Influence of muscle mass in the assessment of lower limb strength in COPD: Validation of the Prediction Equation

Introduction:

Measurement of lower limb muscle strength is valuable in the clinical management of patients with Chronic Obstructive Pulmonary Disease (COPD). Muscle weakness is common, independently relates to mortality and morbidity, and is modifiable by exercise rehabilitation and potentially anabolic drug therapy[1-4]. Assessment of lower limb strength can be easily and reproducibly performed in clinical settings through Quadriceps Maximal Voluntary Contraction (QMVC) measurement. Establishment of reference ranges in healthy adults is required to identify weakness to assist decisions regarding therapies and assess outcomes in both clinical and research settings[1, 5]. Prediction equations previously used to study strength in COPD populations have included fat-free mass (FFM) thereby incorporating a measure of muscle mass. The inclusion of FFM may underestimate the prevalence of muscle weakness, particularly in populations where muscle mass is frequently low, as in COPD[2]. We aimed to examine the influence of muscle mass measurement on prediction equations for QMVC by determining the prevalence of weakness in two separate COPD cohorts using prediction equations with and without fat-free mass derived from healthy subjects.

Methods

Prediction equations were derived using multiple linear regression from an existing cohort of healthy adults (HC). Age, gender, weight and height were entered in the first model. A whole-body measure of FFM was added for the second. The derived equations were used to calculate individual percent predicted (%pred) values of QMVC in two COPD cohorts; one recruited from primary care (COPD-PC) and the other from a complex COPD outpatient clinic (COPD-CC). The lower limit of normal was used as a threshold for the presence of

weakness. A further description of the participants, measurements and analysis is provided in the supplementary material.

Results:

175 HC participants were included and 301 patients with COPD (n=112 COPD-PC, n= 189 COPD-CC). Baseline characteristics can be found in the supplementary material (Table S1).

Prediction Models Derived from Healthy Subjects:

Model without FFM (FFM-):

QMVC= (-0.318xA) + (13.138xG) + (0.245xW) + (29.781xH) - 18.072

QMVC (kg), A:age(yrs) G:gender: (F=0), W:weight: (kg), H:Height (m)

R: 0.773, R^2: 0.598, SEE: 8.86 p≤0.005

Model including FFM (FFM+):

QMVC = (-0.320xA) + (10.670xG) + (0.566xFFM) + 20.952

FFM: fat-free mass (kg)

R: 0.770, R^2: 0.585, SEE: 8.90 p≤0.005

Application of the prediction equations in patients with COPD

The predicted values for QMVC using the FFM- and the FFM+ model in the two COPD cohorts were calculated. Individual measured values were then compared to respective predictions as percentages to yield the percent predicted value (%pred) for both models in all cohorts, presented in Table 1.

Table 1: QMVC values expressed as percent predicted values and number classed as weak using the FFM- and FFM+ models for the COPD cohorts

	Primary Care COPD n=112	Complex Care COPD n=189
FFM- Model %pred QMVC:	88.3 (23.6)	54.0 (16.4)
Number classed as weak (%):	17 (15.2%)	101 (53.4%)
FFM+ Model %pred QMVC:	88.8 (22.4)	59.2 (17.8)
Number classed as weak (%):	13 (11.6%)	78 (41.3%)

Mean values and SD of measured Quadriceps Maximal Voluntary Contraction (QMVC) presented as a percentage of the values predicted (%pred) and the number in each cohort classed as weak using the FFM- and FFM+ models.
Abbreviations: FFM+: Fat-free mass model, FFM- model without fat-free mass, SD: standard deviation, n: number in each group.

QMVC Weakness:

The number and proportion of each cohort classified as weak is presented in Table 1.

The FFM- model increased the percentage defined as weak (3.6% increase in COPD-PC and 11.9% in COPD-CC) compared to the FFM+ model.

The distribution of the Standardised Residuals calculated using the FFM- and FFM+ equations for the HC, Primary Care and Complex Care COPD cohorts in relation to the threshold of weakness are shown in Figure 1.

