Body Mass, Fat-Free Body Mass, and Prognosis in Patients with Chronic Obstructive Pulmonary Disease from a Random Population Sample

Findings from the Copenhagen City Heart Study

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Rationale: **Low body mass index (BMI) is a marker of poor prognosis in chronic obstructive pulmonary disease (COPD). In the general population, the harmful effect of low BMI is due to the deleterious effects of a low fat-free mass index (FFMI; fat-free mass/weight^2).**
Objectives: **We explored distribution of low FFMI and its association with prognosis in a population-based cohort of patients with COPD.**
Methods: **We used data on 1,898 patients with COPD identified in a population-based epidemiologic study in Copenhagen. FFM was measured using bioelectrical impedance analysis. Patients were followed up for a mean of 7 yr and the association between BMI and FFMI and mortality was examined taking age, sex, smoking, and lung function into account.**
Main Results: **The mean FFMI was 16.0 kg/m^2 for women and 18.7 kg/m^2 for men. Among subjects with normal BMI, 26.1% had an FFMI lower than the lowest 10th percentile of the general population. BMI and FFMI were significant predictors of mortality, independent of relevant covariates. Being in the lowest 10th percentile of the general population for FFMI was associated with a hazard ratio of 1.5 (95% confidence interval, 1.2–1.8) for overall mortality and 2.4 (1.4–4.0) for COPD-related mortality. FFMI was also a predictor of overall mortality when analyses were restricted to subjects with normal BMI.**
Conclusions: **FFMI provides information in addition to BMI and assessment of FFM should be considered in the routine assessment of COPD.**

Keywords: body mass index; chronic obstructive pulmonary disease; epidemiology; lung function; prognosis

Body mass index (BMI) is an independent prognostic factor in chronic obstructive pulmonary disease (COPD), with a clear association between decreasing body mass and increasing mortality, both in patients with COPD undergoing clinical care (1–3) and in patients with COPD from a population sample (4). Further weight loss increases the risk (5), whereas observational data indicate that those able to gain weight improve their prognosis (3, 5). For these reasons, BMI has been suggested as one of four parameters suitable for staging COPD (6).

The prognostic value of a low BMI could just be the result of wasting in the terminal phase of COPD as in any other terminal disease. However, if the prognostic value of low BMI in mild–moderate COPD were just a reflection of terminal disease, it would mainly be limited to the first few months or years after the assessment. This was not the case in previous studies (4, 5), and it contradicts the theory of low BMI being a finding in terminal COPD only. The body mass can be divided into two compartments: fat mass and fat-free mass (FFM). The first is, in principle, a metabolic inactive energy store, whereas the latter contains the metabolic active organs, skeletal muscle being the largest of these organs. It seems biologically reasonable to assume that loss of or a low FFM is unfavorable. This assumption is supported by observations from epidemiologic studies of general population samples where it is known that the effects of BMI on mortality can be separated into an inverse association between FFM and mortality and a direct relationship between fat mass and mortality (7, 8). In COPD, loss of lean body mass could be a result of the systemic effects of the disease. Systemic effects are not merely believed to be consequences of loss of ventilatory capacity but rather to reflect ongoing systemic inflammation and to include changes in skeletal muscles (9–11). Thus, low FFM rather than low total body mass could be a critical parameter of prognostic value in COPD. Support for this comes from a study by Marquis and coworkers (12) showing midthigh muscle cross-sectional area to be a better predictor of mortality than BMI and from a recent study by Bolton and colleagues (13) showing that loss of FFM was associated with loss of bone mineral density and frank osteoporosis—an important systemic complication of COPD.

Most studies on BMI and systemic effects in COPD have included patient series, and it is essential for our understanding of the natural history of COPD that studies of the role of systemic effects of COPD are performed in populations free of referral bias. For this purpose, we studied the distribution and prognostic importance of body mass and FFM in patients with COPD identified from an ongoing population study, the Copenhagen City Heart Study (CCHS).

