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Association between chronic hepatitis C virus infection and low muscle mass in U.S. adults

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Abstract

Given that low muscle mass can lead to worse health outcomes in patients with chronic infections, we assessed if chronic HCV infection was associated with low muscle mass among U.S. adults. We performed a cross-sectional study of the National Health Examination and Nutrition Study (1999-2010). Chronic HCV-infected patients had detectable HCV RNA. Low muscle mass was defined as <10th percentile for mid-upper arm circumference (MUAC). Multivariable logistic regression was used to determine adjusted odds ratios (aORs) with 95% confidence intervals (CIs) of low muscle mass associated with chronic HCV. Among 18,513 adults, chronic HCV-infected patients (n=303) had a higher prevalence of low muscle mass than uninfected persons (13.8% versus 6.7%; aOR, 2.22; 95% CI, 1.39-3.56), and this association remained when analyses were repeated among persons without significant liver fibrosis (aOR, 2.12; 95% CI, 1.30-3.47). This study demonstrates that chronic HCV infection is associated with low muscle mass, as assessed by MUAC measurements, even in the absence of advanced liver disease.

Keywords

Chronic hepatitis C; Low muscle mass; Malnutrition; NHANES

INTRODUCTION

Low muscle mass, an important initial indicator of malnutrition (1), has been reported with chronic infections, particularly tuberculosis and human immunodeficiency virus (HIV) (2-4), and can lead to adverse health outcomes and increased risk of death (5-7). However, it is unknown if chronic hepatitis C virus (HCV) infection is associated with low muscle mass,

especially prior to the development of cirrhosis. Determination of the prevalence and risk factors for low muscle mass among chronic HCV-infected patients is important because such results could help heighten awareness of the need to screen these patients for malnutrition and identify modifiable risk factors that should be addressed by clinicians. We determined if chronic HCV infection was associated with low muscle mass in the U.S. adult population and explored potential risk factors for this outcome in chronic HCV-infected patients.

METHODS

Study Design and Data Source

We conducted a cross-sectional study using data collected at enrollment in the National Health and Nutrition Examination Survey (NHANES), a nationwide study of U.S. adults and children, between January 1, 1999 and December 31, 2010 (8, 9). As has been previously detailed (8, 9), NHANES is a nationally representative survey of the U.S. population designed to assess the health and nutritional status of adults and children. Participants were chosen according to a stratified, multistage algorithm to produce a representative sample of the civilian, non-institutionalized U.S. population. Participants completed a self-reported questionnaire providing demographic data, clinical and nutritional information, and substance use practices. Physical examinations and anthropometric measurements were performed, and each participant provided blood samples. Study procedures were approved by the NHANES Institutional Review Board (10). This study was approved by the University of Pennsylvania Institutional Review Board.

Study Population

NHANES participants were included if they had: 1) 20 - 60 years of age, 2) available HCV status, and 3) anthropometric data. Chronic HCV-infected patients had detectable HCV RNA. HCV-uninfected persons had negative HCV antibody and/or RNA results.

Main Study Outcome

The main outcome was low muscle mass, defined by a mid-upper arm circumference (MUAC) below the 10th percentile for age- and sex-matched reference values (11-14). MUAC accurately captures loss of protein and muscle (15-17). The use of anthropometric measurements to determine nutrition status in patients with liver disease is less likely to be subject to misclassification compared to other measures, including body mass index (BMI) or serum markers (e.g., albumin, prealbumin) (18, 19). To account for peripheral fat tissue in the determination of muscle mass, as a secondary outcome, we evaluated low muscle mass defined as <10th percentile for mid-arm muscle circumference (MAMC), calculated by: $MUAC - (\pi * \text{triceps skinfold thickness})$ (20-22).

Data Collection

Variables extracted from the NHANES datasets included: age; sex; race/ethnicity; educational level; alcohol use; history of injection/non-injection drug use; diabetes mellitus; self-assessment of current health status; BMI; HIV antibody status; aspartate aminotransferase (AST); platelet count; and fat-free mass determined by multiple frequency

bioelectrical impedance analysis (MF-BIA). The AST-to-platelet ratio index (APRI), a non-invasive measure of liver fibrosis, was calculated by: $[(\text{AST [U/L]}/\text{upper limit of normal [considered as 40 U/L]})/\text{platelet count (10}^9\text{/L)}] \times 100$ (23). An APRI >1.5 accurately identifies significant liver fibrosis (METAVIR stage F2-F4) (23, 24). MF-BIA was performed using the HYDRA ECF/ICF Bio-Impedance Spectrum Analyzer (Xitron Technologies, San Diego, CA), as described in the NHANES study protocol (25).

