Lipodystrophy and Inflammation Predict Later Grip Strength in HIV-Infected Men: The MACS Body Composition Substudy

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Abstract

Body fat changes in HIV-infected persons are associated with increased systemic inflammation and increased mortality. It is unknown whether lipodystrophy is also associated with declines in physical function. Between 2001 and 2003, 33 HIV-infected men with evidence of lipodystrophy (LIPO⁺), 23 HIV-infected men without lipodystrophy (LIPO⁻), and 33 seronegative men were recruited from the Multicenter AIDS Cohort Study (MACS) for the Body Composition substudy. Visceral adipose tissue (VAT) was assessed by quantitative computed tomography. Lean body mass (LBM) and extremity fat were measured by dual-energy x-ray absorptiometry. Insulin resistance was estimated by Homeostatic Model Assessment (HOMA). Serum interleukin (IL)-6, soluble tumor necrosis factor (TNF)- α receptors I and II (sTNFRI and sTNFRII), and highly sensitive C-reactive protein (hs-CRP) concentrations were quantified from archived serum samples. These measurements were correlated with grip strength measured in 2007 using linear regression. At the substudy visit, the LIPO⁺ group had higher HOMA, sTNFRI, sTNFRII, and IL-6 levels than the LIPO⁻ group. In 2007, the LIPO⁺ group had lower median grip strength than the LIPO⁻ group (34.4 vs. 42.7 kg, $p=0.002$). Multivariable analysis of HIV⁺ men showed older age, lower LBM, higher sTNFRII concentrations, and LIPO⁺ status [adjusted mean difference -4.9 kg ($p=0.045$)] at the substudy visit were independently associated with lower subsequent grip strength. Inflammation, lower LBM, and lipodystrophy in HIV-infected men were associated with lower subsequent grip strength. These findings suggest that inflammation may contribute to declines in functional performance, independent of age.

Introduction

WITH THE ADVENT of highly-active antiretroviral therapy (HAART) in the mid-1990s, HIV infection has been transformed from a fatal disease into a chronic, manageable illness, with life expectancy among HIV-infected persons more than doubling during the HAART era.^{1,2} As a result of extended survival and increased numbers of new diagnoses among older individuals, the HIV-infected population in the United States is becoming older. It is estimated that the majority of HIV-infected persons in the United States will be 50 years or older by 2015.³

With reports of the premature appearance of age-related comorbidities among HIV-infected persons, including cardiovascular disease, diabetes mellitus, osteoporosis, and

cognitive dysfunction, it has been hypothesized that HIV infection represents an accelerated aging phenotype.⁴ Supportive of this hypothesis are data suggesting that the immune system, immune activation, and immune senescence among younger HIV-infected persons are similar to age-related immune changes occurring in HIV-uninfected persons several decades older.⁵ In addition, HIV-infected persons may experience a premature decline in functional status. In the Multicenter AIDS Cohort Study (MACS), the prevalence of a frailty-related phenotype (unintentional weight loss, exhaustion, weakness, slow walking speed, low physical activity) in 55-year-old HIV-infected men was similar to that of HIV-uninfected men >65 years old.⁶ Onen *et al.* reported a frailty prevalence of 9% in a group of HIV-infected individuals whose mean age was 41.7 years.⁷

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Grip strength is an important index of physical function in older HIV-uninfected persons and has been strongly associated with bone density,^{8,9} fall risk,^{10,11} and bone fracture,¹² as well as all-cause mortality.¹³ Grip strength in geriatric populations tends to decline with lower lean body mass (LBM), increased systemic inflammation, and increased central fat distribution.^{14–16} In observational studies of elderly adults, tumor necrosis factor (TNF)- α and its receptors, interleukin (IL)-6, and C-reactive protein (CRP) have been associated with sarcopenia and decreased grip strength.^{14,17,18} In part, these cytokines may be derived from excess adiposity, particularly in the visceral compartment.¹⁹ Both central fat accumulation and fat atrophy are associated with increased systemic inflammation among HIV-infected persons.^{20,21} Given that chronic inflammation and abnormalities in fat distribution are common in HIV-infected persons and contribute to morbidity and mortality, even among persons receiving effective therapy,^{22,23} these factors could potentially contribute to the younger onset of frailty and concomitant functional decline observed in HIV-infected populations.