METHODS

Population and Design

The study is based on data from the CCHS, which has previously been described in detail (14). The population was derived from a random, age-stratified sample of 19,329 individuals aged 20 yr or more recruited in 1976. At subsequent follow-up surveys, additional subjects have been invited. The present study uses data on the 10,049 subjects attending the third examination, 1991–1994 (response rate, 58%).

A total of 2,404 subjects with COPD were identified on the basis of a ratio of FEV_1 to FVC of less than 0.7 or presence of chronic mucus hypersecretion. Exclusion of subjects with self-reported asthma (n = 313) or missing data left 1,898 subjects available for the analyses.

(*Received in original form June 23, 2005; accepted in final form September 16, 2005*)

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Am J Respir Crit Care Med Vol 173. pp 79–83, 2006
Originally Published in Press as DOI: 10.1164/rccm.200506-969OC on September 15, 2005
Internet address: www.atsjournals.org

Variables of Interest

The variables of main interest were BMI and FFM. BMI was calculated as weight/height^2 (kg/m^2) and categorized into four groups using World Health Organization guidelines (15): underweight (< 18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obese (30+ kg/m^2); the two latter groups were combined in some subsequent analyses. Electrical impedance was measured using a BIA-103 RJL system analyzer (RJL Systems, Clinton Twp., MI) with a 30-kHz microampere device. The measurement was taken with the subject lying relaxed on a couch, using a tetra polar electrode placement. The algorithms used to estimate lean body mass from impedance are those given by Segal and colleagues (16). FFM was standardized for height similar to BMI: FFM index (FFMI) = FFM/height^2 (kg/m^2). Because no official guidance for categorizing FFM or FFMI exists, we chose two ways of dichotomizing the variable. First, we chose the lower 10th percentile derived from the total CCHS population sample, determined for men and women separately. For women, the cut-off value was 14.62 kg/m^2 and for men, 17.05 kg/m^2. Second, we used the cut-offs suggested by Schols and coworkers (17): 15 kg/m^2 for women and 16 kg/m^2 for men.

A dry wedge spirometer (Vitalograph; Maids Moreton, Buckinghamshire, UK) was used to obtain FEV_1 and FVC values; the spirometer was calibrated daily with a 1-L syringe. Three sets of values with two measurements differing by less than 5% were obtained. The highest measurements of FEV_1 and FVC were used in the analyses as absolute values and as percentages of predicted values using internally derived reference values based on a subsample of healthy never-smokers (18). Subjects were classified according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines: stage 0, FEV_1/FVC of 0.7 or greater and presence of chronic productive cough; stage 1, FEV_1/FVC less than 0.7 and FEV_1 of 80% predicted or greater; stage 2, FEV_1/FVC less than 0.7 and FEV_1 of 50% predicted or greater but less than 80% predicted; stage 3, FEV_1/FVC less than 0.7 and FEV_1 of 30% predicted or greater but less than 50% predicted; and stage 4, FEV_1/FVC less than 0.7 and FEV_1 of less than 30% predicted (19). Subjects were classified as never-, ex-, or current smokers. Information on duration of smoking, the current amount of tobacco consumed, and inhalation was used to describe smoking habits in more detail. Plasma fibrinogen was used as a marker of systemic inflammation and was measured by a standard colorimetric assay (Boehringer Mannheim, Mannheim, Germany).

Follow-up

Notification of deaths and cause of death were obtained from the National Board of Health. COPD-related deaths were defined as deaths where the immediate or contributory cause of death was registered as codes 490–93 according to the International Classification of Diseases eighth revision (ICD-8) until January 1, 1994, and as codes J42.9 to J45.9 according to the 10th revision (ICD-10) for the remaining period; ICD-9 was never used in Denmark. All subjects were monitored until December 2002 for all-cause mortality and until January 1, 2000, for COPD-related mortality.