Statistical Analysis

Differences in characteristics between chronic HCV-infected and uninfected participants were assessed using Chi-square tests for categorical data and t-tests or Wilcoxon rank-sum tests, as appropriate, for continuous data. We then determined the prevalence and 95% confidence intervals (CIs) of low muscle mass between these groups. To exclude the possibility of advanced liver disease contributing to low muscle mass, we compared the prevalence of low muscle mass between chronic HCV-infected and uninfected persons without significant liver fibrosis (APRI $\leq$ 1.5). In addition, we evaluated differences in the prevalence of low muscle mass by chronic HCV status among those with normal BMI to assess the frequency of low muscle mass among participants with a normal BMI.

Multivariable logistic regression was used to determine the adjusted odds ratio (aOR) with 95% CIs of low muscle mass associated with chronic HCV, controlling for confounding variables. Variables evaluated as potential confounders included age, sex, race, education level, alcohol use, history of injection/non-injection drug use, diabetes mellitus, HIV infection, and self-reported health-status. Confounders remained in the model if the unadjusted OR changed by at least 15% after adjustment for the candidate factor or if a variable was considered *a priori* to be clinically important (i.e., alcohol use and history of drug use). To evaluate the association between chronic HCV and low muscle mass in the absence of advanced liver disease, we performed the above analysis, excluding patients with APRI >1.5. Analyses were repeated using MAMC as the outcome.

Multivariable logistic regression was then used to evaluate risk factors for low muscle mass among chronic HCV-infected patients. Hypothesized risk factors included current alcohol use, history of injection/non-injection drug use, and HIV infection.

To confirm that MUAC accurately detected low muscle mass, we conducted a secondary analysis to examine the correlation between MUAC measurements and fat-free mass determined by MF-BIA among 18-49-year-old participants who underwent MF-BIA testing in NHANES from 1999 to 2004 and had available reference values for fat-free mass (n=4,416).

RESULTS

Among 21,060 participants between the ages of 20 and 60 years who were enrolled in NHANES between 1999 and 2010, 2,547 (12.1%) were excluded because they either did not have HCV status (n=2,103) or anthropometric measurements (n=1,517). The final sample included 18,513 participants (**Table 1**), of whom 303 (1.6%) had chronic HCV.

The characteristics of the study sample are reported in **Table 1**. Patients with chronic HCV more commonly were older, male, non-Hispanic black, less educated, currently using alcohol, and had a history of injection/non-injection drug use. HCV-uninfected participants more commonly were obese. Among those tested for HIV, the prevalence of this infection was higher among chronic HCV-infected patients.

Mean MUAC and triceps skinfold thickness (TSF) measurements were significantly lower in chronic HCV-infected persons (**Table 1**). The prevalence of low MUAC was higher in chronic HCV-infected than uninfected persons (13.8% [9.4-19.8%] versus 6.7% [6.1-7.3%]; $p<0.001$). Among participants without significant liver fibrosis (APRI 1.5), chronic HCV-infected patients more frequently had low MUAC than uninfected individuals (13.5% versus 6.7%; $p<0.001$). Among persons with normal BMI ($n=5,564$), those with chronic HCV more commonly had low MUAC compared to uninfected individuals (31.0% [95% CI, 22.0-41.7%] versus 15.4% [95% CI, 14.1-16.9%]; $p<0.001$).

The association between chronic HCV and low muscle mass, as determined by MUAC, is reported in **Table 2**. After adjustment for race, history of injection/non-injection drug, current alcohol use, and diabetes mellitus, which were the only confounders identified, chronic HCV-infected persons had a 2.2 times greater odds of having low MUAC compared to uninfected persons (aOR, 2.22; 95% CI, 1.39-3.56). This association remained when analyses were repeated among persons without significant liver fibrosis (aOR, 2.12; 95% CI, 1.30-3.47). The association between chronic HCV infection and low MUAC remained significant when additionally adjusted for HIV infection (aOR, 2.51; 95% CI, 1.36-4.64). Inclusion of self-reported health status in multivariable models did not change the results.

When low muscle mass as determined by MAMC was evaluated, the association between chronic HCV and low MAMC persisted among a subgroup of 17,011 participants for whom MAMC could be calculated (aOR, 1.89; 95% CI, 1.00-3.59).

