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# RELATIONSHIP BETWEEN GRIP STRENGTH AND NONALCOHOLIC FATTY LIVER DISEASE IN MEN LIVING WITH HIV REFERRED TO A METABOLIC CLINIC

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**Abstract:** This study aimed to assess the relationship between grip strength (GS) and nonalcoholic fatty liver (NAFLD) in treated HIV-infected men. We included 169 HIV-infected men. GS was assessed using a hand-grip dynamometer. NALFD was defined by liver-spleen attenuation ratio <1.1 on computed tomography. Mean (SD) age was 57 (6) years and BMI 24.5 (2.9) kg/m2. NAFLD was diagnosed in 33% of men; sarcopenia was present in 28%. Mean (SD) hand grip strength in the dominant hand was 37.5 (7.6) kg. In multivariate logistic regression, intermediate and low GS were associated with higher risk of NAFLD (OR 3.05; CI 1.27-7.61, p=0.01; OR 2.47; CI 1.01-6.19, p=0.05, respectively). GS has an inverse association with NAFLD prevalence in HIV-infected men. Specific mechanisms through which muscle weakness and NAFLD are related require further exploration but are not accounted for merely by the burden of comorbid illness, HIV disease stage, or ART exposure.

**Keywords**: Fatty liver, HIV, grip strength, sarcopenia.

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## Introduction

With increasing numbers of aging people living with HIV (PLWH), increasing prevalence of age-related metabolic comorbidities, such as non-alcoholic fatty liver disease (NAFLD, defined as ≥5% hepatic steatosis without other demonstrable causes), are observed. Persistent inflammation and metabolic dysregulation have become hallmarks of aging with HIV infection. Combined with HIV-/antiretroviral therapy (ART)-specific contributors (such as dyslipidemia and mitochondrial dysfunction), NAFLD severity in PLWH may be enhanced (1).

The discovery of associations between typical geriatric syndromes, such as sarcopenia, and metabolic comorbidities, including NAFLD, are relatively new among PLWH. Sarcopenia is highly prevalent among aging PLWH despite CD4+ T lymphocyte (CD4 cell) reconstitution and virologic suppression with ART (2). Recent studies show correlations of sarcopenia with NAFLD, independent of obesity or insulin resistance (IR) (3–5). Although a causal relationship has not been established, working skeletal muscle participates in the regulation of insulin secretion and IR, a shared pathophysiological mechanism with NAFLD (6).

Grip strength (GS) assessment is a simple and valid test that can be used as a reliable estimator of sarcopenia and frailty (7). To better understand relationships between functional decline and metabolic disease in PLWH, we assessed the relationship between GS and NAFLD in ART-treated PLWH.

## Methods

This is a cross-sectional, observational study of 169 men living with HIV and receiving care in the multidisciplinary Modena HIV Metabolic Clinic (MHMC, University of Modena and Reggio Emilia, Italy) between October 2010 date and February 2015. The MHMC was initiated in 2003/2004 to comprehensively assess longitudinal metabolic changes among PLWH (8). All male participants who had GS and body composition (whole body dual-energy X-ray absorptiometry [DXA] and abdominal computed tomography [CT]) assessments at the same visit were included. The study was restricted to men due to the low number of women with available GS measurements. Nineteen patients (11%) that were included were classified as having liver cirrhosis on the basis of Fib-4 score >3.25. Sixty-eight patients reported moderate alcohol intake (<20 g/day), but none reported heavy alcohol intake.

Demographic characteristics, duration of HIV infection, type and duration of ART, and lifestyle characteristics were collected during patient encounters. Smoking status was classified as being intensive or moderate (>10 or ≤10 cigarettes per day, respectively). Anthropometric measurements (weight and height) were performed using standardized techniques. Body mass index (BMI) was calculated as weight(kg)/height(m)2. Diabetes mellitus was diagnosed if the fasting plasma glucose was >125 mg/dL or participant was currently on insulin or oral hypoglycemic medication(s). Hypertension was diagnosed if the participant had a systolic pressure >140 mmHg, diastolic pressure >90 mmHg, or was currently on

