Original Article

Relation of Plasma High-Density Lipoproteins-Cholesterol with Sarcopenia in Patients with Chronic Obstructive Pulmonary Disease

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Abstract

Background: Plasma high-density lipoproteins-cholesterol (HDL-C) is a marker of metabolic health; however, its association with age-associated muscle loss, termed sarcopenia, is unknown. We evaluated the clinical importance of HDL-C in predicting sarcopenia in patients with chronic obstructive pulmonary disease (COPD). **Methods:** We investigated male healthy elderly and COPD patients, 54–79 years old (n = 55–59/group) through clinical examination, laboratory investigation, and spirometry. Sarcopenia was evaluated as low handgrip strength (HGS), appendicular skeletal mass index (ASMI), and gait speed. Enzyme-linked immunosorbent assays were used to measure the circulating markers of inflammation (C-reactive protein [CRP]) and oxidative stress (8-isoprostanes). **Results:** The COPD patients exhibited reduced HGS, ASMI and gait speed, and higher CRP and 8-isoprostanes levels and incidence of sarcopenia than controls (all $P < 0.05$). Plasma HDL-C levels exhibited significant correlations with CRP, HGS, and 8-isoprostane levels (all $P<0.05$) but not with ASMI and gait speed in both cohorts. Additionally, plasma HDL-C was an independent predictor of sarcopenia in controls and COPD patients (AUC = 0.631, $P<0.05$). **Conclusion:** Altogether, our data show that plasma HDL-C levels are a valuable marker of muscle decline and sarcopenia in healthy elderly and patients with COPD.

Keywords: 8-isoprostanes, chronic obstructive pulmonary disease, C-reactive protein, handgrip strength, High-density lipoprotein-cholesterol, sarcopenia

Introduction

Common consequences of aging include skeletal muscle weakness and atrophy, leading to a disorder called sarcopenia.[1] Sarcopenia involves a gradual development of muscle weakness and atrophy, which compromises lifestyle and may increase morbidity and mortality.[2] However, sarcopenia is underappreciated in clinics due to a lack of available diagnostic testing and uniform diagnostic criteria.[3] The standard definition of sarcopenia involves the presence of low handgrip strength (HGS; <27 kg), low appendicular skeletal mass index (ASMI; <7 kg/m^2), and reduced walking speed (< 0.8m/s). HGS is a helpful measure of morbidity and mortality in several diseases.[4] ASMI is the measure of lean mass while walking speed measures the physical capacity of the participants.

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In addition to sarcopenia, aging also results in elevated systemic inflammation and oxidative stress, which are associated with aging and related diseases.[5] Elevated plasma levels of 8-isoprostanes are a sign of high oxidative stress. On the other hand, plasma C-reactive protein (CRP) levels are used as biomarkers for inflammation. Elevated inflammation and oxidative stress can contribute to weak and atrophied muscles and increased susceptibility to developing sarcopenia.[6]

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High-density lipoprotein-cholesterol (HDL-C) has antioxidant and anti-inflammatory properties.[7] Accordingly, the patients with elevated oxidative stress and chronic inflammation frequently demonstrate reduced plasma HDL-C levels. In addition, HDL-C may have a predictive and prognostic value in metabolic diseases, including coronary artery diseases.[8] HDL-C levels can vary due to many factors; older age groups and those living a sedentary lifestyle, which can be observed in chronic obstructive pulmonary disease (COPD) patients, tend to have decreased HDL-C levels. Low levels of HDL-C indicate poor health and may be important in predicting sarcopenia and physical activity.

Muscle loss and weakness can be accelerated by various systemic diseases, such as COPD. COPD is a heterogeneous group of chronic respiratory diseases common in the elderly population.[9] Patients usually present with several inflammations and oxidative stress in multiple body systems, including the muscular system. Muscle dysfunction in COPD involves weakness of both respiratory and locomotor (peripheral) muscles.[10] Loss of strength and/or endurance in respiratory muscles can result in ventilatory insufficiency, while exercise volume and routine life activities are affected when peripheral muscles are involved. Sarcopenia in COPD is usually more severe and can lead to worsening lung functions.[4] Most patients with COPD exhibit decreased HGS, body mass index (BMI), ASMI, walking speed and step count, partly explained by accelerated muscle loss and weakness. Moreover, these patients also have elevated systemic inflammation and oxidative stress.