Discussion:

We present two prediction equations for QMVC that estimate the presence of lower limb muscle weakness, one including and one without muscle mass (estimated using whole body measures of FFM). In healthy adults, inclusion of FFM did not affect explained variance of the prediction. However, when applied to COPD cohorts there was a difference in the assessment of weakness between the two equations, which was amplified in those with more severe disease.

Whilst percentage predicted values were similar in the Primary Care COPD (COPD-PC) cohort using both equations there was a marginally greater number classed as weak with the FFM- model. A larger difference occurred between models in the Complex Care Cohort (COPD-CC). Using the FFM+ model %pred values were higher and fewer were assigned as weak (Table 1 and Figure 1). This results from the partial adjustment for the lower muscle mass associated with more severe disease by the inclusion of FFM in the prediction equation. Where muscle mass is not abnormally low within the COPD-CC the difference in the classification of weakness between the models is reduced (details of this sub-analysis are supplied in the supplementary material).

The prevalence and magnitude of muscle weakness observed and the finding that this occurred in milder disease (managed in primary care) but was more pronounced in those with more severe COPD is consistent with other reports[2, 4, 6]. Previous reference equations for QMVC have variably included muscle mass[2, 4]. A negligible difference in predictions with the inclusion of muscle mass in healthy subjects was reported in an examination of isokinetic muscle strength[7]. A comparison of different reference equations for muscle strength in patients with COPD, one including FFM, demonstrated differences between them[8]. We advance previous studies by directly comparing how model components influence predictions by using the same healthy cohort to derive equations and applying them to separate COPD cohorts of differing severities, from different healthcare sectors. We have

identified statistical thresholds of “normality” for muscle strength both in absolute terms and relative to an individual’s muscle mass. The prediction does not encompass regional differences in muscle mass that might be important in some patients with COPD and clearly has relevance to the prediction of QMVC, a measure of regional muscle function. The impact of the identification of muscle weakness using this method on treatment stratification (e.g. for local muscle reconditioning or whole body anabolic therapies) requires further investigation.

We acknowledge some limitations. Different methods were used to measure FFM in the two COPD cohorts, which could affect the predicted values but would have minimal effect on comparison of the prediction models[9]. The functional and prognostic relevance of the identified lower limit of normal for muscle strength requires confirmation through linkage with outcomes such as functional status and mortality.

Proximal lower limb muscle dysfunction has significant implications for mortality, morbidity and healthcare utilisation in COPD[4]. Measurement is important in clinical assessment with the potential to aid targeting of therapeutic interventions such as strength training, nutritional support and anabolic drug therapy, availability of accessible reference values for interpretation will assist implementation[1, 10].

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Supplementary Material

Participants

The Healthy adult control (HC) group and the COPD-PC were participants in the Physical Activity and Respiratory Health (PhARaoH) Study in which healthy adults were recruited through community advertisement and patients with COPD through primary care clinics located in Leicestershire, UK[1]. The following inclusion criteria for the HC group were used for analysis; FEV_1> 80% predicted, FEV_1/FVC ratio >0.7, mMRC <2, age ≤40. Patients were included if they had a physician diagnosis of COPD that was confirmed by spirometric testing at baseline using established guidelines[2].

The COPD-CC was recruited from a Leicestershire based hospital complex COPD service designed for patients with advanced COPD. Referrals were from General Practitioners and other respiratory specialists as previously described[3]. The two studies from which participants for this study are drawn had relevant ethical approval (13-EM-0389, 13/EM/0287).

Measurements

In all three groups height was measured using a stadiometer to the nearest 0.01 metre (m) and weight using digital weighing scales to the nearest kilogram (kg). Body Mass Index (BMI(kg/m^2)) was then derived from these measures (weight(kg)/height($m)^2$). In the HC group and the COPD-PC body composition was measured using Bio-electrical impedance analysis (BIA) (Tanita MC780MA). Body composition was measured by Dual energy x-ray absorptiometry (DEXA) (LUNAR DEXA scanner) in the COPD-CC. Fat-free mass (FFM) was then calculated using the established method of the sum of lean mass and bone mineral content[4]. All participants underwent spirometry and measurements are expressed as a percentage of reference values[5].

