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Original Article

Associations of muscle depletion with health status. Another gender difference in COPD?

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SUMMARY

Background & aims: Muscle mass depletion occurring in chronic obstructive pulmonary disease still leaves questions regarding its relation with health status. How health status should be conceived and assessed is a significant obstacle in answering these questions. This study tries to appoint which domains of health status are challenged by muscle depletion and evaluates evidence of gender difference.
Methods: 135 Patients enrolled in a cohort study with initial assessment of health status by the Nijmegen Integral Assessment Framework. In here 4 main domains and 16 sub-domains are recognized. These sub-domains were correlated with fat free mass index using baseline data. Associations of fat free mass and diffusion parameters with sex were elaborated.
Results: Muscle depletion occurred predominantly in those with low body mass index, and did not correlate with sub-domains of 3 main domains: Complaints, Functional Impairment and Quality of Life. In Physiological Functioning Hyperinflation correlated weakly. Diffusion capacity significantly correlated with fat free mass index in separate analyses of pulmonary function data. Interestingly, diffusion capacity was significantly lower in women than in men.
Conclusions: Muscle depletion hardly affects health status in COPD. Physiological correlations, however, do exist, pointing to severe disease, especially emphysema, and female sex as important concomitant factors.

1. Introduction

In patients with chronic obstructive pulmonary disease (COPD) a distinction is currently made between local pulmonary and systemic non-pulmonary effects. By far the most important systemic effect in COPD is loss of muscle mass.[1] Other systemic disease manifestations include loss of fat mass and bone mass.[2,3] Although seen fairly often in persons with advanced disease, these changes in body composition are not obligatory, not even for the most severe stage of COPD.[4] Among the deficiencies of these three tissue compartments, loss of muscle mass has achieved most of the research attention during the last two decades.

It became evident that loss of muscle mass has significant impact on muscle function[5], thereby challenging exercise capacity, and prognosis on survival.[6–8] This seems to be an independent effect, considering the association of lean body mass with risk of exercise limitation and 6-MWD, after correction for age, height, race, pulmonary function, smoking history and education level.[9] Strikingly, the prevalence of muscle mass depletion seems higher in women than in men, as several reports have demonstrated for moderate and severe COPD, although this has not gained much interest.[1,5,10] Studies of the pathophysiological mechanism of its development, suggested that low fat free mass (FFM) is associated in some way, to the phenotype of COPD, being more prevalent in the emphysematous than the bronchitic type.[11] This idea is challenging because the coincidence of emphysema and pulmonary cachexia could be regarded as a more or less distinct disease form within the COPD spectrum. How these data fit with each other, however, remains obscure.

Association of low muscle mass with Health Related Quality of Life (HRQL) is another field of interest, yielding some recent clinical reports. Dyspnoea for example, presumably is correlated with FFM. But until now, only a handful of authors have addressed this issue.[10,12–14] Thus far, no sound conclusions can be drawn regarding the relationship between nutritional depletion and aspects of health status (HS), usually measured by different instruments including those for dyspnoea. One study showed significant differences between low and normal FFM index for Saint Georges Respiratory Questionnaire (SGRQ) subscales Activity and Impact and concerning the domain 'Invalidity' of another specific

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questionnaire on HRQL.[14] However, in a multicenter study of larger scale no differences in MRC dyspnoea scale or SGRQ scores were observed between depleted and non-depleted patients.[10]

These inconclusive findings to a certain extent may be attributed to the use of a multitude of questionnaires that address only a limited concept of health status in studies to date. Our research group developed a validated and well differentiated concept of HS that allows an integral assessment, and introduced a clinical instrument for measuring this integral HS (Nijmegen Integral Assessment Framework: NIAF). This proved a worthwhile single HS instrument, feasible in clinical practice.[15] The hallmark of the NIAF is that it covers four independent main domains, Physiological Functioning, Complaints, Functional Impairment and Quality of Life, which could be subdivided into 16 independent sub-domains. This HS instrument thus has the potential to meet the objections of many instruments for HRQL that we know of today.

So at present, we can not be quite certain that muscle wasting in COPD has no correlation with any aspect of Health Status assessed by this broad concept. In addition, there is emerging evidence that gender may play a role in the occurrence of muscle wasting in connection to a specific type of COPD.

This study was planned with the hypothesis that muscle wasting is not associated with the non-physiological aspects of health status, and only has association with some physiological variables such as diffusion capacity, and with gender. Two questions were to be answered:

Is FFMI only related to health status in its physiological components, not in patient relevant outcomes, when an integrated HS assessment tool is applied? And, if so, what might be the role of gender in the association of low FFMI with the emphysematous type of COPD?

