were non-significant. These results differ from those in African-American males where lean body mass in the upper tertile (total, trunk, arm and leg) was uniformly associated with 70% increased risk of high FPR, though individual effects were non-significant. Although the excess risk conveyed by overweight and obesity were similar in African-Americans and Whites in race-stratified multivariate analyses, both % body fat and body fat mass were more strongly associated with FPR risk in African-Americans only.

Prevalence of advanced inflammatory grade (A2-A3) was significantly greater in Whites compared to African-Americans (43% vs. 36%, respectively). In univariate analysis, White HCV+ veterans with advanced inflammation were significantly more likely to have BMI ≥ 30 (53% vs. 32%, $p<0.01$), to have been overweight/obese for the last five or more years (66% vs. 48%, $p=0.047$), and to have both a personal and parental history of overweight/obesity (29% vs. 20%, $p=0.04$) than White HCV+ veterans with mild hepatic inflammation (A0-A1/A2). (Supplementary Table 2) These results differed from the univariate associations in African-Americans where the likelihood of obesity or of having a combined personal and parental history of overweight/obesity was similar in African-American advanced inflammation cases and African-American mild inflammation controls (24% vs. 23%, $p=0.75$ for obesity and 23% vs. 19%, $p=0.79$ for personal/parental adiposity, respectively). Further, in contrast to Whites where the prevalence of diagnosed diabetes was the same (27%) in White advanced inflammation cases and White mild disease controls, the prevalence of diabetes in chronically HCV-infected African-American male veterans was significantly higher in those with advanced compared to those with mild hepatic

inflammation (34% vs. 19%, $p=0.01$). Race-stratified multivariate models for the association between each individual anthropometric measurement and risk of advanced hepatic inflammation (A2-A3) are reported in Table 3. In White HCV+ males after adjusting for age and chronic alcohol abuse, the strongest effect was the significant 231% increased advanced inflammation risk in the obese in comparison to those with normal BMI, with a non-significant 96% excess risk in the overweight compared to those with normal BMI. A combined parental as well as personal history of overweight/obesity was also associated with an over 3-fold significant excess risk of advanced inflammation compared to those with absence of both personal and parental adiposity history ($OR_{adj}=3.08$, $p=0.04$), an effect slightly higher than that conveyed by only personal history of adiposity ($OR_{adj}=2.93$, $p=0.03$). Results differed in African-American HCV+ males where there was no significant excess inflammation risk associated with either overweight or obesity in multivariate analysis ($OR_{adj}=1.10$ and 1.21 , respectively). Additionally, neither increased body fat mass nor % body fat was strongly or consistently associated with increased hepatic inflammation risk. Diabetes was the strongest predictor of advanced inflammation risk in African-American males ($OR_{adj}=3.01$, $p<0.001$), an effect larger than observed in Whites ($OR=1.41$, $p=0.43$).

In a sensitivity analyses where advanced fibrosis as defined as F3/F4-F4, the ethnic divergence where increased lean mass was associated with high FPR risk in African-Americans and decreased risk in Whites, was replicated (e.g., $OR_{adjTrunkMassUpperTertile}=0.44$, 95% CI 0.32–1.03, $p=0.06$ and $OR_{adjTrunkMassUpperTertile}=1.70$, 95% CI 0.60–2.90, $p=0.18$ in White and African-American HCV+ males, respectively). (data not shown)

We also conducted parallel exploratory multivariate analyses that adjusted for race/ethnicity (as opposed to race-stratified analyses presented in Tables 2 and 3). Race-adjusted point estimates did not adequately reflect those for one and often both subgroups obtained in race-stratified multivariate analysis in many instances. For example, White males with BMI ≥ 30 (obese) compared to BMI <25 (normal) had 3.3-fold excess risk of advanced hepatic inflammation in race-stratified multivariate analysis (Table 3), but only a 1.9-fold excess risk in race-adjusted analysis. (data not shown)

Overall, most bioimpedance measurements of adiposity were significantly correlated with BMI and WHR, with a similar magnitude and direction of these associations in Whites and African-Americans (e.g., Kendall's tau=0.755 and 0.796 for African Americans and Whites, respectively). (data not shown) The single largest interethnic difference in correlation with BMI was the 7.5% greater correlation between BMI and % body fat among Whites compared to African-Americans. The single largest interethnic difference in correlation between WHR and a BIA adiposity measure was also with % body fat (Kendall's tau=.301 and 0.168 for African-American and White males, respectively).