Statistical Analyses

Fibrinogen was adjusted for variation due to age and BMI using standardized residuals from a regression with fibrinogen as dependent and age and BMI as independent variables; these residuals were used for significance testing of differences in fibrinogen level. To assess the independent contribution of BMI and FFMI to mortality in COPD, the Cox proportional hazards model was used (20); BMI and FFMI were not analyzed in the same model. Data were analyzed using SPSS 12.0 for Windows (SPSS, Inc., Chicago, IL). The results of regression analyses are given in terms of estimated relative risks (hazard ratios [HRs]) with corresponding 95% confidence intervals.

RESULTS

Baseline characteristics of subjects by GOLD stages are shown in Table 1. Mean weight, BMI, and FFMI were lower in stage 4 than in the other stages. Figure 1 shows distribution of BMI categories in each GOLD stage for men and women. Underweight increased with increasing severity of COPD, especially in women.

TABLE 1. BASELINE CHARACTERISTICS OF THE 1,898 SUBJECTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE ACCORDING TO STAGING OF SEVERITY BY GOLD CRITERIA

Stage	0	1	2	3	4
n	704	649	428	100	17
Age, yr	57.6	64.7	66.0	67.9	64.1
Men, %	48	55	52	49	41
Smokers, %	70	67	72	69	59
Ex-smokers, %	17	23	19	23	41
FEV_1, L	2.74	2.40	1.59	0.94	0.58
FEV_1, % predicted	103	97	67	42	25
Weight, kg	74.2	70.7	70.3	69.0	62.0
BMI, kg/m^2	26.1	24.6	25.2	25.2	22.2
FFMI, kg/m^2	17.7	17.2	17.3	17.1	16.1
Died during follow-up, %	25	34	49	67	71
COPD-related deaths, %	1	1	4	22	41

Definition of abbreviations: BMI = body mass index; COPD = chronic obstructive pulmonary disease; FFMI = fat-free mass index; GOLD = Global Initial for Chronic Lung Disease.

Mean FFMI was 16.0 kg/m^2 for women and 18.7 kg/m^2 for men. FFMI decreased with increasing severity of COPD: for stage 0–4, mean values for women were 16.3, 15.8, 16.0, 15.8, and 15.0 kg/m^2, and for men, 19.2, 18.4, 18.5, 18.4, and 17.7 kg/m^2, respectively. Prevalence of a low FFMI depended on cut points. Using 10th percentiles from the CCHS population, 15.8% of women and 15.1% of men with COPD had low FFMI; the corresponding values using the Dutch values were 24.6 and 2.9%. Figure 2 shows the proportion of patients with a low FFMI in GOLD stages for men and women. Figure 3 shows similar distribution in the group with normal BMI; GOLD stages 3 and 4 have been combined because of small numbers, 41 subjects with stage 3 and 11 with stage 4. Risk of a low FFMI increased with increasing severity of COPD, and among subjects in stages 3 and 4 with normal BMI, approximately 50% had low FFMI. In the total patient population, 83.8% had normal or high BMI and FFMI above the 10th percentile, 13.1% had normal or high BMI and FFMI below the 10th percentile, 0.7% had a low BMI and FFMI above the 10th percentile, and 2.4% had a low BMI and FFMI below the 10th percentile.

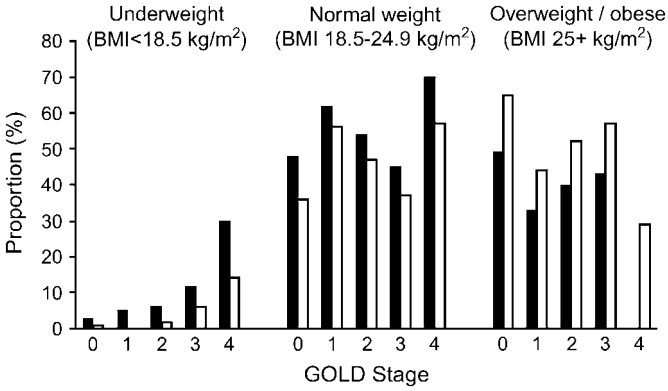

Figure 1. Distribution of body mass index (BMI) categories according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage for men (*white bars*) and women (*black bars*).