Using data from the MACS Body Composition substudy,²⁴ we examined the association between lipodystrophy status, differences in regional adiposity, and markers of systemic inflammation assessed in 2001–2002 with reduced grip strength in 2007.

Materials and Methods

Study population

The MACS is an ongoing multicenter (Pittsburgh, PA, Baltimore, MD–Washington DC, Chicago, IL, and Los Angeles, CA) prospective cohort study of men who have sex with men (MSM) who are followed on a semiannual basis. At the time of initiation of recruitment into the Body Composition substudy (2001), there were 1,952 men under observation, including 849 HIV-infected men and 1,103 HIV-uninfected men. Each semiannual MACS visit includes a detailed medical history, a physical examination, and collection and storage of biological specimens including plasma, serum, and peripheral blood mononuclear cells. The institutional review boards at each site approved the study protocols and forms, and each participant provided written informed consent both for the overall study and the substudy.

Sampling methods for the body composition substudy

Participants were recruited from the MACS cohort between 2001 and 2003 for a single substudy visit. Cases were identified by standardized clinical examinations that were completed semiannually at each study site from 1999, as previously described.²⁵ As recorded by the examining clinician, those HIV-infected men with (1) mild, moderate, or severe fat atrophy involving the face, legs, arms, or buttocks, and (2) mild, moderate, or severe fat hypertrophy involving the breast or abdomen were eligible for recruitment. “Mild” was defined as “only noted after close inspection.” “Moderate” was defined as fat changes “noticed by the clinician without specifically looking for it.” “Severe” was defined as fat changes “easily noted by a casual observer.”

Two control groups were also recruited: (1) HIV-infected men without evidence of lipodystrophy by clinical examination and (2) HIV-uninfected men. Controls were matched to

cases for age within 5 years and by MACS site. All HIV-infected men were required to have consistently received the same type of antiretroviral treatment [i.e., none, monotherapy/ combination therapy, or highly active antiretroviral therapy (HAART)] during the 2 years prior to identification. HAART was defined according to the U.S. Department of Health and Human Services (DHHS) Kaiser Panel guidelines²⁶ as previously described.²⁷ Men with diabetes mellitus or those who reported using androgens, anabolic steroids, or other hormonal agents such as megestrol were not eligible for participation in the substudy.

Of the HIV-infected men followed between 1999 and 2002, 281 met the case definition for lipodystrophy after screening (LIPO⁺) and had sufficient data to establish eligibility. Of these 281 men, 135 were excluded for use of hormonal agents, 34 were excluded for diabetes, and 35 were excluded due to inconsistent antiretroviral therapy use in the 2 years prior to the first visit at which clinical evidence of lipodystrophy was observed. Thirty-three men were recruited from this pool (LIPO⁺) of 77 men, for whom matched HIV-infected without lipodystrophy (LIPO[−]) and HIV-uninfected controls were also enrolled in the Body Composition substudy ($n=86$ for the combined groups).

Study procedures and measurements

Men recruited into the substudy underwent body composition measurements, including anthropometry, quantitative computed tomography (QCT) of the abdomen, and total body dual energy x-ray absorptiometry (DXA) at the substudy visit. QCT was used to measure visceral adipose tissue (VAT) with the intervertebral space between the fourth and fifth lumbar vertebrae as the origin point as previously described.²⁴ Images were read centrally (Obesity Research Center, Columbia University, New York) using image analysis software (Tomovision Inc., Montreal, Canada). The coefficient of variation (CV) was 2–5 %. Whole body DXA was undertaken to assess whole body tissue composition (total lean body mass) and extremity fat. Procedures were done using a Lunar Prodigy (GE Medical Systems, Madison, WI) in conjunction with Encore 2002 software at the Pittsburgh site and Hologic 4500A machines with QDA4500A software version 9.03 (Hologic Inc., Waltham, MA) at the other sites.