Discussion

This is the first study to evaluate race/ethnicity-specific differences in the association between multiple individual anthropometric measurements and risk of advanced hepatic fibrosis and inflammation in males with chronic HCV infection. This is also the largest study to employ bioimpedance analysis (BIA)-based anthropometric measures in the background of HCV and to report on previously unexamined measures like %BF and lean mass. Several suggestive potential differences in associations were identified in race-stratified analyses including stronger associations between % body fat and body fat mass and risk of high FPR than were observed with the traditional gold standard measure of BMI in African-American males only. The association between measures of lean body mass

(trunk, leg and arm) and advanced liver disease risk also consistently differed among race/ethnicity defined groups. In African-American males, those with highest lean trunk, leg, or arm mass had >50% increased risk of high FPR in multivariate analyses, while in contrast White males with highest lean trunk, leg or arm mass had 92–133% decreased risk, though individual effects closely approached significance only for trunk mass in Whites. The same ethnic divergence was observed for lean leg mass and advanced inflammatory activity risk. Given the limits of our cross-sectional study, we were unable to identify potential causes for these observed differences. However, based on our preliminary findings of interethnic differences we propose that: 1) additional anthropometric measures like % body fat and lean mass, particularly lean leg mass, should be investigated further in other HCV-infected populations as they may better predict risk of advanced liver disease and have potential etiopathogenic implications; and 2) given observed variability in magnitude, direction and correlation of many anthropometric measures and risk of HCV-related liver disease in White and African Americans, simple traditional adjustment for race/ethnicity in multivariate analyses may not always be adequate as it may mask potentially important race-specific differences in the effect of anthropometric variables.

Only one other study examined BIA measures and risk of advanced HCV-related liver disease. Antaki et al. found no association between measures of whole body, trunk and upper quadrant phase angle, resistance, and reactance and risk of biopsy-determined advanced fibrosis (F3-F4) or advanced inflammation (A2-A3).²⁸ However, their sample size was small (n=20, including 6 women), with insufficient power to adjust for confounding from strong risk factors like age and gender. Additional contributions of our study include evaluating ethnicity-specific differences in multiple additional measures of relative adiposity in males, and also examining FPR risk as opposed to solely fibrosis risk as FPR incorporates both the magnitude of fibrosis and duration of infection.

There are several known differences between African-Americans and Whites with respect to HCV, including a greater prevalence of HCV-infection especially genotype 1 in African-Americans, and a higher prevalence of the TT interleukin 28B genotype that is associated with lower rates of spontaneous viral clearance and sustained virological response.^{31,43–45} In spite of the increased prevalence of these factors, African-Americans have been reported,^{2–7} though not uniformly,^{3,8–10} to have significantly lower fibrosis progression rates and lower risk of cirrhosis than Whites. BMI and waist circumference/WHR have also been implicated increase HCV-related cirrhosis risk, though they have been less well-examined with respect to ethnic/racial differences in HCV-related liver disease risk. In this study, the prevalence of advanced hepatic inflammation and high FPR was only modestly higher in Whites than in African-Americans. However, we found several suggestive findings of potential intra-and inter-race/ethnicity differences in the association between individual anthropometric variables and each type of advanced liver disease risk. For example, in African-American males, there were stronger associations between % body fat and body fat mass and high FPR risk than with the traditional measure of BMI as well as lack of strong, significant or dose-dependent associations between traditional and BIA-based measures of adiposity and risk of advanced inflammation. In contrast, in White males there was evidence of moderate to strong excess risk (55%–230%) of advanced inflammation with highest traditional BMI-based and BIA-based measures of adiposity. Although WHR was neither strongly nor significantly associated with high FPR risk in either African-Americans or Whites, nor with advanced inflammation risk in African-Americans, there was evidence suggestive of moderate to strong excess risk of advanced inflammation in White males with increasing WHR, with over 130% excess inflammation risk in those with moderate compared to those in low WHR categories (p=0.07). However, unlike for % body fat where there was only a small 7% difference in its high correlation with BMI among White and African-American

males, there was almost a two-fold difference in the modest correlation between WHR and % body fat among White and African-Americans.