Owing to the essential contribution of sarcopenia to functional dependency in COPD, it is critical to timely characterize the muscle loss in these patients. Plasma HDL-C is routinely measured in clinical laboratories and may be a predictive biomarker of muscle loss and functional capacity in these patients. However, the diagnostic and predictive potential of HDL-C in sarcopenia remains unknown in COPD patients. This study aimed to address this gap by analyzing the relationship of HDL-C with sarcopenia indexes and functional performance in COPD patients. We hypothesized that low HDL-C levels are related to muscle decline and functional compromise. We addressed this hypothesis by conducting a cross-sectional study in healthy elderly and COPD patients.

Methods

Study design

We recruited healthy individuals (n = 59) and COPD patients (n = 55) at the teaching hospital (anonymized for review) after obtaining ethical approval from the regional ethical committee. The study is part of an ongoing project investigating sarcopenia in COPD and associated diseases.[1,4,11-13] COPD patients and healthy participants then underwent anthropometric measurements, plasma collection, body composition measurements, and handgrip strength. We randomly selected participants from an established cohort of controls and COPD patients to avoid selection bias.[12] All participants were nonvegetarian. The study was conducted in the line with principles of the Declaration of Helsinki.[14]

Handgrip strength and body composition

HGS was measured using a digital handgrip dynamometer (CAMRY, South El Monte, CA, USA).[1] The participants squeezed the dynamometer with their maximal strength in a supine position on a chair. The procedure was performed three times and the maximal reading was used for the analysis.

Spirometry

We used a portable spirometer (Contec SP10, China) to measure FEV1 and FVC as standardized by the American Standard Society.[15] During recordings, a maximal inhalation was followed by maximal exhalation into the spirometer.[16] The procedure was repeated thrice, and the predictive FEV1% was calculated and used for grading the severity of COPD.[17]

Measurements of plasma 8-isoprotanes, C-reactive protein, and high-density lipoprotein-cholesterol

The biochemical analysis involved enzyme-linked immunosorbent assay kits for measuring 8-isoprostanes (Cayman Chemical, Ann Arbor, MI, USA) and CRP (R&D Systems, Minneapolis, MN, USA) levels and the high-density lipoproteins-cholesterol (HDL-C) using CardioCheck® equipment (Maxglobal SA, Parsippany, NJ, USA), as described previously.[4,11]

Statistical analysis

We used *t*-tests to compare the continuous variables and the Pearson correlation to determine the strength of the relationship of HDL-C with sarcopenia and systemic health parameters. The incidence of sarcopenia according to various criteria was compared using a two-sample *t*-test. All data are presented as mean and standard deviation, and a $P < 0.05$ was statistically significant. All statistical analysis was conducted using GraphPad Prism version 8 (Dotmatics, San Diego, California, USA).

Results

Characteristics of the participants

The basic characteristics of both participants are summarized in Table 1. We found no significant difference in age among both groups. The COPD patients had higher plasma levels of 8-isoprostanes (COPD; 99.96 ± 23.19, healthy; 60.43 ± 15.28, $P < 0.05$) and CRP (2.84 ± 0.44, 2.11 ± 0.31, $P < 0.05$) than controls. COPD patients also had significantly lower HGS (23.11% lower), walking speed (21.2% lower), step count (29.2% lower) and ASMI (6.33% lower) than controls (all $P < 0.05$). We hypothesized that levels of the HDL-C molecule, associated with antioxidant and anti-inflammatory effects, may be lower in the COPD group than in healthy controls. Consistent with our hypothesis, we observed low plasma HDL-C levels in COPD patients than in healthy controls (COPD; 37.44 ± 3.24, healthy; 42.74 ± 3.75, $P < 0.05$). In addition, the occurrence of comorbidities,

including hypertension and diabetes mellitus was higher in the COPD patients than the control group [Table 1].

