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Citation for published version (APA):


Document status and date:
Published: 01/05/2016

DOI:
10.1016/j.jamda.2015.12.094

Document Version:
Publisher's PDF, also known as Version of record

Document license:
Taverne

Please check the document version of this publication:

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Download date: 17 Sep. 2023
Original Study

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

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Journal homepage: www.jamda.com

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 Ix 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.

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Muscle wasting is a major hallmark of patients with chronic obstructive pulmonary disease (COPD) besides impaired lung function and contributes to impaired exercise capacity, decreased health status, and increased mortality. Besides, 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 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. Its application is relatively new in COPD, but might in theory be highly relevant as COPD is suggested as disease of accelerated aging. Indeed, we recently identified sarcopenia in the majority of Dutch patients with COPD eligible for pulmonary rehabilitation across all body mass index (BMI) categories. 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, this does not apply for the loss of endurance, which is rather associated with loss of oxidative phenotype. 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. More specifically, quadriceps muscle in advanced COPD is characterized by predominant atrophy of type IIx fibers as well as a loss of oxidative phenotype (ie, a shift from oxidative type I to glycolytic II muscle fibers). Furthermore, van den Borst et al 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. Moreover, intrinsic abnormalities in peripheral muscle seem more aggravated in emphysematous patients who are also more susceptible to weight loss. Whereas decreased muscle strength directly results from loss of peripheral muscle mass by subtracting FFM from body weight. Sarcopenia was determined according to cut-offs for ASMI by dividing FFM (lean mass + bone mineral content) by height squared and fat mass by subtracting FFM from body weight. Sarcopenia was defined according to cut-offs for ASMI (<7.23 kg/m² for men; <5.67 kg/m² for women).

Muscle Fiber Typing

Quadriceps muscle biopsy analyses have previously been described in detail for the 3 individual studies. 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 assessed using the Shapiro-Wilk test. Discrete variables were compared by the $\chi^2$ 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...
moderate to severe impaired lung function, as 6.4% of patients were classified in GOLD stage I, 36.2% in GOLD stage II, 48.9% in GOLD stage III, and 8.5% in GOLD stage IV.

Applying the gender-specific cut-offs for ASMI revealed presence of sarcopenia in 3 male healthy controls, 1 female patient with COPD, and 13 male patients with COPD, resulting in a total of 5.8% of healthy controls, compared with 31.1% in patients with COPD (P < .01). In males, 8.6% of control participants were sarcopenic, compared with 44.8% in patients with COPD (P < .01). Healthy controls with sarcopenia were excluded in further analyses because of the low number of participants.

Table 1 shows the participant characteristics per metabolic phenotype. Sarcopenic patients with COPDs were of similar age as nonsarcopenic patients, but were slightly older compared with the nonsarcopenic healthy controls (68 vs 64 years of age; P < .001). In addition, airflow limitation was more pronounced in sarcopenia compared with nonsarcopenic patients with COPD (FEV1 42.1% predicted vs FEV1 57.3% predicted). However, age and FEV1 were no significant predictors for ASMI in a regression model, whereas participant group (control or COPD) significantly predicted ASMI (P < .01). Nonsarcopenic patients with COPD had a higher fat percentage compared with nonsarcopenic controls. In line with a lower ASMI, sarcopenic patients with COPD showed a lower BMI, FFMI, and FMI than nonsarcopenic patients with COPD. Similar results were found in males only (Supplemental Table 1).

**Quadriceps Muscle Fiber Type Composition**

Figure 1 shows the proportion of type I muscle fibers across groups. In comparison with nonsarcopenic controls, a significantly lower proportion of type I fibers was found in both sarcopenic (26.0% vs 50.7%, P < .001) and nonsarcopenic patients with COPD (38.7 vs 50.7%, P < .01). Furthermore, the proportion of type I fibers was significantly lower in sarcopenic patients with COPD than nonsarcopenic patients (P = .048). Analyses in males showed similar results (Supplemental Figure 1).

The comparison of muscle fiber types CSA across groups is shown in Figure 2. In general, patients with COPD showed a significantly lower CSA of type Ila/IIX muscle fiber compared with nonsarcopenic controls (3464 vs 4472 μm²; P < .05), but no differences were found across sarcopenic phenotypes in COPD. In addition, CSA of type I fibers were significantly lower in sarcopenic patients with COPD compared with nonsarcopenic patients (5726 vs 7879 μm²; P < .05). No significant differences were found in CSA of type Ila/IIX, Ila/IIX muscle fiber, or mean CSA, although CSA of type Ila/IIX and mean CSA tended to be lower in sarcopenic patients. Comparisons in males showed an additional difference in CSA of type Ila/IIX fibers, which were significantly lower in sarcopenic patients than nonsarcopenic patients (4280 vs 6411 μm²; P < .05) (Supplemental Figure 2).

**Discussion**

This is the first study investigating quadriceps muscle fiber-type characteristics in relation to sarcopenia in patients with COPD and in healthy controls. Previous studies have already demonstrated a loss of muscle oxidative phenotype, including a muscle fiber type I→II shift,13,14 and selective atrophy of the type IIX fibers12 in patients with COPD. Added to the existing knowledge, the novelty of the current study is that it demonstrates a more pronounced decrease in oxidative type I fiber proportion in patients with COPD and sarcopenia.
Moreover, these sarcopenic patients are characterized by selective atrophy of the type I fibers, which seems independent of the more generalized type II atrophy in COPD as a whole.