There are recent data suggesting that there are interethnic differences in adipose tissue distribution and partitioning and metabolic syndrome presentation including for insulin resistance and hepatic steatosis.^{47–49} Overall, African-Americans had significantly lower abdominal or visceral adiposity, extremity fat, intramyocellular fat, and liver fat than other ethnic groups in these reports. These effects persisted even after controlling for total adiposity or among comparably obese groups, and even with African-Americans having comparably high or higher insulin resistance than other ethnic groups. Our results suggesting interethnic differences in the association between anthropometric measures and risk of advanced HCV-related liver disease in males is broadly consistent with these findings. In addition, there is growing evidence for interethnic differences in cutoff values for traditional anthropometric measurements like BMI and waist circumference, with a World Health Organization expert panel recommending use of lower BMI cutoffs for overweight/obesity in Asian populations necessary to trigger public health action given accruing evidence Asians have greater risk of cardiovascular disease and diabetes at lower BMIs than observed in non-Asian populations.⁴⁶ Our findings also suggest there may be potentially important race/ethnicity specific differences in the association between several anthropometric measurements and risk of advanced HCV-related liver disease including on what measures of adiposity best predict FPR risk in African-American males with HCV (% body fat or body fat mass vs. traditional BMI cutoffs). However, given our cross-sectional design, performance in a single HCV-infected population, and reductions in study power due to use of race-stratified analyses over ordered categories for individual anthropometric measurements, additional research in larger mixed ethnicity HCV-infected cohorts will be needed to determine if ethnicity-specific anthropometric cut-off values are optimal for research in HCV-infected populations.

Strengths of the current study include direct prospective recruitment of all consecutive study eligible male veterans with clinically-scheduled visits at a VA Hepatitis C clinic. Together with our high participation rates, this helps mitigate concerns about potential selection bias. Additionally, we excluded HCV+ male veterans with any clinical evidence of ascites or decompensated disease as large water imbalances can negatively impact validity of BIA-based measurements. Although we therefore cannot comment on the association between anthropometric measures and liver disease risk in this subgroup, our consistent findings of no significant association between total body water and risk of advanced HCV-related liver disease suggests substantial water imbalance was unlikely to systematically or substantially bias our BIA-based measurements.

Our study has limitations that are important to acknowledge. The cross-sectional design where measures of adiposity and liver disease status were collected concomitantly precludes a temporal assessment necessary to demonstrate a causal association. Although liver biopsy is generally considered the gold-standard for individual patient diagnosis, it is of limited applicability in large-scale epidemiological studies due to attendant costs and invasiveness and is also well-known to be subject to sampling variability. We therefore used the validated FibroSURE test which has been demonstrated to have good test performance characteristics in multiple HCV+ populations^{31,37–41} However, as the FibroSURE-ActiTest test does not provide a measure of hepatic steatosis, future research will be needed to determine if there are also interethnic differences in the association between BIA-based measures of adiposity and risk of advanced hepatic steatosis between White and African-American males with chronic HCV. Our use of a uniform standardized diagnostic test in addition to *a priori* defined dichotomized outcomes (advanced or upper tertile FPR and advanced activity A2-A3) should minimize the potential for any differential misclassification. We used a single

BIA scale which employs the newest 8-point multifrequency direct segmental BIA technology which has high reported validity and reliability^{31,35,36} to obtain anthropometric measurements; but we do not have DXA-based validation data in our study population. However, as we performed comparisons across ordered grouped levels for anthropometric variables (e.g., tertiles of % body fat), small differences in absolute values would be unlikely to substantially or systematically bias relative risk estimates. Our study was limited to males who self-identified as members of only two race/ethnic groups, White or African-American and not of Hispanic ancestry. It is therefore unknown how well these results would generalize to HCV+ males of other ethnic groups. As our study was performed in a single male veteran population, the generalizability of these findings to non-veterans and women with HCV is unknown. Finally, although our evaluation of race-stratified estimates of association over ordered levels of anthropometric measures allowed an assessment of potential dose-response relationships, we had reduced power to detect statistically significant associations or to adjust for either multiple comparisons. Therefore, our findings must be qualified as only suggestive pending verification in additional large cohorts.

In conclusion, we observed several differences in the association between select anthropometric measurements like % body fat and risk of advanced HCV-related liver disease between White and African-American males that suggest the potential importance of obtaining additional anthropometric measurements beyond the more traditionally collected BMI and WHR, and for careful assessment of whether race-stratification or race-adjustment are more appropriate in multiethnic populations where anthropometric measurements are a key covariate of interest. Additional prospective research is needed to evaluate how interethnic differences in anthropometric associations may help explain observed interethnic differences in HCV-related liver disease risk between African-American and White males.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BIA	bioimpedance analysis
DEXA	dual x-ray absorbiometry
FPR	fibrosis progression rate
HCV	hepatitis C virus
HBV	hepatitis B virus
OR	odds ratio
WHR	waist-to-hip ratio

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Table 1

Background characteristics of 330 male study participants with chronic hepatitis C.