Comparison of sarcopenia and its indexes between the two groups

We next measured the incidence of sarcopenia in healthy controls and COPD patients according to four internationally recognized diagnostic criteria, including EWGSOP; European Working Group on Sarcopenia in Old People, AWSG; Asian Working Group for Sarcopenia, IWGS; International Working Group of Sarcopenia, FNIH; Foundation for the National Institute of Health, as described elsewhere.[18] Among different classifications of sarcopenia, irrespective of diagnostic criteria, the COPD group had a higher proportion of sarcopenic participants than the healthy controls [Figure 1]. We found that the IWGS classification yielded the highest number of sarcopenic participants in the healthy controls and COPD patients. When comparing the two groups, FNIH was the only classification with a significant difference between the proportion of sarcopenic participants in the controls and COPD patients ($P < 0.01$).

Comparison of markers of oxidative stress and inflammation between the two groups

Different factors such as systemic inflammation and oxidative stress can contribute to sarcopenia. Accordingly, we next measured the plasma CRP and 8-isoprostanes levels as molecular biomarkers of systemic inflammation and oxidative stress in controls and COPD patients.[11] We found significantly higher circulating 8-isoprostanes in the COPD patients than in healthy controls (COPD; 99.96 ± 23.19, healthy; 60.43 ± 15.28, $P < 0.0001$). Systemic inflammation is often coupled with oxidative stress, both of which are implicated in muscle atrophy. Hence, we next measured plasma CRP levels as a marker of systemic inflammation.[19] We observed that the COPD group had higher CRP levels than the healthy controls (COPD; 2.84 ± 0.44, healthy; 2.11 ± 0.31, $P < 0.0001$).

Table 1: Age, body composition, measures of physical capacity and plasma biomarkers in healthy controls and patients with chronic obstructive pulmonary disease

	Healthy controls	COPD
Age (years)	63.54±3.63	66.18±5.16
Body composition		
BMI (kg/m^2)	25.26±2.78	23.48±3.35*
ASMI (kg/BMI)	0.83±0.17	0.85±0.20
ASMI (kg/m^2)	7.54±1.12	7.06±1.00*
Physical parameters		
HGS (kg)	30.64±4.38	23.56±3.80*
4MWT (m/s)	0.97±0.18	0.76±0.17*
Step count (steps/d)	4514±1303	3193±651
Plasma biomarkers		
CRP (mg/l)	2.11±0.31	2.84±0.44*
8-isoprostanes (pg/ml)	60.43±15.28	99.96±23.19*
HDL-C (mg/dl)	42.74±3.75	37.44±3.24*
Comorbidities, *n* (%)		
Hypertension	4 (6.7)	17 (30.9)
Diabetes mellitus	3 (5.1)	13 (23.6)
CADs	3 (5.1)	5 (9.1)
Depression	1 (1.7)	3 (5.4)
Osteoporosis	4 (6.7)	6 (10.9)

*P <0.05 versus healthy controls; (n=55-59/group). Values are expressed as mean±SD. BMI: Body mass index, ASMI: Appendicular skeletal mass index, HGS: Handgrip strength, 4MWT: 4-meter walking test, CRP: C-reactive protein, HDL-C: High-density lipoproteins, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, SD: Standard deviation

Association of plasma high-density lipoprotein-cholesterol with indexes of sarcopenia and physical capacity

Owing to the well-established negative effects of oxidative stress and systemic inflammation on skeletal muscle and antioxidant and anti-inflammatory properties of HDL-C, we next asked if plasma HDL-C levels have a positive association with HGS, ASMI, and gait speed [Figure 2a and b]. Among different indexes of sarcopenia, HGS showed a significant correlation with plasma HDL-C in healthy controls ($r^2 = 0.140$, $P = 0.004$) and COPD patients ($r^2 = 0.238$, $P < 0.001$) [Figure 2a]. Plasma HDL-C also exhibited significant correlations with gait speed in COPD patients ($r^2 = 0.155$, $P = 0.002$) but not in healthy controls [Figure 2c]. Conversely, plasma HDL-C levels had no correlations with ASMI, and steps count per day for controls and COPD patients [Figure 2d].

Association of plasma high-density lipoproteins-cholesterol with markers of inflammation and oxidative stress

We next investigated the associations of plasma HDL-C levels with markers of inflammation and oxidative stress and found a negative correlation with CRP (healthy; $r^2 = 0.108$, COPD; $r^2 = 0.151$, $P < 0.05$) and 8-isoprostanes levels (healthy; $r^2 = 0.073$, COPD; $r^2 = 0.126$, $P < 0.05$) [Figure 2e and f].