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**Table 1**
Baseline Demographic & Clinical Characteristics

| Variable | Total (N=169) | Patients without NAFLD (N=112, 66.3%) | Patients with NAFLD (N=57, 33.7%) | P |
|---|---|---|---|---|
| Age, years (SD) | 56.8 (5.9) | 57 (6.1) | 56.5 (5.5) | 0.8 |
| BMI, value kg/m$^2$ (SD) | 24.6 (2.9) | 24.1 (2.9) | 25.5 (2.7) | 0.005 |
| CD4 cell count nadir, cells/$\mu$L (SD) | 200 (90-290) | 205 (100-300) | 200 (79.25-290) | 0.81 |
| CD4 absolute cell count, cells/$\mu$L (SD) | 628 (479-792) | 651 (496-799) | 602 (424-764) | 0.46 |
| HIV-1 VL ≤50 (%) | 90 (96.7) | 60 (96.7) | 30 (96.7) | |
| HIV duration, years (%) | 227.33 (78.89) | 225.88 (85.82) | 230.18 (63.74) | 0.82 |
| Current smoker (%) | 39 (23.1) | 28 (25) | 11 (19.3) | 0.75 |
| Moderate smoker (%) | 15 (8.8) | 10 (8.9) | 5 (8.8) | |
| Intense smoker (%) | 24 (14.2) | 18 (16.1) | 6 (10.5) | |
| Metabolic parameters, (SD) | | | | |
| Triglycerides, mg/dL | 174.91 (130.48) | 176.68 (136.42) | 171.4 (118.97) | 0.48 |
| Total cholesterol, mg/dL | 190.16 (38.59) | 193.59 (39.77) | 183.36 (35.53) | 0.09 |
| LDL cholesterol, mg/dL | 119.66 (33.73) | 121.63 (35.01) | 115.76 (30.97) | 0.294 |
| HDL cholesterol, mg/dL | 48.71 (13.62) | 49.39 (13.07) | 47.36 (14.69) | 0.2 |
| Glucose, mg/dL | 102.12 (22.49) | 99.39 (18.54) | 107.39 (28.06) | 0.06 |
| HOMA-IR | 2.77 (2.9) | 2.28 (1.75) | 3.74 (4.22) | <0.01 |
| CRP mg/dL | 0.35 (0.59) | 0.35 (0.65) | 0.36 (0.47) | 0.09 |
| D-Dimer $\mu$/mL | 282.54 (185.17) | 272.26 (164.22) | 302.7 (220.94) | 0.43 |
| Hand grip dominant hand, Kg (SD) | 37.37 (7.85) | 37.47 (8.2) | 37.17 (7.16) | 0.816 |
| Hand grip non-dominant hand mean, Kg (SD) | 35.48 (7.91) | 35.39 (7.86) | 35.66 (8.08) | 0.93 |
| ASMI kg/m2 (SD) | 7.81 (1.11) | 7.72 (1.22) | 8.01 (0.81) | 0.26 |
| Sarcopenia (%) | 42 (27.8%) | 32 (31.1%) | 10 (20.8%) | 0.27 |
| Liver/Spleen ratio | 1.17 (0.5) | 1.3 (0.56) | 0.92 (0.17) | <0.01 |
| Comorbidities, (%) | | | | |
| Dyslipidemia | 155 (91.72%) | 103 (91.96%) | 52 (91.23%) | 0.99 |
| Hypertension | 119 (70.41%) | 75 (66.96%) | 44 (77.19%) | 0.23 |
| Diabetes Mellitus | 30 (17.75%) | 16 (14.29%) | 14 (24.56%) | 0.15 |
| Liver cirrhosis | 19 (11.24%) | 11 (9.82%) | 8 (14.04%) | 0.57 |
| Cardiovascular disease | 20 (11.83%) | 8 (7.14%) | 12 (21.05%) | 0.02 |
| Osteopenia/Osteoporosis | 48 (28.4%) | 34 (30.36%) | 14 (24.56%) | 0.54 |
| COPD | 7 (4.14%) | 5 (4.46%) | 2 (3.51%) | 0.99 |
| Chronic kidney disease | 28 (16.57%) | 21 (18.75%) | 7 (12.28%) | 0.39 |
| Frailty Index | 0.28 (0.09) | 0.25 (0.08) | 0.33 (0.09) | <0.01 |