	African-American males (n=194)	White males (n=136)	p-value
Characteristic			
	n (%)	n (%)	
Age			0.01
40–49	9 (4.5%)	19 (14.0%)	
50–59	120 (61.9%)	74 (54.4%)	
60–69	65 (33.5%)	43 (31.6%)	
HCV Genotype			<0.001
1 or 4	187 (96.4%)	103 (75.7%)	
2 or 3	5 (2.6%)	33 (24.3%)	
Missing	2 (0.6%)	0 (0%)	
Median log₁₀ Viral load [IQR]	6.62 [0.90]	6.66 [0.98]	0.90
Primary HCV risk factor			
Blood transfusion pre-1992	11 (5.7%)	18 (13.2%)	0.001
Injection Drug Use (IDU)	112 (57.7%)	79 (58.1%)	
Tattoo	18 (9.3%)	22 (16.2%)	
Intranasal cocaine	23 (11.9%)	4 (2.9%)	
Other percutaneous exposure	18 (9.3%)	11 (8.1%)	
No identifiable risk factor	12 (6.2%)	2 (1.5%)	
Median duration Infection [IQR]	32.0 [13]	33.0 [14.5]	0.65
Diabetes			0.88
Non-diabetic, HOMA-IR<3	84 (44.9%)	57 (43.5%)	
Non-diabetic, HOMA-IR ≥ 3	55 (29.4%)	37 (28.2%)	
Diabetes diagnosis	48 (25.7%)	37 (28.2%)	
Chronic alcohol abuse			0.19
Negative	75 (38.7%)	43 (31.6%)	
Positive	119 (61.3%)	93 (68.4%)	
BMI category			<0.01
Mild thinness	2 (1.0%)	0 (0%)	
Normal	57 (29.4%)	40 (29.4%)	
Overweight	89 (45.9%)	40 (29.4%)	
Obese	46 (23.7%)	56 (41.2%)	
FibroSURE-determined METAVIR fibrosis stage			0.44
F0	0 (0%)	0 (0%)	
F0/F1	14 (7.2%)	9 (6.6%)	
F1	2 (1.0%)	3 (2.2%)	
F1/F2	32 (16.5%)	29 (21.3%)	
F2	33 (17.0%)	14 (10.3%)	

	African-American males (n=194)	White males (n=136)	p-value
Characteristic			
	n (%)	n (%)	
F3	50 (25.8%)	29 (21.3%)	
F3/F4	6 (3.1%)	5 (3.7%)	
F4	57 (29.4%)	47 (34.6%)	
FibroSURE-determined METAVIR inflammatory grade			<0.01
A0	23 (11.9%)	25 (18.4%)	
A0/A1	39 (20.1%)	20 (14.7%)	
A1	20 (10.3%)	10 (7.4%)	
A1/A2	42 (21.6%)	22 (16.2%)	
A2	26 (13.4%)	14 (10.3%)	
A2/A3	7 (3.6%)	0 (0%)	
A3	37 (19.1%)	45 (33.1%)	

Table 2

Fibrosis Progression Rate (FPR) Upper Tertile: Multivariate logistic regression models evaluating association between individual anthropometric measurements and high FPR risk in chronically HCV-infected male veterans.⁴