Determination of markers of inflammation and insulin resistance

Inflammatory markers measured were high sensitivity C reactive protein (hs-CRP), IL-6, and the soluble receptors of TNF- α (sTNFR1 and sTNFR2). Assays were completed at the Advanced Chemistry Laboratory at the Johns Hopkins University using stored serum samples obtained during visits between 1999 and 2002. Markers were measured in duplicate using commercially available enzyme-labeled immunosorbent sandwich assays (ALPCO Diagnostics, Windham, NH) and values were averaged for analysis. The intraassay precision of these assays ranged from 4.4% to 7.6% CV (average 5.6% CV). The sensitivity of this assay system for these cytokines ranged from 0.5 pg/ml to 16 pg/ml. CRP was measured using a highly sensitive ELISA assay (hs-CRP, ALPCO Diagnostics, Windham, NH). The linear range of the assay standards is 0.0019–0.15 mg/liter and samples with values

greater than the highest standard were diluted and re-analyzed. Participants were stratified as high risk vs. average to low risk for atherothrombosis using an hs-CRP concentration of 3 mg/liter as a cutoff.²⁸

Insulin resistance was estimated using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR = [fasting plasma insulin (μ IU/ml) $\times$ fasting plasma glucose (mmol/liter)] / 405)²⁹ at the substudy visit. Insulin concentrations were measured using radioimmunoassay (CV = 2.6%, Linco Research, St. Charles, MO). Fasting plasma glucose levels were measured by the combined hexokinase/glucose-6-phosphate dehydrogenase method (CV 1.8%). Glucose and insulin have been measured at each semiannual MACS visit since 1999 and are processed at a central laboratory (Heinz Laboratory, Pittsburgh, PA). Fasting plasma glucose and insulin in our analysis were taken from the MACS study visit closest to the substudy visit.

Measurement of grip strength

Each semiannual MACS visit since 2006 has included an assessment of grip strength using a Jamar Dynamometer (Sammons Preston Rolyan, Bolingbrook, IL). In this procedure, participants are seated and instructed to use their dominant hand and to squeeze as tightly as possible, holding the instrument with a 90° angle bend at the elbow. The test was performed three times and an average was taken of the three measurements. We used the second available visit's grip strength average measurement for each participant. The median (interquartile range) time elapsed between the substudy visit and the grip strength visit was 5.52 years (5.06, 6.03).

Statistical methods

Comparisons of means across the three studied groups (LIPO⁺, LIPO⁻, and HIV⁻) were performed using ANOVA with Bonferroni adjustments. Pairwise comparison of covariate medians was performed using the Wilcoxon rank sum test, when data were not normally distributed. Comparisons of medians across the three groups were performed using the Kruskal-Wallis test. Univariate and multivariate linear regression was performed using grip strength as the outcome among the HIV-infected participants and the covariates evaluated included age, race, lipodystrophy status, body mass index (BMI), lean body mass, quantitative body fat measurements, serum concentrations of inflammatory markers, HOMA-IR, exposure to antiretroviral therapy (ART) (individual drugs were assessed as cumulative exposure from enrollment), and immunological and virological parameters. Cytokine and inflammatory marker concentrations (IL-6, sTNFRI, and sTNFRII) were log-transformed to closer approximate normal distributions for regression analyses. hs-CRP concentrations were categorized for analysis using a 3 mg/liter cut-off. Covariates demonstrating a significant ($p < 0.1$) correlation with grip strength in univariate analyses were tested in the multivariate model and included whether their coefficient was significant at the 0.1 level except that age, race, and HOMA-IR were forced into the multivariate model. Inclusion of covariates in the final model was additionally based on Akaike's Information Criteria (IAC).³⁰ Data were analyzed using SAS 9.2 (SAS Institute, Cary, NC).

Results

Demographic and body composition variables

Of the 86 seropositive and seronegative men initially included in the body composition substudy,²⁴ 80 had grip strength data available, including 27 HIV-infected men with clinical evidence of lipodystrophy (LIPO⁺), 23 HIV-infected men without lipodystrophy (LIPO⁻), and 30 HIV-uninfected men (HIV⁻). Table 1 compares baseline characteristics between the three groups. Men in the LIPO⁺ group had a lower average BMI, lean body mass, and extremity fat than those in the other groups. VAT was similar among groups, despite the differences in BMI. There was a significantly greater proportion of LIPO⁺ men receiving HAART, yet the median CD4⁺ cell counts both at the study visit and nadir were lower compared to men in the LIPO⁻ group. We observed no significant differences in the proportion of smokers between the groups.