Among chronic HCV-infected patients, current alcohol use (aOR, 10.1; 95% CI, 2.67-39.1), but not history of drug use (aOR, 1.08; 95% CI, 0.44-2.67) or HIV coinfection (aOR, 1.20; 95% CI, 0.13-11.0), was a risk factor for low MUAC.

Finally, in our analysis evaluating if MUAC could accurately detect low muscle mass, we found that MUAC measurements correlated well with fat-free mass as determined by MF-BIA ($r=0.67$; $p<0.001$).

DISCUSSION

This study demonstrates that low muscle mass, as assessed by MUAC or MAMC, is more prevalent among chronic HCV-infected than uninfected adults. While prior studies have demonstrated that cirrhosis is associated with malnutrition (18, 26-28), this study is the first to show that even in the absence of significant liver fibrosis, chronic HCV is associated with low muscle mass as determined by MUAC. Since low muscle mass is a modifiable factor associated with worse health outcomes (7, 29-32), clinicians should consider evaluating the nutritional status of their chronic HCV-infected patients at the time of diagnosis and periodically afterwards. The increased prevalence of low muscle mass in chronic HCV

patients is of particular significance because this finding is indicative of malnutrition even among those with a normal BMI. In fact, 90% of chronic HCV-infected individuals identified with low muscle mass by MUAC had a normal body weight by BMI. Although nutrition is generally recognized as an important component of health, it is often neglected and rarely addressed during clinical visits (33-35). This may be because of competing priorities during the limited time available for clinical assessments. In addition, most clinicians rely on weight and thereby BMI as the primary markers of nutritional status, but these may not provide an adequate assessment of nutritional status, particularly of protein malnutrition, in patients with viral hepatitis (26, 36). However, MUAC and MAMC are simple, inexpensive anthropometric measurements that could be incorporated alongside height and weight during clinic examinations, making them feasible as nutritional screening tools.

The mechanisms for the higher prevalence of low muscle mass among chronic HCV-infected patients remain unclear. Previous data have shown that patients with cirrhosis are more likely to be malnourished (18, 22, 26, 27). These studies have suggested that hepatic decompensation, possibly due to intestinal edema from ascites, causes changes in macronutrient absorption and metabolism that can lead to malnutrition (18, 26). In addition, the development of hepatic encephalopathy is often associated with decreased oral intake, particularly of protein-rich foods, which may further contribute to malnutrition (37). However, we observed that low muscle mass is prevalent even among chronic HCV-infected individuals without advanced liver fibrosis, suggesting that there may be alternative pathways leading to malnutrition. Chronic HCV infection might induce a chronically heightened inflammatory state, which may impose both depressed appetite and greater metabolic/ nutrient demands that, if unmet, could lead to malnourishment. Furthermore, alcohol use, which was identified as a risk factor for low muscle mass among chronic HCV-infected persons in this study, might lead to decreased oral intake of important macro- and micronutrients (38). Alcohol use also is associated with chronic pancreatitis, which could result in fat malabsorption (26). Additional studies are needed to further understand the mechanisms contributing to malnutrition in chronic HCV infection.

Poor health status may lead to reduced food availability and intake, thereby mediating the relationship between chronic HCV infection and malnutrition. However, self-reported health status, which attempted to capture a participant's overall health, was not significantly associated with low muscle mass in this study sample. This is likely due to the fact that an overwhelming majority of the population (85%) considered their health to be good or excellent. Thus, the relationship between chronic HCV and low muscle mass observed in this study is likely not explained by extreme changes in food intake behavior that might be associated with overall poor health.

Our study has several potential limitations. First, it was cross-sectional, but it is unlikely that low muscle mass increases the risk of HCV acquisition independent of risk behaviors such as alcohol or injection drug use. Second, the outcome of low muscle mass was ascertained using a surrogate marker, MUAC. However, we found good correlation between MUAC measurements and fat-free mass estimated by an alternative technique (MF-BIA) in subgroup analysis. Lastly, other factors, such as HCV RNA level, history of HCV treatment,

and other medical or psychiatric comorbidities, were not completely ascertained by NHANES but may be confounders in the association between chronic HCV and low muscle mass. Future studies should evaluate these factors and define their contributions to low muscle mass in chronic HCV infection.

In summary, our study suggests an association between chronic HCV infection and low muscle mass, determined by MUAC, among U.S. adults, even in the absence of advanced liver disease. MUAC measurement may be an inexpensive, clinic-based screening tool that can identify chronic HCV-infected patients at risk for malnutrition. Future studies should explore the mechanisms for low muscle mass among chronic HCV-infected patients and determine the impact of low muscle mass on liver disease progression and response to HCV treatment.