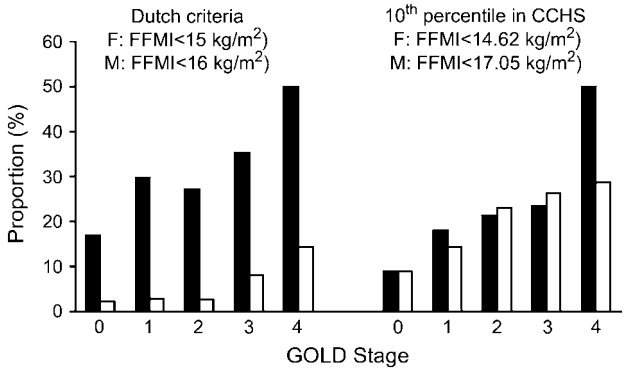

Figure 2. Proportion of patients with a low fat-free mass index (FFMI) according to GOLD stage for men (*white bars*) and women (*black bars*). CCHS = Copenhagen City Heart Study.

Fibrinogen was significantly higher in subjects with an FFMI lower than the 10th percentile of the general population than in those with a normal FFMI, but the numeric difference was small: 3.47 versus 3.27 g/L ($p = 0.02$). A slightly larger difference was seen when the analysis was restricted to subjects with a normal BMI: 3.48 versus 3.06 g/L ($p < 0.001$).

During the follow-up period, 683 subjects died (60% men). A total of 59 subjects died of COPD-related causes (49% men); 29 of the COPD deaths (49%) occurred in the 117 subjects (6.2%) with COPD stage 3 or 4 at baseline. The overall mortality rates in underweight, normal weight, and overweight/obese subjects were 53, 36, and 35%, respectively. Mortality in subjects with FFMI below and above the lower 10th percentile was 57 and 32%. Survival was further analyzed using the multivariate Cox regression analysis including the baseline variables significantly associated with survival in a model without BMI or FFMI: age, male sex, smoking, mucus hypersecretion, and FEV_1 in percentage of predicted as a continuous variable. FEV_1 provided better prediction than GOLD stages and was used in all subsequent models, including BMI or FFMI. Various additional smoking descriptors, including amount smoked and inhalation, were associated with mortality in a simpler model but lost significance when including FEV_1 in the model. In a model including age, sex, smoking, and mucus hypersecretion, and with GOLD stage 0 as reference, mortality rose with increasing stage; HRs for stages 1–4 were 1.4 (95% confidence interval [CI], 1.1–1.8), 2.1 (1.6–2.7), 3.2 (2.3–4.4), and 5.5 (3.0–10.1), respectively. There was a tendency toward a stronger effect of higher GOLD stages in women but the interaction was not statistically significant ($p = 0.11$). BMI with normal weight as a reference and the categories of overweight and obese combined was also a significant predictor of overall mortality ($p < 0.0001$). Underweight was associated with an increased mortality (HR = 1.8; 95% CI, 1.3–2.7), whereas overweight/obesity tended to decrease risk of death (HR = 0.9; 95% CI, 0.7–1.0; $p = 0.07$). Having an FFMI below the 10th percentile of the total population increased mortality significantly as shown in Table 2. In the group with normal BMI (n = 944, 335 deaths), a low FFMI was also associated with mortality (HR = 1.3; 95% CI, 1.0–1.6; $p = 0.03$). When a low FFMI was defined according to the second set of criteria, an association with mortality was no longer seen in the subgroup with normal BMI.

A total of 59 patients died of COPD, and multivariate analyses are restricted by the limited number of deaths. With adjustments for age, sex, smoking, and mucus hypersecretion, and with GOLD stage 0 as reference, HRs for GOLD stages 1–4 were 1.9 (0.6–5.7), 4.9 (1.9–13), 31 (13–74), and 108 (36–328), respectively. After adjusting for age, sex, smoking, mucus hypersecretion, and FEV_1%predicted, BMI was a strong predictor of COPD-related mortality ($p < 0.0001$) as shown in Table 2. Again, overweight/obesity tended to decrease risk of death (HR = 0.6; 95% CI, 0.3–1.0; $p = .06$). Being in the lowest 10th percentile of FFMI increased risk of mortality in the total sample but not significantly in the group with normal BMI only; however, only 29 subjects with normal BMI died of COPD. A weaker association was seen defining low FFMI with the other criteria.