Markers of inflammation and insulin resistance

Table 2 compares concentrations of markers of inflammation across the three groups. Comparisons were made between the HIV-uninfected group and the pooled HIV-infected group (LIPO⁺ and LIPO⁻ combined) and between the two groups of HIV-infected (LIPO⁺ vs. LIPO⁻) groups. LIPO⁺ participants had significantly higher concentrations of all the inflammatory markers compared to LIPO⁻ subjects, while only TNF α RII differed when comparing pooled HIV-infected subjects (LIPO⁺ and LIPO⁻) with HIV-uninfected controls ($p = 0.006$, Table 2). HOMA-IR was significantly higher in LIPO⁺ men than in LIPO⁻ participants (Table 1).

Grip strength: univariate and multivariate models

The median grip strength of the combined HIV-infected group (LIPO⁺ and LIPO⁻) did not differ from HIV⁻ men [38.5 (IQR 33.0–42.0) vs. 37.7 kg (IQR 33.0–40.0), respectively; $p = 0.36$], however, among HIV-infected men, LIPO⁺ men had significantly lower grip strength than LIPO⁻ men [35.0 (IQR = 29.0–39.0) vs. 41.0 kg (IQR = 36.0–51.0); $p = 0.0037$] (Fig. 1).

To identify independent predictors of grip strength, univariate and multivariate linear regression analyses were performed among HIV-infected men (Table 3). In univariate analysis, lipodystrophy status, lower lean body mass, older age, higher sTNFRI, higher sTNFRII, and higher hs-CRP (>3 mg/liter) levels were each associated with lower grip strength. We did not identify an association between grip strength and current or nadir CD4⁺ cell count, use of HAART, HIV RNA <400 copies/ml, or smoking status. Exposure to stavudine was associated with a marginal decrease in grip strength of 0.83 kg for each year of stavudine use ($p = 0.06$). VAT and extremity fat at the substudy visit were not associated with grip strength.

In multivariable analysis (Table 3), lipodystrophy status, lower lean body mass, and higher sTNFRII remained independently associated with lower grip strength. In light of the relationship between lipodystrophy status and grip strength noted in the previous model, we explored the extent to which accounting for central hypertrophy (VAT) and subcutaneous lipoatrophy (extremity fat) changed the association between lipodystrophy status and grip strength. When VAT and

TABLE 1. STUDY POPULATION CHARACTERISTICS

Characteristics	HIV ⁻	HIV ⁺ LIPO ⁻	HIV ⁺ LIPO ⁺	p-value	Pairwise comparisons		
					HIV ⁻ vs. HIV ⁺ LIPO ⁺	HIV ⁻ vs. HIV ⁺ LIPO ⁻	HIV ⁺ LIPO ⁺ vs. HIV ⁺ LIPO ⁻
Number of subjects	30	23	27	—	—	—	—
Age (years)	50.5 (1.2)	48.4 (1.2)	50.4 (1.3)	0.45	0.26	0.98	0.27
% White	96%	78.3%	72.7%	0.03	0.007	0.03	0.64
BMI (kg/m ²)	28.7 (0.9)	26.8 (1.5)	23.6 (0.4)	<0.001	0.16	<0.0001	0.02
Lean body mass (kg)	73.9 (2.6)	71.3 (2.8)	66.8 (2.4)	0.07	0.51	0.08	0.16
Total percent fat (%)	26.0 (1.0)	20.3 (1.3)	17.5 (0.8)	<0.0001	<0.001	<0.0001	0.08
CD4 ⁺ cell count (cell/mm ³)	—	589 (445–778)	494.5 (315–708)	0.08*	—	—	0.08
Nadir CD4 ⁺ cell count % < 400 cps/ml	—	267 (172–381)	211 (108–328)	0.014*	—	—	0.014*
% participants on ART	—	66.7%	50.0%	0.24	—	—	0.24
Time on HAART (years)	—	60.1%	90.1%	0.02	—	—	0.02
% current smokers at substudy visit	—	5.38 (0.27)	5.48 (0.4)	0.94	—	—	0.84
HOMA-IR	13.3%	8.7%	18.5%	0.588	0.59	0.60	0.32
Extremity fat; DXA (kg)	3.0 (1.7–4.2)	2.18 (1.7–4.4)	3.7 (2.5–6.4)	0.09**	—	—	0.039*
Visceral fat; CT scan (cm ³)	9.4 (3.6)	6.7 (3.9)	4.5 (2.3)	<0.001	0.014	<0.001	0.022
	149.2 (62.18)	121 (66.49)	143.5 (56.10)	0.276	0.139	0.725	0.22

Median values were compared across groups in pairwise combinations (Wilcoxon rank sum test*).