NAFLD, nonalcoholic fatty liver disease; BMI, body mass index; VL, viral load; LDL, low density lipoprotein; HDL, high density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; CRP, C-reactive protein; ASMI, appendicular skeletal muscle index; COPD, chronic obstructive pulmonary disease.

antihypertensive medication. Prior cardiovascular events were defined as myocardial infarction, coronary revascularization, stroke, or peripheral vascular disease. Individuals with a glomerular filtration rate of <60 mL/min/1.73m$^2$ were classified as having chronic kidney disease. Metabolic syndrome was defined according to National Cholesterol Education Program criteria.

Plasma HIV-1 RNA levels, CD4 and CD8 cell counts (most

recent value and nadir) were recorded. Serum fasting glucose, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, high-sensitivity C-reactive protein, and D-dimer levels were assessed after an overnight fast. IR was calculated using the homeostasis model assessment (HOMA) equation (HOMA-IR=fasting insulin [mU/mL] X fasting glucose [mmol/L]/22.5).

Muscle mass was evaluated by DXA scan. Sarcopenia was defined using Baumgartner's criteria, using DXA-derived appendicular skeletal muscle index (ASMI) <7.26 kg/m$^2$ for males (9). Voluntary isometric muscle strength (measured in kg) was measured using a handheld dynamometer (Camry 200 lbs / 90 kgs digital hand dynamometer grip strength measurement). GS forces were measured three different times for each hand. The GS score was the mean value of the measurements. GS was classified using percentile values cut points: less than 25th as poor GS, 25th-75th as moderate GS, and >75th as good GS. A frailty index was calculated based on the established deficit accumulation approach that has previously been described, with its validity assed in HIV-infected cohorts (8). Osteopenia and osteoporosis were defined according to the World Health Organization criteria based on T-score criteria (10).

Hepatic and splenic attenuation values (in Hounsfield Unites, HU) were measured using non-contrast CT (64-multislice CT; LightSpeed VTC; General Electric Medical System). All measurements were manually obtained in regions of uniform parenchymal attenuation, with care taken to avoid vessels and other areas that might give spuriously increased or decreased measurements. Measurements from each point of the liver were averaged. The liver:spleen (L:S) HU ratio was calculated as follows: L:S ratio = average attenuation value of liver (4 points)/attenuation value of spleen. NAFLD was defined by a liver-to-spleen ratio <1.1 (11). The FIB-4 index was calculated as a predictor of severe fibrosis, with a FIB-4 index >3.25 used as a cutoff for significant fibrosis (12).

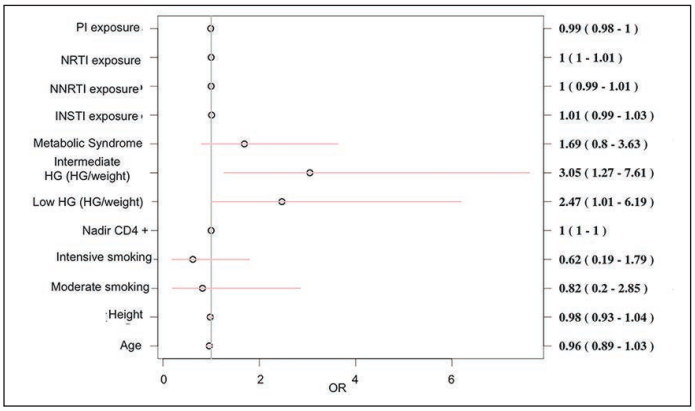
Comparisons between continuous variables were performed using the Student's t test, and the $X^2$ test was used for qualitative variables. Logarithmic transformation was performed on data that were not normally distributed. A P value <0.05 was considered to be statistically significant. Univariate and multivariate logistic regression analysis were performed to identify factors associated with NAFLD; GS was evaluated in tertiles, with the highest (strongest) hand GS tertile as the reference. Odds ratio (OR) and 95% confidence intervals (CI) were reported with two-sided p values ($\alpha$=0.05). All analysis were performed using the statistical software R Project for Statistical Computing, version 3.1.