We correlated FFMI with all 16 sub-domains of HS, and then evaluated the prevalence of low FFMI in both sexes. Also, HS sub-domains were analysed for sex differences, and associations of sex with diffusion parameters were investigated.

2. Methods

2.1. Patients

Patients with stable COPD were recruited from three different respiratory clinics to form a prospective cohort. Patients were recruited on a voluntary basis by their respiratory physician in two neighbouring hospitals, or a senior staff member (J.M.) of the Department of Respiratory Diseases in the University Lung Centre Dekkerswald. The study was approved by the institutional ethical committee (Radboud University Nijmegen Medical Centre). All participants gave written informed consent to the study protocol. The inclusion– and exclusion criteria have been published elsewhere.[16] In brief, patients were included if:

1. COPD was ascertained by the GOLD criteria with a FEV1/VC post bronchodilator $<70\%$, and current or past smoking, and
2. FEV1 %predicted post-bronchodilatation was >30 and <80, presenting a sample of GOLD stages II and III, and
3. patients were in stable clinical condition with no prior exacerbation in the last 6 weeks before enrollment, and
4. did not participate within the last 6 months in a pulmonary rehabilitation program.

Asthma with persistent airflow obstruction was excluded by review of the medical records (J.M.,T.V.). Asthma was defined as a long history of attacks of dyspnoea and marked reversibility of the airway obstruction confirmed by spirometry, dating from childhood.

All measurements were performed at enrollment (baseline) and after one year (follow up), as part of a prospective study. Here only baseline measurements are reported.

2.2. Measurements

2.2.1. Body composition

Body mass index (BMI) was derived from weight divided by square height. Body composition was measured by bioelectrical impedance (Bodystat, 1500, Douglas, Isle of Man, UK 1997). FFM (kg) was transposed to FFM index (FFMI) using the standard formula differentiated by sex. Three weight classes were distinguished, partly based on criteria used by others,[10,17] underweight: BMI ≤ 21 kg/m^2, normal weight: >21 and ≤ 26 kg/m^2, and overweight: >26 kg/m^2. Accordingly, patients were divided into depleted, FFMI <15 kg/m^2 (females) and FFMI <16 kg/m^2 (males), and non-depleted individuals whose FFMI was ≥ 15 and ≥ 16 respectively.

2.2.2. Muscle function

Four different muscle groups were tested for maximal strength: M. Quadriceps, handgrip, inspiratory and expiratory muscles. Leg force was tested in sitting position with a 90° knee flexion, asking the patients to extend the leg as hard as possible against a fixed resistance, using a Microfet 2 (Biometrics Europe, Almere, the Netherlands). Handgrip force was measured by a hand-held dynamometer. Respiratory muscle function was determined by mouth pressures expressed as Pi max and Pe max at RV and TLC level respectively with a Validyne pressure gauge. The best of three acceptable maneuvers was recorded. The predicted values published by Wilson were used to calculate Pi max and Pe max % predicted.[18]

2.2.3. Pulmonary function

Routine spirometry with reversibility testing with a short-acting bronchodilator was performed by Masterscreen PFT, 2002, Jaeger Ltd., Würzburg, Germany. Also static lung volumes and diffusion capacity (DLCO s.b.) were measured with this instrument, by the Helium dilution technique according to ERS recommendations. Exercise capacity was evaluated at baseline by the use of a maximal incremental cycle ergometry (Corival 906900, Lode). During the tests patients were connected to the V_{max} 29 (Sensormedics, Bilthoven, the Netherlands), for measuring gas exchange and ventilation with concurrent electrocardiographic and oxymetric monitoring (Datex, Helsinki, Finland). Arterial blood gas samples were drawn at rest, at maximum exercise and after 3 min rest.

2.2.4. Health status

Health Status was assessed by the recently published NIAF, which captures the integral health status of patients with COPD by four main domains and 16 more concrete sub-domains[15] (originally 15 sub-domains were discriminated; later on fatigue proved to be a separate sub-domain in main domain Complaints; paper by J.B. Peters & J. Vercoulen et al., submitted). Consequently, the individual condition is represented in 16 scores, covering the main domains Physiological Functioning, Complaints, Functional Impairments and Quality of Life. Existing instruments were selected to measure these 16 sub-domains, resulting in Sub-domain Total Scores (STS). Higher scores represent worse clinical condition, because all test results were mirrored before computing them by factor analysis. An overview of the 16 independent sub-domains of HS and its underlying parameters and instruments is given in Appendix 1.

2.3. Statistics

Sex difference of low muscle mass frequencies (i.e. persons with depletion) was tested by X^2 test. Correlations of FFMI with lung