Means (standard errors) were compared pairwise by Student's *t* test and across groups by ANOVA.

Medians were compared across groups by the Kruskal-Wallis test.**

Proportions across groups and pairwise were compared by Chi square.

HIV⁻, HIV-uninfected control men; HIV⁺ LIPO⁻, HIV-infected men without clinical evidence of lipodystrophy; HIV⁺ LIPO⁺, HIV-infected with clinical evidence of lipodystrophy; BMI, body mass index; HAART, highly active antiretroviral therapy; DXA, dual energy x-ray absorptiometry; CT, computed tomography.

extremity fat were added to the previous multivariable model, the effect of lipodystrophy decreased from -4.95 kg to -3.1 kg and the association was no longer significant ($p=0.2$). The magnitude and strength of the association between sTNFRII and grip strength, however, were slightly increased (-9.4 to -10.2). In contrast, the magnitude of the relationship between elevated hsCRP and grip strength decreased (from -4.9 to -3.7 kg) and was no longer significant with the addition of these fat covariates.

Discussion

In this substudy of a well-characterized cohort of HIV-infected and HIV-uninfected men, we found that lipodystrophy status, lower lean body mass, and increased systemic

inflammation (sTNFRII) among the HIV-infected men were independently associated with lower grip strength count; detectable HIV RNA levels or antiretroviral exposure were not associated with lower grip strength.

Declining physical function, including decreased grip strength, and the development of a frailty phenotype are characteristic of aging in the general population. Emerging data suggest that these complications may be more common in older HIV-infected patients compared to HIV-uninfected controls, and are related to HIV-staging variables, although we failed to identify such a relationship in our data set. In a cross-sectional analysis of the entire MACS population,³¹ HIV-infected men between the ages 50 and 59 had a prevalence of frailty phenotype that was 80% greater than HIV-uninfected men in the same age range. In the Women's

TABLE 2. COMPARISON OF INFLAMMATORY MARKERS ACROSS STUDY GROUPS

Cytokine	HIV ⁻ (n=30)	HIV ⁺ LIPO ⁻ (n=23)	HIV ⁺ LIPO ⁺ (n=27)	HIV ⁻ vs. HIV ⁺	HIV only LIPO ⁻ vs. LIPO ⁺
hsCRP (mg/liter)	2.26 (0.68–04.83)	0.91 (0.56–3.64)	2.05 (1.07–4.37)	$p=0.083$	$p=0.08$
IL-6 (pg/ml)	1.47 (1.05–1.74)	1.13 (0.97–1.59)	1.50 (1.14–2.92)	$p=0.96$	$p=0.03$
sTNFR I (pg/ml)	1,295.4 (1,145–1,507)	1,220.1 (1,041.7–1,364.4)	1,416.6 (1,150.8–1,620.5)	$p=0.94$	$p=0.03$
sTNFR II (pg/ml)	2,105.9 (1,798.4–2,636.0)	2,211.2 (1,949.4–2,694.1)	3,031.9 (2,291.9–4,356.2)	$p=0.006$	$p=0.01$

Median concentrations (interquartile range) of high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), and soluble tumor necrosis factor α receptor I and II (sTNFR I, sTNFR II) were compared pairwise among HIV-uninfected controls (HIV⁻) and all HIV-infected individuals, and HIV-infected individuals with lipodystrophy (HIV⁺ LIPO⁺) vs. HIV-infected individuals without lipodystrophy (HIV⁺ LIPO⁻), by Wilcoxon rank sum test.