Increasing fibrinogen was associated with increasing mortality but not COPD mortality ($p = 0.08$). Inclusion of fibrinogen in the Cox model did not significantly alter the HR for FFMI or the level of significance.

DISCUSSION

Our study has shown that low FFM is a frequently occurring phenomenon in unselected patients with COPD. Regarding BMI, a low FFMI is associated with mortality, and even in patients with normal BMI, a low FFMI is associated with an unfavorable prognosis.

BMI is a well-described indicator of prognosis in COPD (1–4). However, we found smaller effects of BMI on mortality than

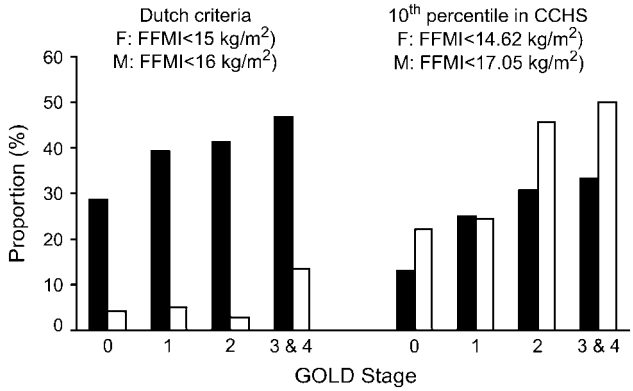

Figure 3. Proportion of patients with a low FFMI in GOLD stages for men and women with normal BMI. GOLD stages 3 and 4 have been combined because of small numbers. *White bars*, men; *black bars*, women.

TABLE 2. MORTALITY RISK ASSOCIATED WITH LOW FAT-FREE MASS INDEX AND LOW BODY MASS INDEX

	Low FFMI†	Low BMI‡
All subjects with COPD		
Overall mortality	1.5 (1.2–1.8)	1.8 (1.3–2.7)
COPD mortality	2.4 (1.4–4.1)	3.2 (1.5–7.0)
Subjects with normal BMI*		
Overall mortality	1.3 (1.1–1.7)	—
COPD mortality	2.0 (0.9–4.5)	—

Definition of abbreviations: BMI = body mass index; COPD = chronic obstructive pulmonary disease; FFMI = fat-free mass index.

Values are expressed as hazard ratios, with 95% confidence intervals in parentheses. Hazard ratios are from a Cox regression model, with age, sex, smoking, chronic mucus hypersecretion, and FEV_1 % predicted as covariates.

* Normal BMI defined as 18.5 kg/m^2 ≤ BMI < 25 kg/m^2.

† Low FFMI is defined as FFMI < 14.62 kg/m^2 for women and < 17.05 kg/m^2 for men.

‡ Low BMI defined as BMI < 18.5 kg/m^2.

previously shown in the same population study (4). Two explanations seem likely. First, we used data from the third survey, which had fewer subjects than the first survey on which the previous analyses were based. Second, using the third panel study of the population, some selection may have taken place. Any predictor of mortality will lose some of its predictive power when the same cohort is monitored over time because the most vulnerable subjects die and will no longer contribute to the predictive value of BMI. Unfortunately, FFM was not measured in the initial surveys of the CCHS. The association between BMI and mortality in randomly sampled patients with COPD (4) seems to differ from that found in the general population (21) where a J-shaped relationship is often reported. In contrast, the association between low FFM values and mortality in this study does not differ much from that found in studies on the general population (7, 8).