QMVC measurement

The methodology for QMVC measurement was consistent across the cohorts[6]. Measurements were performed with participants seated, knees bent at a 90° angle, with the torso secured with adjustable belts. The dynamometer was attached to the lower leg just above the level of the malleoli ensuring a straight vector. Participants were encouraged to push out the lower leg and exert maximal effort for six seconds. The best reading from the dominant leg following at least 3 attempts was recorded (in kg).

Statistical Analysis

The prediction equations were derived within the HC group using multiple linear regression with bootstrapping of 1000 samples. Forced entry method was used for the model without fat-free mass (FFM-). Age, gender, weight and height were entered initially as they are theoretically implicated and previous relationships have been found[7, 8]. A hierarchical approach was then used for the second model (FFM+) with fat-free mass entered first followed by age and gender and then weight and height. This order was chosen to prioritise the inclusion of fat-free mass. Only variables that reached significance ($p \leq 0.05$) were retained in the models. Weight and height were removed from the second model due to collinearity and non-significance. The distribution of residual values was assessed for normality and models checked for absence of multicollinearity and heteroscedasticity. There was one extreme outlier (>3 standard deviations above mean QMVC) which skewed the distribution of the residuals so was removed from further analyses. The linearity of relationships was also assessed and established. Only complete cases were entered in the analyses.

The prediction equations were used to classify weakness in each of the cohorts using a threshold of the lower limit of normal (LLN) corresponding to the threshold above which 95% of the healthy cohort lie. This equates to a standardised residual below -1.645 using the

prediction equations and the standard error of the estimate (SEE) for the healthy cohort. The standardised residual for an individual was calculated as:

(Measured QMVC-Predicted QMVC)/standard error of the estimate (SEE)*

*SEE from HC

Participants with QMVC values below this would therefore be classified as having quadriceps weakness.

A sub-analysis was performed to calculate the percent predictions and the number classified as weak for each model in those within the COPD-CC without a low fat-free mass index ($FFM/height^2$)[10]. The results of this are shown in Table S2.

Differences in baseline characteristics between the HC and COPD cohorts, and between the standardised residuals of the models within the cohorts, were analysed using independent t-tests, or Mann-Whitney U tests if parametric assumptions were not met. All analyses were performed using SPSS (version 22). The TRIPOD checklist for developing prediction models was used to check the methodology and reporting[9].

Table S1: Baseline characteristics of the Healthy Control, Primary Care COPD and Complex Care COPD cohorts

	HC	Primary Care COPD	Complex Care COPD
n	175	112	189
Age (yrs)	54 (14)	68 (9)*	66 (12)†
BMI(kg/m^2)	25.8 (6.3)	27.4 (6.4)	24.7 (9.5)†
FFM (kg)	47.7 (14.9)	58.1 (17.6)*	45.4 (14.6)†
QMVC (kg)	32.0 (18)	33.0 (16.8)	17.1 (8.4)†
FEV1 (%predicted)	102.0 (20)	66.1 (24.8)*	29.0 (16)†
Gender	M=55(31.4%)	M=74(66.1%)*	M=108(57.1%)†

Displayed as median and Interquartile Range (IQR) unless stated.
Abbreviations: n: number of subjects, HC: Healthy Control, IQR: interquartile range, BMI: body mass index, FFM: fat-free mass, QMVC: quadriceps maximal voluntary contraction, FEV_1: forced expiratory volume in 1 second, M: male. *Statistical difference between Healthy Control Group and Primary Care COPD group ($P<0.05$) †Statistical difference between Healthy Control Group and Complex Care COPD group ($P<0.05$).

Table S2: QMVC values expressed as percent predicted values and number classed as weak using the FFM- and FFM+ models in COPD-CC without low Fat-free Mass Index

n	56
FFM- Model %pred QMVC:	60.4 (16.8)
Number classed as weak (%):	22 (35.5%)
FFM+ Model %pred QMVC:	66.7 (18.5)
Number classed as weak (%):	19 (30.6%)

Mean values and SD of measured Quadriceps Maximal Voluntary Contraction (QMVC) presented as a percentage of the values predicted (%pred) and the number classed as weak using the FFM- and FFM+ models.
Abbreviations: FFM+: Fat-free mass model, FFM- model without fat-free mass, SD: standard deviation, n: number in COPD-CC without low fat-free mass index.

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