Variable	White n=130			Black n=177		
	OR	(95% CI)	p-value	OR	(95% CI)	p-value
BMI						
<25 ^{AA}	1 (ref)	-	-	1 (ref)	-	-
25–29	1.48	(0.53–4.09)	0.45	1.57	(0.72–3.41)	0.26
30+	1.51	(0.60–3.83)	0.39	1.50	(0.60–3.75)	0.38
Waist: Hip ratio						
T1 (<0.97)	1 (ref)	-	-	1 (ref)	-	-
T2 (0.97–1.0)	1.06	(0.40–2.84)	0.91	0.80	(0.39–1.65)	0.55
Waist: Height Ratio						
T1 (<0.51)	1 (ref)	-	-	1 (ref)	-	-
T2 (0.51 – 0.57)	1.32	(0.47–3.67)	0.60	1.06	(0.49–2.29)	0.89
T3 (>0.57)	1.09	(0.41–2.84)	0.87	1.59	(0.69–3.62)	0.27
Trunk Lean Body Mass (lbs)						
T1 (<60.6)	1 (ref)	-	-	1 (ref)	-	-
T2 (60.6–68.6)	0.76	(0.30–1.94)	0.57	0.85	(0.36–1.97)	0.70
T3 (>68.6)	0.43	(0.17–1.09)	0.08	1.58	(0.70–3.58)	0.27
Body Fat Mass (lbs)						
T1 (<40)	1 (ref)	-	-	1 (ref)	-	-
T2 (40–62.8)	0.92	(0.32–2.65)	0.88	1.79	(0.84–3.85)	0.13
T3 (>62.8)	1.19	(0.48–2.94)	0.70	2.08	(0.83–5.23)	0.12
Body Fat (%)						
T1 (<22.9)	1 (ref)	-	-	1 (ref)	-	-
T2 (22.9–30.7)	1.27	(0.44–3.72)	0.66	1.96	(0.92–4.21)	0.08
T3 (>30.7)	1.60	(0.62–4.13)	0.33	1.95	(0.79–4.80)	0.15
Right Leg Lean Mass (lbs)						
T1 (<19.7)	1 (ref)	-	-	1 (ref)	-	-
T2 (19.7–22.3)	0.86	(0.35–2.10)	0.74	1.73	(0.75–3.98)	0.20

Variable	White n=130			Black n=177		
	OR	95% CI	p-value	OR	95% CI	p-value
T3 (>22.3)	0.62	(0.21–1.79)	0.38	1.73	(0.73–4.10)	0.21
Left Arm Lean Mass (lbs)						
T1 (<7.67)	1 (ref)	-	-	1 (ref)	-	-
T2 (7.67–9.02)	0.45	(0.18–1.21)	0.12	0.79	(0.34–1.83)	0.58
T3 (>9.02)	0.52	(0.21–1.28)	0.16	1.74	(0.55–2.82)	0.60
Body Water (lbs)						
T1 (<95.2)	1 (ref)	-	-	1 (ref)	-	-
T2 (95.2–107.8)	0.67	(0.26–1.72)	0.41	0.92	(0.40–2.13)	0.85
T3 (>107.8)	1.00	(0.39–2.56)	1.00	1.71	(0.76–3.82)	0.19
Parental/Patient Adiposity						
Neither	1 (ref)	-	-	1 (ref)	-	-
Parent only	1.10	(0.16–7.84)	0.92	1.06	(0.23–4.82)	0.94
Patient only	1.68	(0.60–4.73)	0.32	1.42	(0.61–3.32)	0.42
Both	0.89	(0.28–2.80)	0.84	1.62	(0.60–4.37)	0.34
Timing Overweight/Obese (BMI ≥ 25)						
Never	1 (ref)	-	-	1 (ref)	-	-
Current only	3.77	(0.18–80.65)	0.61	1.94	(0.49–7.69)	0.34
Current + 1 yr	0.62	(0.08–4.55)	0.64	0.55	(0.13–2.43)	0.43
Current+1+5	1.24	(0.42–3.69)	0.70	2.06	(0.90–4.74)	0.09
Diabetes or Insulin Resistance						
No Diabetes-IR-	1 (ref)	-	-	1 (ref)	-	-
No Diabetes-IR+	0.79	(0.32–1.98)	0.62	2.37	(1.09–5.17)	0.03
Diagnosed Diabetes	0.80	(0.31–2.08)	0.65	1.39	(0.59–3.29)	0.45

[^] Restricted to N=307 veterans who had reported both at least one risk factor HCV transmission and dates/ages of possible exposures (n=14 no known exposure and n=9 refused provide dates/ages) and adjusted for age and alcohol abuse.

^{^^} Only 3 in category mild thinness (BMI 16–18.5, included with normal).

^{^^^} Insulin resistance defined as fasting HOMA-IR ≥ 3 in non-diabetic.