FIG. 1. Distribution of grip strength (median, interquartile range) in HIV-infected men with lipodystrophy (LIPO⁺), HIV-infected men without lipodystrophy (LIPO⁻), and HIV-uninfected controls. Grip strength among LIPO⁺ men is significantly less than among LIPO⁻ men ($p=0.0037$). •, (value >75th percentile + [1.5 × interquartile range])

Interagency HIV Study, HIV-infected women with CD4⁺ cell counts <100 cells/mm³ had slower four meter walk times, lower grip strength, and a higher prevalence of the frailty phenotype compared to HIV-uninfected women.³²

In addition to persons with more advanced HIV disease, other HIV-infected subgroups may experience an accelerated functional decline with aging. We found that although grip strength was similar in the combined HIV-infected groups and the HIV-uninfected group, HIV-infected men with clinical evidence of mixed lipodystrophy (both lipoatrophy and lipohypertrophy) had a 4.9 kg lower subsequent grip strength

compared to men without lipodystrophy in a multivariable model. Comparing this effect size to the effect of age (−0.27 kg/year), the presence of lipodystrophy exerted an effect upon grip strength equivalent to an 18-year increase in age. If we compare this effect to age-stratified normative data from the general population using the same measurement technique, the observed difference by lipodystrophy status is similar to the difference between men aged 50–59 years and men aged 60–69 years.^{33,34}

The mechanisms underlying the difference in grip strength by lipodystrophy status remain unclear. Systemic markers of inflammation including IL-6, sTNFRI, sTNFRII, and hsCRP were higher in the HIV-infected men with clinical evidence of lipodystrophy compared to men without lipodystrophy. In the general elderly population, reduced muscle function, including grip strength, has been associated with higher levels of systemic inflammation.^{14,17,18} Inflammatory cytokines such as TNF- α and IL-6 can directly inhibit muscle protein synthesis, can stimulate apoptosis in muscle cell precursors, and are thought to play a major role in the functional decline and sarcopenia associated with aging.³⁵ In the multivariate analysis, sTNFRII was associated with grip strength independent of the presence of lipodystrophy. However, we also observed that the magnitude of the association between lipodystrophy status and subsequent grip strength was attenuated by about 40% (from −8.28 kg to −4.9 kg) with the inclusion of sTNFRII and the other covariates (e.g., HOMA-IR) in the model. Taken together, these findings suggest that the observed effect of lipodystrophy may in part be mediated by high levels of systemic inflammation. This observation is consistent with the observed relationship between systemic inflammation and physical disability in other populations with or at high risk for functional decline, including those with congestive heart

TABLE 3. FACTORS ASSOCIATED WITH SUBSEQUENT GRIP STRENGTH: UNIVARIATE AND MULTIVARIATE LINEAR REGRESSION

Covariate	Univariate		Multivariate		Multivariate + VAT + extremity fat	
	Coefficient	p value	Coefficient	p value	Coefficient	p value
Mixed lipodystrophy	−8.28	0.001*	−4.9	0.045	−3.1	0.2
Lean body mass(kg) ^a	0.28	0.005*	0.25	0.005	0.21	0.035*
Age (years) ^b	−0.48	0.038*	−0.27	0.16	−0.4	0.046*
log sTNF α RII (pg/ml) ^{*c}	−10.58	0.003*	−9.4	0.01	−10.16	0.008*
CRP >3 mg/liter	−7.51	0.009*	−4.9	0.05	−3.7	0.2
log sTNF α RI (pg/ml)	−15.04	0.0004*				
HOMA-IR ^d	−0.47	0.097	−0.048	0.8	−0.06	0.8
White (race)	2.06	0.5	−0.66	0.8	−0.69	0.8
Visceral fat (cm ²)	0.0033	0.88			0.01	0.48
Extremity fat (kg)	0.56	0.19			0.017	0.97
Nadir CD4 ⁺ cell count	0.63	0.36				
CD4 ⁺ at substudy visit	0.85	0.13				
Stavudine exposure (year)	−0.84	0.06*				
Body mass index (kg/m ²)	0.004	0.55				
Log interleukin-6	−4.8	0.046*				
HIV RNA <400 at substudy visit (cps/ml)	−0.4	0.88				
Smoking status at substudy visit (yes/no)	−3.54	0.44				

^aCentered at 70 kg.

^bCentered at 55 years.

^cCentered at 8 pg/ml.

^dCentered at 3.0.

Covariates were measured during the Body Composition Substudy visit on average 5.5 years earlier than grip strength. In the last analysis (Multivariate + VAT + extremity fat), quantitative measures of fat distribution were added to the multivariate model.