## Results

The clinical characteristics of the 169 men included in the study are shown in Table 1. Mean age was 56.8 years. Most men (96%) had undetectable HIV-1 RNA, with mean (standard deviation, SD) duration of HIV infection 227 months (78.1) and mean (SD) current CD4 count of 628 cells/$\mu$L (479-792). Mean (SD) BMI was 24.6 kg/m2 (2.9). NAFLD was prevalent in 53 (33.0%) of individuals. Significant liver fibrosis by FIB-4 was present in 19 (11.2%). Sarcopenia was present in 42 (27.8%) men. The mean (SD) hand grip measurement in the participant's dominant hand was 37.4 kg (7.9).

In univariable analyses (Table 1), men with NAFLD had higher BMI (25.5, vs 24.1, p=0.005), HOMA-IR (3.7 vs 2.3, p<0.01), cardiovascular event history (21.1% vs 7.1%, p=0.02), and frailty index scores (0.33 vs 0.25, p<0.01). Figure 1 shows the results of the logistic regression analysis. The odds of NAFLD were statistically higher among individuals classified as having intermediate (OR 3.05; CI 1.27-7.61, p=0.01) and low (OR 2.47; CI 1.01-6.19, p=0.05) GS. Exposure to ART was not associated with increased risk of NAFLD.

**Figure 1**
Multivariate Logistic Regression




Points represent adjusted ORs and whiskers 95% confidence intervals. OR, odds ratio; PI, protease inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; INSTI, integrase strand inhibitor; HG, hand grip.

## Discussion

In this cross-sectional sample of men with HIV infection and a high prevalence of metabolic disease, greater hand GS was independently associated with lower NAFLD prevalence, whereas HIV-specific factors, such as ART exposure/type and CD4 cell count nadir, were not. This is the first study to assess the relationship between GS and NAFLD prevalence in PLWH.

NAFLD is a systemic condition that has a bi-directional relationship with the components of the metabolic syndrome (13). Among PLWH, NAFLD is an emergent clinical entity of significant prevalence (1). The documentation of an association between fat accumulation in liver and muscle is recent. Recent studies from the Korea Health and Nutrition Examination Survey demonstrate substantial evidence of a correlation between liver fat content and skeletal muscle mass determined by DXA scan (3, 4). Decreased muscle mass is not only associated with NAFLD, but also with its severity (4).

Sarcopenia and NAFLD may share a number of

pathophysiological mechanisms. The discovery of hundreds of proteins secreted by skeletal muscle, collectively called myokines (including myostatin and interleukin-6), and their role in the regulation of metabolic processes reinforces the notion that skeletal muscle may have an active role in regulating insulin secretion and the development of IR, a key factor in the pathophysiology of NAFLD (14). Additionally, the recently discovered myokines myonectin and irisin appear to be involved in the regulation of IR and lipid metabolism, resulting in increased free fatty acid uptake into cells in other tissues, including the liver (15). Finally, Hong et al reported an inverse correlation between IR and muscle mass, and a direct correlation between IR and liver fat accumulation, supporting a common pathophysiological mechanism (5).

Our study has several limitations. The cross-sectional nature of our study meant we could not assess a causal relationship between GS and NAFLD. This study included only men with HIV, and we cannot exclude a selection bias of patients referred to our metabolic clinic. Finally, the diagnosis of NAFLD was based on CT measurements, and histologic confirmation of NAFLD by liver biopsy was not available.

In conclusion, this is the first study to demonstrate an inverse association of GS with NAFLD prevalence among HIV-infected men. Specific pathophysiologic mechanisms through which muscle weakness and NAFLD are related require further exploration but are not explainable merely by the burden of comorbid illness, HIV disease stage, or ART exposure. Further studies are needed to investigate the role of skeletal muscle strength on NAFLD incidence, particularly as it may result in further therapeutic approaches.

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