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Original Study

Muscle Quality is More Impaired in Sarcopenic Patients With Chronic Obstructive Pulmonary Disease

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A B S T R A C T

Background: Quadriceps muscle fiber atrophy and a loss of oxidative type I muscle fibers and mitochondrial content often occur in chronic obstructive pulmonary disease (COPD), which adversely affects exercise performance. Sarcopenia is an age-related syndrome characterized by wasting and weakness of muscle mass. We recently showed in a large cohort of patients that COPD-related sarcopenia, in particular in male patients, was not only associated with impaired quadriceps muscle strength but also with decreased exercise performance endurance, which could imply involvement of altered muscle fiber type composition. Hence, we hypothesized that both the fiber atrophy and loss of oxidative muscle fibers are more pronounced in sarcopenic compared with nonsarcopenic patients with COPD.

Objective: The objective of this study was to investigate quadriceps muscle fiber-type characteristics in relation to presence of sarcopenia in patients with COPD and in healthy age-matched controls.

Design: For this retrospective cross-sectional study, body composition (assessed by dual-energy x-ray absorptiometry) and quadriceps muscle biopsy (fiber type distribution and sizes) data were collected from 45 patients with COPDs (aged 42–77 years) and 52 healthy controls (aged 50–77 years). Sarcopenia was based on assessment of appendicular skeletal muscle mass index.

Results: Sarcopenia was found in 5.8% of healthy controls and in 31.1% of patients with COPD ($P < .01$). The proportion of oxidative type I fibers and size of type IIx muscle fibers were decreased in patients with COPD, and the sarcopenic subgroup showed a further decreased proportion as well as a lower size of type I fibers.

Conclusions: Type I muscle fiber proportion is lower in sarcopenic compared with nonsarcopenic patients with COPD. Longitudinal studies may elucidate if the loss of muscle oxidative phenotype drives or accelerates the process of muscle wasting.

Muscle wasting is a major hallmark of patients with chronic obstructive pulmonary disease (COPD) besides impaired lung function and contributes to impaired exercise capacity,[1] decreased health status,[2] and increased mortality.[3,4] Alongside the development and positioning of new radiographic measurements of body composition as integrated part of disease phenotyping, nutritional assessment has shifted from a body weight-centered to a body composition-centered approach. Recently, the European Respiratory Society taskforce on Nutritional assessment and therapy in COPD[5] proposed dual energy x-ray absorptiometry as the most appropriate method for body composition analysis in COPD, as it allows for screening of osteoporosis combined with assessment of fat mass (FM) and fat-free mass (FFM) at regional levels in addition to whole body level. Assessment of the appendicular skeletal muscle mass index (ASMI) traditionally originates from identification of age-related low muscle mass in elderly populations, a syndrome described as sarcopenia.[6] Its application is relatively new in COPD, but might in theory be highly relevant as COPD is suggested as disease of accelerated aging.[7] Indeed, we recently identified sarcopenia in the majority of Dutch patients with COPD eligible for pulmonary rehabilitation across all body mass index (BMI) categories.[8] Moreover, in this large cohort of patients (n = 505), we demonstrated that low ASMI was not only associated with

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impaired quadriceps muscle strength but, in particular in men, also with decreased cycle exercise endurance and walking distance. Whereas decreased muscle strength directly results from loss of peripheral skeletal muscle mass,[9] this does not apply for the loss of endurance, which is rather associated with loss of oxidative phenotype.[10] Consequently, it could be hypothesized that sarcopenia in COPD is characterized by intrinsic muscular alterations as well. In COPD, consistent intrinsic alterations in peripheral skeletal muscles have indeed been described.[11] More specifically, quadriceps muscle in advanced COPD is characterized by predominant atrophy of type IIx fibers[12] as well as a loss of oxidative phenotype (ie, a shift from oxidative type I to glycolytic II muscle fibers).[13] Furthermore, van den Borst et al[14] previously demonstrated that loss of quadriceps oxidative phenotype and decreased quadriceps endurance was already present in patients with mild-to-moderate COPD in the absence of muscle and fiber atrophy.

These alterations culminate in reduced muscle endurance, but in addition, could also drive or accelerate muscle wasting because the loss of muscle oxidative phenotype may render muscle in COPD less energy efficient, and (the remaining) type II fibers are more sensitive to atrophying disease-related triggers.[15–17] Moreover, intrinsic abnormalities in peripheral muscle seem more aggravated in emphysematous patients who are also more susceptible to weight loss.[18–20] In addition, Gouzi et al[21] recently identified an atrophic cluster of patients with COPD with reduced BMI, FFMI, type I fiber proportion, and fiber cross-sectional area (CSA) using an unsupervised clustering method.