In our study, the pattern of distribution of FFM was not similar to that of BMI. In our population, 13% of subjects had a normal BMI but a low FFMI; in fact, more subjects with a low FFMI had a normal BMI than a low BMI. This is somewhat in contrast to findings by Schols and colleagues (22), and some of the difference may stem from the source of the subjects examined; we looked at patients with COPD identified in a population survey, whereas the Maastricht patients were patients with moderate to severe COPD undergoing inpatient rehabilitation. We also find it remarkable that differences in body composition can already be seen in early COPD where patients are not generally considered to have a wasting disorder due to their pulmonary disease. FFM can easily be assessed using commercially available equipment. It is generally advised that measures are made with the subject in a fasting state. Our findings are based on measures performed in a nonfasting state. This has probably led to less precise measures and wider confidence intervals, whereas it is unlikely that the predictive value is erroneous. The method is quick, cheap, and without discomfort, and there is nothing that precludes body impedance measurement as part of routine assessment in COPD. The principle behind electrical impedance is based on the different electric properties of the fat mass and FFM, and is the pure resistance of a biological conductor to the flow of an alternating current. Assessment of body composition using bioelectric impedance analysis may be less precise than dual-energy X-ray absorptiometry scanning and may underestimate FFM (23). Loss of precision may, nevertheless, be outweighed by easier access. No studies have studied the association between FFM assessed by dual-energy X-ray absorptiometry and prognosis in COPD. The main problem with using FFMI seems to be the choice of cut-off values. We found substantial differences in prevalence, especially in men, and to some extent predictive value using two different approaches. We chose a pragmatic way of defining lowest 10th percentile in the general population and our cut points are likely to be affected by prevalence of other chronic diseases. Cut points for application across populations still need further validation, and continued research in this area is clearly needed. Also, decisions as whether to use general algorithms for calculating FFM as the one we have applied or to use disease-specific algorithms need further discussion.

Our study has other limitations. Loss of FFM has been reported to be more frequent in patients with emphysema-type COPD based on high-resolution computed tomographic scanning than in chronic bronchitis (24), but in our population study, we are unable to differentiate COPD subtypes. Likewise, we do not have dietary information enabling us to differentiate weight loss, and in particular loss of FFM, due to increased energy expenditure rather than decreased dietary intake. Other studies, however, have addressed this in more detail. It seems clear that an elevated resting metabolic rate is found in patients with moderate and severe COPD (25) and that, independent of resting metabolic rate, total energy expenditure is increased in COPD (26). The exact mechanisms of muscle wasting in different stages of COPD are, nevertheless, not yet fully understood (27).

However, our study benefits from being population-based. Most other studies in this area have examined selected patients from respiratory clinics, presumably referred because of progressive symptoms. These patients may represent a group with particularly high rates of systemic inflammation leading to loss of FFM, deconditioning, and subsequent increased dyspnea. Our findings demonstrate that a systemic component resulting in a low FFMI is present in unselected patients with COPD. We have previously related fibrinogen to prognosis in COPD (28), and fibrinogen was significantly higher among subjects with low FFM in this study. Other studies have shown high levels of tumor necrosis factor α in weight-losing patients with COPD but those findings have not been related to prognosis (29, 30). An association between body composition and markers of systemic inflammation has previously been reported by Eid and colleagues (31) using a creatinine–height index; however, neither their measures of body composition nor their selected inflammatory markers have been associated with prognosis. The association between fibrinogen and body composition in our study indicates that systemic inflammation may be directly involved in the depletion of lean muscle mass. COPD is characterized by an increasing frequency of exacerbations and it seems likely that exacerbations are also associated with loss of FFM. Unfortunately, we did not have questions directed at quantifying exacerbation rate and we are therefore unable to determine if the short bursts of acute inflammation are more closely linked to loss of muscle mass than the chronic low-grade inflammation seen in stable COPD. Further studies are needed to address this.

In conclusion, our study indicates that patients with COPD are at risk of a low FFM and that a low FFM is prevalent even among subjects with normal BMI. Because FFMI is associated with prognosis, it seems that assessment of FFM provides important information in COPD and should be considered in the routine evaluation of patients with this condition.

Conflict of Interest Statement: None of the authors have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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