Applying the ASMI cut-offs in our study population revealed sarcopenia in 31.1% of the patients with COPD and 5.8% of the healthy control participants. A comparable proportion of sarcopenic patients with COPD was found in a South Korean noninstitutionalized civilian population, in which 32.8% of male and 12.2% of female patients with COPDs were sarcopenic, as well as in a Brazilian COPD outpatient clinic, in which sarcopenia was observed in 39.6% of the patients. We recently reported a considerably higher proportion of sarcopenia in more patients with advanced COPD eligible for a pulmonary rehabilitation program. This is not surprising as skeletal muscle weakness is an important determinant of impaired exercise performance as important indication for referral to pulmonary rehabilitation.

Regarding muscle fiber composition, we found a significant decrease in CSA of type IIx fibers in the patient group compared with the (nonsarcopenic) healthy control group, which is in line with previous reports. The type IIx muscle fiber atrophy was not related to sarcopenia, as it was present in both sarcopenic and nonsarcopenic patients. Nonetheless, CSA of type IIa/IIx fibers tended to be lower in sarcopenic patients than in nonsarcopenic patients reaching statistical significance in the male subgroup (Supplemental Figure 2). Multiple disease-related triggers, occurring in isolation or combined, have been suggested to contribute to the atrophy of type II muscle fibers in COPD. Putative catabolic triggers include nutritional depletion, inflammation, oxidative stress, and myostatin. Nutritional depletion often occurs in COPD and is a likely contributor to atrophy of type II fibers based on collective findings of studies on anorexia nervosa, chronic heart failure, AIDS, and chronic renal failure. In addition, the majority of patients with COPD, especially muscle-wasted patients, exhibit chronic low-grade inflammation with elevated circulating concentrations of tumor necrosis factor-α, mediating muscle atrophy via the inflammatory signaling pathway nuclear factor κB. Furthermore, muscle-wasted patients with COPD show elevated concentrations of myostatin and systemic oxidative stress, which have also been shown to correlate negatively with muscle mass in patients with COPD.

In addition to muscle atrophy, peripheral muscle in COPD is characterized by a I-to-II fiber type shift, leading to an impaired oxidative phenotype. Long-term disuse has been described as catabolic trigger preferentially affecting type I muscle fibers. Indeed, our patients with COPD displayed a decreased proportion of type I fibers in comparison with healthy controls. Moreover, this shift was even more pronounced in sarcopenic patients with COPD, accompanied by a clear reduction in the CSA in the type I muscle fibers. In the literature, prolonged inactivity has indeed been described as an important driver for sarcopenia, as the sarcopenic process seems attenuated by higher levels of physical activity and effects of inactivity result in accelerated loss of skeletal muscle and functional capacity.

Collectively, the present findings confirm our hypothesis of a more pronounced loss of oxidative phenotype in sarcopenic patients with COPD and correspond with our previous finding of decreased muscle strength and endurance in sarcopenic patients with COPD. In addition to reduced exercise capacity, loss of oxidative phenotype might potentially accelerate muscle wasting. First, a shift toward more type II fibers will lead to an increased reliance on glycolytic metabolism, contributing to metabolic inefficiency. Furthermore, type II fibers are more susceptible to atrophying disease-related triggers as inflammation-induced and oxidative stress-induced damage.
Moreover, fiber shifting in the vastus lateralis of patients with COPD was recently identified as an independent predictor of mortality in patients with severe to very severe COPD. Some limitations of the present study deserve discussion. Nowadays, the European Working Group on Sarcopenia in Older People recommends using the presence of low physical function (strength or performance) next to low ASM. The current study design was retrospective, restraining the availability of a functional measure performed in each of the 3 study populations. Therefore, sarcopenia was diagnosed based on the presence of low ASM only. None of the subgroups was confined to a single study population and because only standardized and routine measurements were studied, we are confident that this did not introduce selection bias. Furthermore, the study design was cross-sectional, and although this was suitable to answer the current research question, longitudinal studies monitoring how fiber type alterations develop as the muscle wasting process progresses are required to disentangle the cause and consequence. Finally, the unequal gender distribution between the subgroups does not rule out putative gender differences in the association between sarcopenia and oxidative phenotype regulation.

The current study supports exercise training programs for patients with COPD that combine resistance and aerobic exercises as commonly applied in pulmonary rehabilitation, or combining endurance exercise with anabolic. Myostatin inhibitors, for example, are currently investigated as promising anabolic pharmacologic agents for restoring muscle mass. However, some studies suggest that inhibition of myostatin might have detrimental effects on the oxidative capacity of muscle fibers, which could be combated by a multimodal intervention approach.

In conclusion, this study shows evidence for a more pronouncedly decreased type I fiber proportion in sarcopenic patients with COPD. These findings could reflect a cross-talk between muscle mass and oxidative phenotype regulation, which might accelerate the muscle wasting process in patients with COPD.

Supplementary Data
Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jamda.2015.12.094.

References