Activity (FibroSURE-ActiTest A2-A3 vs. A0-A1/A2): Multivariate logistic regression models evaluating association between individual anthropometric measurements and advanced inflammation risk in chronically HCV-infected male veterans.⁴

Table 3

Variable	White n=136			Black n=194		
	OR	(95% CI)	p-value	OR	(95% CI)	p-value
BMI						
<25 ^{AA}	1 (ref)	-	-	1 (ref)	-	-
25–29	1.96	(0.76–5.04)	0.16	1.10	(0.55–2.22)	0.78
30+	3.31	(1.38–7.95)	0.01	1.21	(0.53–2.73)	0.65
Waist: Hip ratio						
T1 (<0.97)	1 (ref)	-	-	1 (ref)	-	-
T2 (0.97–1.0)	2.30	(0.94–5.63)	0.07	0.86	(0.44–1.68)	0.66
T3 (>1.0)	1.55	(0.61–3.90)	0.36	0.89	(0.39–2.06)	0.79
Waist: Height Ratio						
T1 (<0.51)	1 (ref)	-	-	1 (ref)	-	-
T2 (0.51–0.57)	1.72	(0.67–4.41)	0.26	0.77	(0.38–1.56)	0.47
T3 (>0.57)	1.86	(0.77–4.47)	0.17	1.07	(0.51–2.25)	0.87
Trunk Lean Body Mass (lbs)						
T1 (<60.6)	1 (ref)	-	-	1 (ref)	-	-
T2 (60.6–68.6)	0.99	(0.41–2.33)	0.97	1.19	(0.56–2.54)	0.65
T3 (>68.6)	0.95	(0.42–2.13)	0.89	1.34	(0.64–2.84)	0.44
Body Fat Mass (lbs)						
T1 (<39.9)	1 (ref)	-	-	1 (ref)	-	-
T2 (39.9–62.8)	1.31	(0.49–3.49)	0.59	0.74	(0.38–1.47)	0.39
T3 (>62.8)	2.02	(0.88–4.64)	0.10	1.27	(0.57–2.80)	0.56
Body Fat (%)						
T1 (<22.9)	1 (ref)	-	-	1 (ref)	-	-
T2 (22.9–30.6)	1.12	(0.43–2.95)	0.82	0.89	(0.46–1.74)	0.74
T3 (>30.6)	1.67	(0.71–3.89)	0.24	1.04	(0.47–2.30)	0.92
Right Leg Lean Mass (lbs)						
T1 (<19.7)	1 (ref)	-	-	1 (ref)	-	-

Variable	White n=136			Black n=194		
	OR	(95% CI)	p-value	OR	(95% CI)	p-value
T2 (19.7–22.3)	0.84	(0.38–1.87)	0.67	1.39	(0.64–3.01)	0.40
T3 (>22.3)	0.58	(0.22–1.48)	0.25	1.65	(0.76–3.56)	0.21
Left Arm Lean Mass (lbs)						
T1 (<7.67)	1 (ref)	-	-	1 (ref)	-	-
T2 (7.67–9.02)	0.78	(0.33–1.82)	0.56	1.18	(0.55–2.52)	0.67
T3 (>9.02)	1.01	(0.45–2.27)	0.99	1.25	(0.59–2.67)	0.56
Body Water (lbs)						
T1 (<95.2)	1 (ref)	-	-	1 (ref)	-	-
T2 (95.2–107.8)	1.23	(0.54–2.80)	0.63	1.11	(0.52–2.37)	0.79
T3 (>107.8)	1.18	(0.50–2.81)	0.70	1.55	(0.75–3.22)	0.24
Parental/Patient Adiposity						
Neither	1 (ref)	-	-	1 (ref)	-	-
Parent only	2.10	(0.37–12.02)	0.41	0.13	(0.02–1.11)	0.06
Patient only	2.93	(1.10–7.84)	0.03	0.90	(0.43–1.89)	0.78
Both	3.08	(1.05–9.00)	0.04	1.05	(0.44–2.53)	0.91
Timing Overweight/Obese (BMI ≥25)						
Never	1 (ref)	-	-	1 (ref)	-	-
Current only	8.78	(0.76–102.09)	0.08	0.30	(0.06–1.52)	0.15
Current + 1 yr	2.22	(0.42–11.77)	0.35	0.71	(0.21–2.42)	0.59
Current+1+5	2.61	(0.97–7.03)	0.06	1.48	(0.72–3.03)	0.28
Diabetes or Insulin Resistance (IR)[^]						
No Diabetes-IR-	1 (ref)	-	-	1 (ref)	-	-
No Diabetes-IR+	1.74	(0.74–4.09)	0.20	1.65	(0.79–3.44)	0.18
Diagnosed Diabetes	1.41	(0.60–3.33)	0.43	3.01	(1.40–6.47)	0.00

[^] All models adjusted for age and ethnicity.

^{^^} Only 3 in category mild thinness (BMI 16–18.5, included with normal).

^{^^^} Insulin resistance defined as fasting HOMA-IR ≥3 in non-diabetic.