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Abbreviations

AST	aspartate aminotransferase
ALT	alanine aminotransferase
APRI	aspartate aminotransferase-to-platelet ratio index
BMI	body mass index
HCV	hepatitis C virus
HIV	human immunodeficiency virus
NHANES	National Health Examination and Nutrition Survey
MAMC	mid-arm muscle circumference
MUAC	mid-upper arm circumference
MF-BIA	multiple frequency bioelectrical impedance analysis

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Table 1

Characteristics of chronic hepatitis C virus (HCV)-infected and uninfected participants at enrollment in the National Health and Nutrition Examination Survey, 1999 - 2010.

Characteristic ^a	HCV-Uninfected	Chronic HCV-Infected	P-value
Unweighted, n (%)	18,210 (98.4%)	303 (1.6%)	
Mean age, years (SD)	39.3 (8.5)	47.0 (5.8)	<0.001
Sex, %			
Male	49.0	65.1	<0.001
Female	51.0	34.9	
Race/ethnicity, %			
White	67.9	63.9	<0.001
Black	11.2	22.4	
Hispanic	9.4	5.7	
Other	11.4	8.1	
Highest education level, %			
<12 th grade	16.7	28.1	<0.001
12 th grade or GED	23.8	33.4	
>12 th grade	59.4	38.6	
Alcohol use, %			
Former/Never	23.3	29.9	0.025
Current	76.8	70.1	
History of injection/non-injection drug use^b, %			
Never	79.3	28.0	<0.001
Ever	20.7	72.0	
Diabetes mellitus^c, %			
No	95.1	95.5	0.75
Yes	4.9	4.5	
HIV infection, %			
Negative	99.6	97.2	<0.001
Positive	0.4	2.8	
Body mass index (kg/m²), %			
<18.5	1.9	1.3	0.005
18.5-24.99	32.1	40.4	
25-29.99	32.8	37.3	
30	33.3	21.0	
Mean mid-upper arm circumference, cm (SD)	33.2 (3.9)	32.4 (3.8)	0.006
Mean triceps skinfold thickness, mm (SD)	19.3 (6.4)	15.6 (6.8)	<0.001
Muscle mass^d, %			
Normal	93.3	86.2	
Low	6.7	13.8	<0.001

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus; SD, standard deviation.

^a Percentages for characteristics are weighted (unless specified) due to the complex probability sampling employed by National Health and Nutritional Examination Survey.

^b Specifically asking about cocaine, crack cocaine, heroin or methamphetamine use.

^c Based on participant response to the question: Have you ever been told by a doctor or health professional that you have diabetes or sugar diabetes?

^d Low muscle mass defined as below the 10th percentile for mid-upper arm muscle circumference (using age- and sexbased anthropometric reference curves from National Health and Nutritional Examination Survey data, 1976-1980).

Table 2

Association between chronic hepatitis C virus infection and low muscle mass in the sample of National Health and Nutrition Examination Survey participants, 1999 - 2010, in primary and exploratory analyses.

	Adjusted Odds Ratio of Low Muscle Mass ^{ab} (95% Confidence Interval)	Adjusted Odds Ratio of Low Muscle Mass ^{ac} (95% Confidence Interval)	Adjusted Odds Ratio of Low Muscle Mass ^{ad} (95% Confidence Interval)
Chronic HCV infection			
Uninfected	Ref.	Ref.	Ref.
Infected	2.22 (1.39, 3.56)	2.51 (1.36, 4.64)	2.19 (1.34, 3.59)
HIV			
Negative		Ref.	
Positive		4.94 (2.26, 10.8)	
Self-reported health			
Good/Excellent			Ref.
Fair			0.92 (0.73, 1.16)
Poor			1.49 (0.96, 2.32)

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus.

^aLow muscle mass defined as below the 10th percentile for mid-upper arm circumference (using age- and sex-based anthropometric reference curves from National Health and Nutritional Examination Survey data, 1976-1980).

^bAdjusted for race, alcohol use, injection/non-injection drug use, and diabetes mellitus.

^cAdjusted for race, alcohol use, injection/non-injection drug use, diabetes mellitus, and presence of HIV infection.

^dAdjusted for race, alcohol use, injection/non-injection drug use, diabetes mellitus, and self-reported health status.