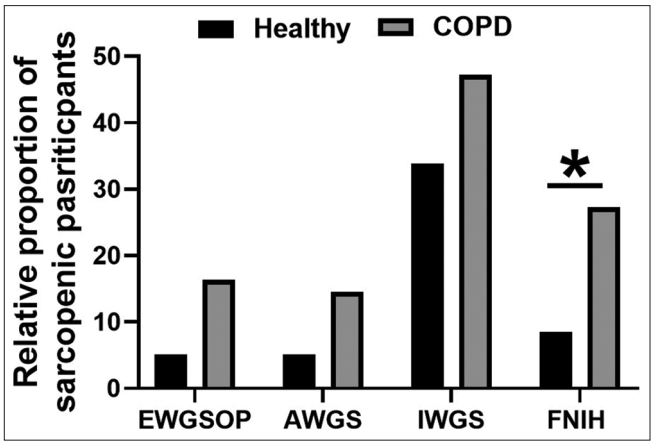

Figure 1: Relationship proportion of sarcopenic individuals in the healthy controls and COPD patients according to various internationally recognized criteria of sarcopenia. *$P < 0.05$. EWGSOP: European Working Group on sarcopenia in old people, AWSG: Asian Working Group for Sarcopenia, IWGS: International Working Group of Sarcopenia, FNIH: Foundation for the National Institute of Health. COPD: Chronic obstructive pulmonary disease

Diagnostic potential of plasma high-density lipoproteins-cholesterol in sarcopenia

We next asked if the plasma HDL-C can be a reliable marker of sarcopenia in the elderly irrespective of age-related diseases. We applied EWSOP2 criteria to define sarcopenia and ran the receiver operating characteristic (ROC) curves to discriminate sarcopenic from nonsarcopenic individuals in healthy controls and COPD patients. HDL-C levels showed a significant area under the curve in diagnosing sarcopenia (AUC = 0.631, $P = 0.02$, 95% confidence interval = 0.525-733) [Figure 3a]. On the other hand, plasma CRP and 8-isoprostanes levels did not discriminate sarcopenic from nonsarcopenic individuals [Figure 3b and c].

Correlations of indexes of sarcopenia, functional capacity, inflammation, and oxidative stress.

We next conducted the linear regression analysis to investigate potential correlations of markers of functional capacity, inflammation, and oxidative stress with each other [Table 2]. Varying degrees of associations were found among different indexes. Among sarcopenia indexes, HGS was significantly correlated with plasma CRP, while the walking speed was associated with BMI in the healthy controls and COPD patients combined [Table 2].

Discussion

The primary aim of this study was to evaluate the potential correlation between the plasma levels of HDL-C and sarcopenia phenotype in elderly males with COPD. We found significant associations of plasma HDL-C with sarcopenia parameters, including HGS, ASMI, and gait speed in controls and COPD patients irrespective of disease status. These findings demonstrate the predictive potential of plasma HDL-C in sarcopenia and physical capacity.

HDL-C is good cholesterol due to its role in transporting cholesterol molecules from the different organs to the liver. In