VAT, visceral adipose tissue.

Asterisks indicate significant covariate.

failure,³⁶ COPD,³⁷ or advanced age (>65 years) in the general population.³⁸

Interestingly, lean body mass was also strongly associated with grip strength, independent of the effects of sTNFRII or lipodystrophy status. In the general population, lean body mass, which includes muscle mass, has been found to be associated with hand grip strength and other indicators of physical function in older men and women.³⁹ It has been hypothesized that higher levels of systemic inflammation may lead to decreased muscle mass and in turn lead to decreased muscle strength.⁴⁰ Our data would suggest that the effect of inflammation on grip strength is not completely mediated through its effect on lean body mass; it is suggested that features of muscle other than mass, such as muscle quality, may be important for muscle function.^{41,42} Further studies are needed to characterize muscle quality in HIV-infected populations and its relationship to physical function.

To better understand the extent to which the observed effect of lipodystrophy on subsequent grip strength could be explained by objective measures of regional fat distribution, we conducted an exploratory analysis that further adjusted for visceral adipose tissue and subcutaneous thigh fat. We found that the effect of lipodystrophy status on grip strength was no longer significant after adjusting for quantitative measures of peripheral and central fat distribution. Abnormal fat distribution is a phenotype of lipodystrophy, a complex metabolic condition possibly resulting from chronic inflammation, endocrine dysregulation, and poor nutrition and physical activity. Elevated inflammatory markers and insulin resistance at the substudy visit associated with abnormal fat distribution may contribute to diminished grip strength at the later study visit. Metabolic factors such as hypogonadism, relative growth hormone deficiency, and vitamin D deficiency, which have been implicated in the pathogenesis of functional decline in the general population^{43–47} and are highly prevalent in HIV-infected populations with lipodystrophy,^{48–50} should be further investigated. In addition, behavioral factors may also be important. HIV-infected patients with lipodystrophy may have reduced quality of life and self-esteem,⁵¹ which may affect their desire to engage in exercise, particularly in a public setting, further accelerating a decline in physical function. Smoking was not found to be associated with grip strength in this study; however, with a small sample size and without quantifying the intensity of smoking, it cannot be ruled out. These possibilities should be explored in further studies.

We evaluated the effect of other variables on grip strength. Insulin resistance has been shown to predict hand grip strength among men in the general population in some,⁵² but not all, studies.⁵³ We found that insulin resistance was marginally associated with grip strength, but this association was no longer significant after adjustment for other variables. In addition, we found that HIV disease-related variables, including CD4 cell count, HIV-RNA levels, and HIV treatment-related variables, were not associated with grip strength, although our study was underpowered to observe small effects.

Our study had several limitations. The sample size was small, highly selected, and included only males. In addition, measurements of inflammatory markers and body composition were performed approximately 5 years before the measurement of grip strength. Although this helps to establish temporal associations, we were unable to assess whether

lipodystrophy, inflammation, or lean body mass were related to *changes* in grip strength. We are currently investigating these relationships in our cohort. Additionally, grip strength is only one measure of functional performance. Including other measures of physical function in future analyses will aid in elucidating predictors of functional decline in HIV-infected individuals.⁵⁴ Finally, MACS men have had prolonged exposure to HIV and ART and many HIV-infected men initially enrolled in the cohort have died. Our HIV-infected men evaluated in this analysis are survivors and may not be generalizable to other populations of HIV-infected persons. Nevertheless, this group of patients is representative of the first cohort of HIV-infected individuals who are aging with chronic HIV infection.

Our findings suggest that HIV-infected persons with lipodystrophy may be at increased risk for age-related functional declines and therefore may represent an important target population for screening aimed at disability prevention. Further work is needed to confirm these findings, understand the underlying mechanisms, and develop intervention strategies to improve physical function in this high-risk population. In addition, our findings regarding the relationship between inflammation and reduced grip strength provide a rationale for the development of pharmacological strategies that target inflammation and immune activation, with the goal of reversing functional declines in HIV-infected persons. As these strategies are being investigated, clinicians should aggressively promote lifestyle changes that include increased physical fitness, optimized nutrition, and smoking cessation in an effort to reduce systemic inflammation, improve physical function, and improve the quality of life among aging HIV-infected patients.

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