Although assessment of muscle fiber alterations is crucial for understanding the process of muscle wasting in COPD, data is lacking on differences in muscle fiber-type characteristics between sarcopenic and nonsarcopenic patients with COPD. Therefore, the aim of this retrospective study was to compare quadriceps muscle fiber-type characteristics in relation to sarcopenia[6] in patients with COPD and in healthy controls. We hypothesize that muscle fiber atrophy and loss of oxidative muscle fibers are more pronounced in the sarcopenic COPD phenotype.

Methods

Participants

The studied population consisted of 45 clinically stable patients with COPD and 52 healthy controls. All patients were recruited from the outpatient clinic of the Maastricht University Medical Center+ (Maastricht, The Netherlands) and via local newspapers advertisement. Exclusion criteria comprised use of long-term oxygen therapy or oral prednisolone, acute exacerbation with hospital admission in the previous 4–8 weeks, or rehabilitation in the previous 6 months. Patients with known comorbidities as diabetes, recent cardiovascular event, inflammatory bowel disease, obstructive sleep apnea, thyroid disease, and cancer were carefully excluded because of potential interference with study outcomes. Healthy controls were recruited via local newspaper advertisement. Absence of diseases was verified through history-taking by a physician, and absence of airflow limitation was verified by pulmonary function tests. All patients participated in 1 out of 3 cross-sectional studies of which data has been previously published.[12,14,22] Participants were included in 1996-1997, July 2007-July 2010, and March 2009-April 2010.

Ethics

The procedures followed were in accordance with the ethical standards of the responsible institutional or regional committee on human experimentation or in accordance with the Helsinki Declaration of 1975 as revised in 1983.

Lung Function Measurement

In accordance with the latest Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines,[23] standardized equipment (Masterlab, Jaeger, Germany) was used to assess post-bronchodilator forced expiratory volume in 1 second (FEV_1) and forced vital capacity. Diffusion capacity of carbon monoxide was assessed by single-breath method. All obtained values were expressed as percentages of the predicted value, by comparison with age and gender-specific reference values.[24]

Body Composition and Muscle Phenotyping

Total body height was measured to the nearest 0.5 cm with a wall-mounted stadiometer and total body weight to the nearest 0.1 kg using a weighing scale. BMI was calculated as weight/height^2 (kg/m^2). Body composition was measured by dual energy x-ray absorptiometry (Lunar Prodigy System, GE Healthcare, Madison, WI; Hologic Discovery, Hologic, Bedford, MA). Fat-free mass index (FFMI) was calculated by dividing FFM (lean mass + bone mineral content) by height^2 and fat mass by subtracting FFM from body weight. Sarcopenia was defined according to cut-offs for ASMI ($<$7.23 kg/m^2 for men; $<$5.67 kg/m^2 for women).[6]

Muscle Fiber Typing

Quadriceps muscle biopsy analyses have previously been described in detail for the 3 individual studies.[12,14,22] In short, needle biopsies were obtained from the vastus lateralis under local anesthesia. Samples were frozen in melting isopentane (precooled in liquid nitrogen) and serial 5 μm cryosections were cut. A combination of myosin ATPase-activity staining and immunohistochemistry (antibodies against different myosin heavy chain isoforms) was applied to determine fiber type proportions and fiber cross-sectional areas using imaging software. All samples were analyzed within a year after collection.

Statistical Analyses

The Statistical Package for Social Sciences version 20.0 (SPSS, Inc, Chicago, IL) was used to perform statistical analyses. Normal distribution was assed using the Shapiro-Wilk test. Discrete variables were compared by the χ^2 test and presented as percentages. Continuous variables were presented as median ± interquartile range (characteristics) or mean ± standard error (muscle fiber composition) and were compared between 2 groups by the Student *t*-test for independent samples (parametric data) or Mann-Whitney test (nonparametric data), and compared between more than 2 groups by 1-way analysis of variance (parametric data) or Kruskal-Wallis test (nonparametric data). Two-sided *P* values of $<$.05 were considered statistically significant.

Because of a too small number of female participants, we could not perform separate analyses for males and females. Nonetheless, separate analyses could be performed for males, which are presented in the online supplement.

Results

Participant Characteristics

Both the COPD and healthy control groups consisted mostly of men (64.6% and 67.9%; $P = .723$). The majority of patients with COPD had