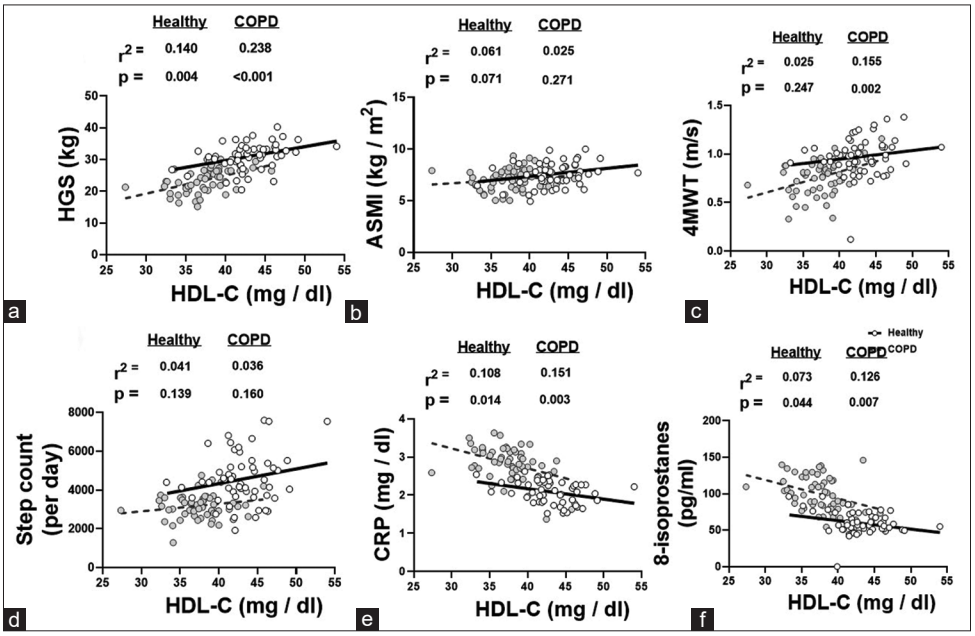

Figure 2: Relationship of HGS (a), ASMI (b), 4MWT (c), daily steps count (d), plasma CRP (e) and 8-isoprostanes (f) with HDL-C levels in healthy controls and COPD patients. HGS: handgrip strength, ASMI: appendicular skeletal mass index, 4MWT: 4-meter walking test, CRP: C-reactive protein, HDL-C: high-density lipoproteins-cholesterol, COPD: Chronic obstructive pulmonary disease, CRP: C-reactive protein

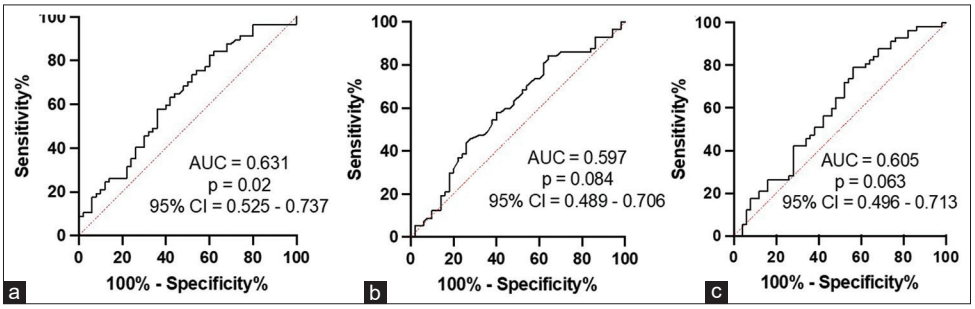

Figure 3: ROC curves showing the capacities of plasma HDL-C (a), CRP (b) and 8-isoprostanes (c) levels in discriminating sarcopenic from non-sarcopenic participants in healthy controls and the patients with COPD. The AUC was calculated for each group to determine the significance of the biomarkers in the diagnosis of sarcopenia. ROC: Receiver operating characteristic, HDL-C: High-density lipoproteins-cholesterol, COPD: Chronic obstructive pulmonary disease, CRP: C-reactive protein, AUC: Area under the curve

Table 2: The regression coefficients showing the relation of different parameters involved in contributing to sarcopenia in chronic obstructive pulmonary disease and healthy patients

	HGS	BMI	ASMI	Walking speed	Step count	CRP	8-isoprostanes
HGS		0.015	0.013	0.003	0.029	0.108*	0.024
BMI	0.015		0.056	0.099*	0.007	0.011	0.006
ASMI	0.013	0.056		0.031	0.074	0.017	0.036
Walking speed	0.003	0.099*	0.031		0.01	0.061	0.005
Daily step count	0.029	0.069	0.012	0.01		0.014	0.001
CRP	0.108*	0.011	0.017	0.061	0.018		0.058
8-isoprostanes	0.024	0.006	0.036	0.005	0.001	0.058	

*P <0.05. HGS: Handgrip strength, BMI: Body mass index, ASMI: Appendicular skeletal mass index, CRP: C-reactive protein

addition, HDL-C also possesses antioxidant, antithrombotic, and anti-inflammatory properties, which can be protective against muscle decline in the elderly.[20] A higher level of inflammation and oxidative stress contributes to sarcopenia while mitigating inflammation and oxidative stress through exercise and a low-calorie diet prevents sarcopenia.[21] We found low HDL-C levels in COPD patients, which may indirectly contribute to sarcopenia. A sedentary lifestyle is a critical contributor to low HDL-C in the elderly.[22] Our finding of lower step count in COPD patients is consistent with this notion. In addition, diseases involving chronic inflammation are frequently associated with reduced plasma HDL-C levels.[8,23] We found a negative relationship between plasma CRP and HDL-C levels in COPD, which agrees with previous reports and the anti-inflammatory properties of HDL-C. Since elevated inflammation is a signature finding in COPD, it may lead to a decrease in the levels of HDL-C.[24]

In our study, the participants with a faster walking speed had higher HDL-C, while participants with slower walking speed had lower HDL-C. Walking speed is a valuable indicator of health status because walking requires adequate joint mobility, muscle strength, and energy production by the body.[25] We found that the patients with COPD had slower walking speed and lower levels of HDL-C while healthy patients had faster walking speed with high HDL-C levels. These observations strengthen the relation between low HDL-C and poor systemic health, which may likely lead to slow walking speed. HDL-C levels had a negative correlation with plasma CRP and 8-isoprostanes. Patients with COPD had high levels of CRP and 8-isoprostane while low levels of HDL-C than healthy controls. HDL-C is an anti-inflammatory and anti-oxidative molecule and protects against systemic inflammation and oxidative stress. Consequently, low levels of HDL-C may lead to higher inflammation and oxidative stress, which may lead to the sarcopenia phenotype.

The COPD patients also had low HGS, low ASMI, and low gait speed than healthy controls, indicating their risk of developing sarcopenia and functional dependency. Since inflammation is a common finding among COPD patients, it can cause significant negative systemic effects such as skeletal muscle wasting. This may indirectly reduce the physical capacity of these patients.[26] In addition, other factors such as chronic inflammation, oxidative stress, physical inactivity, generalize hypoxia, malnutrition, and the use of steroid medications can also contribute to muscle and physical decline in these patients.[26]

The prevalence of sarcopenia was higher in COPD patients than in controls. However, the three criteria of sarcopenia yielded different prevalence in the studied population. These differences are partly due to different diagnostic parameters used by other criteria. For example, both EWGSOP and FNIH define sarcopenia as muscle weakness and atrophy; however, they differ in muscle mass measurement. The EWGSOP criteria calculate muscle mass as ASM/height^2, while the FNIH criteria calculate muscle mass as ASM/BMI.[27] The alterations in BMI and height are not always parallel and may account for different calculations of muscle mass in the same person. The IWGS criteria define sarcopenia as muscle atrophy and a walking speed of <1 m/s.[18] Conversely, the AWGS defines sarcopenia as muscle atrophy with either muscle weakness or reduced physical capacity. Hence, this criterion may diagnose sarcopenia in the absence of muscle weakness. In addition, different criteria use different cut-off points for HGS and ASMI, which may also account for differences in the sarcopenia indexes according to the criteria applied.[18]

Our study has certain limitations. We only recruited male participants, so we cannot confirm similar results in females. In post-menopausal women, the loss of estrogen is an important inducer of muscle atrophy, with different outcomes on muscle mass than men.[28] In addition, menopause is associated with increased cytokine inflammatory changes, which may further compromise muscle quality and/or quantity.[29] This study had a cross-sectional design, so we could not perform serial measurements in our study population. We only measured the HGS as a measure of strength; however, the strength of lower extremities using isometric or isokinetic techniques may be a better indicator of sarcopenia and dependent lifestyle.[30]

Conclusion

Taken together, we show that plasma HDL-C may help evaluate sarcopenia phenotype in the elderly. This notion may have translational potential, as increasing HDL-C levels through modifications in lifestyle, diet, and lipid-lowering drugs may positively affect muscle mass and strength. Future studies

should evaluate the mechanistic of muscle loss in COPD patients of both genders in a longitudinal study design for diagnostic and therapeutic efficacy of sarcopenia.

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Conflicts of interest

There are no conflicts of interest.

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