Dual-energy X-ray absorptiometry in the clinical evaluation of body composition and bone mineral density in patients with chronic obstructive pulmonary disease

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ABSTRACT
Background: Depletion of fat-free mass (FFM) occurs in a considerable number of patients with chronic obstructive pulmonary disease (COPD).

Objective: The goal of the study was to determine whether dual-energy X-ray absorptiometry (DXA) is an applicable method in the clinical evaluation of body composition in COPD.

Design: In a cross-sectional study in 79 COPD patients participating in a pulmonary inpatient program and in 23 healthy volunteers, DXA was compared with deuterium dilution (Deu) in the estimation of FFM. Bone mineral density (BMD), a DXA measurement, was also compared between the 2 groups.

Results: FFM<sub>DXA</sub> was highly related to FFM<sub>Deu</sub> in men (R<sup>2</sup> = 0.93, P < 0.001) and women (R<sup>2</sup> = 0.91, P < 0.001). On average, DXA resulted in higher FFM values than did Deu in COPD patients (3.4 kg; P < 0.001) and in healthy volunteers (2.1 kg; P < 0.001). Furthermore, the intramethod difference in FFM was higher in men than in women in the COPD group (P < 0.05) and in healthy volunteers (P < 0.001). BMD was lower in the COPD group than in the healthy, age-matched volunteers (P < 0.001). In 56% of the COPD patients, there were indications of bone mineral loss, defined as a BMD < 1 SD of a matched reference population provided by the software. BMD was >2 SDs in 36% of the COPD patients.

Conclusions: DXA appears to be a suitable alternative method to Deu for assessing body composition and is also of value in identifying bone mineral loss in COPD patients, and is therefore applicable in the clinical evaluation of these patients. Am J Clin Nutr 1998;68:1298–303.

KEY WORDS Dual-energy X-ray absorptiometry, deuterium dilution, fat-free mass, bone mineral density, chronic obstructive pulmonary disease, COPD, adults

INTRODUCTION
Depletion of fat-free mass (FFM) commonly occurs in patients with chronic obstructive pulmonary disease (COPD) and negatively influences physical capacity, independent of the degree of airflow obstruction (1–3). It is therefore particularly important to assess body composition in COPD patients with special emphasis on FFM. Currently, several established and validated methods are available for the assessment of body composition. Most of these methods rely on a 2-compartment model that separates the body into 2 chemically distinct parts: FFM and fat mass. When relating body composition to physical capacity in COPD, application of a 2-compartment model appears to be appropriate (4). The most commonly used, well-validated methods based on this 2-compartment model are hydrodensitometry and deuterium dilution (Deu). However, these methods are laborious and not easily applicable in clinical practice.

Recently, dual-energy X-ray absorptiometry (DXA) was introduced to differentiate body composition into 3 compartments. DXA directly assesses bone mineral content (5) and the soft tissue surrounding the bone (5, 6) by measuring the amount of fat and lean tissue. For that purpose, it is commonly used for accurate estimation of fat, bone, and bone-free lean mass (5, 7, 8). Also, bone mineral density (BMD; bone mineral content normalized for bone size) of the whole body and subregional compartments can be assessed. Because DXA is accepted as a safe, convenient, and noninvasive method, it is applicable in clinical practice as well as in the elderly, especially because the results are immediately available. However, the validity of this method in specific patient populations (ie, those with COPD) still has to be addressed.

Therefore, we compared FFM by DXA with that measured by Deu in 79 patients with stable, severe COPD, who were recruited cross-sectionally and in 23 healthy, age-matched volunteers. In addition, the BMD of the whole body and subregional compartments of the COPD group was compared with that of the healthy volunteers and with reference values provided by the DXA software to determine the percentage of COPD patients with indications of bone mineral loss.

SUBJECTS AND METHODS
Study population
During an 8-mo period, 99 patients were consecutively admitted to a pulmonary rehabilitation center for inpatient rehabilita-
tion. From this group, 79 patients [64 men and 15 women aged 65.0 ± 8.1 y, with body mass indexes (BMIs; in kg/m²) of 23.5 ± 4.4] were studied. These patients had irreversible COPD, according to American Thoracic Society guidelines (9) with a forced expiratory volume in 1 s (FEV₁) < 70% of the predicted value and with a reversibility after inhalation of a bronchodilating agonist < 10% of predicted. The patients were clinically stable, not suffering from a respiratory tract infection or other concomitant confounding diseases (ie, malignancies and gastrointestinal or endocrine disorders), and were without clinically demonstrable abnormalities in fluid balance (as manifested by clinically visible signs of edema or regular use of diuretics). Maintenance corticosteroid medication in this patient population consisted of oral corticosteroids (prednisone dose < 10 mg/d) (44%) and inhaled corticosteroids (85%). Also, 23 healthy, age-matched volunteers free from acute or chronic diseases and not taking medication influencing bone metabolism participated in the study. The medical ethical committee of the University Hospital Maastricht approved the study.

Assessment of body weight and composition

Body weight was measured by using an electronic beam scale with a digital readout to the nearest 0.1 kg (model 708; Seca, Hamburg, Germany) with patients and healthy volunteers standing barefoot and wearing light indoor clothing. Body height was measured to the nearest 0.1 cm (model 220; Seca).

Whole-body FFM, consisting of lean tissue mass and bone mineral mass, and fat mass were determined by scanning each subject on a DXA software validation phantoms provided by the manufacturer (5, 10, 11). Percentage body fat was calculated as fat mass relative to total tissue mass. FFMDXA was computed as the sum of lean tissue mass and bone mineral mass.

BMD is the bone mineral mass normalized for bone size. BMDs of the patients and healthy volunteers were expressed as g/cm² and as a percentage of healthy age-, sex-, weight-, and ethnicity-matched reference population data provided by the manufacturer. The healthy volunteers, as well as the reference population data provided by the manufacturer, and closely reflecting the attenuation characteristics of the major constituents of the body (lean mass, fat mass, and bone), were scanned.

Total body water (TBW) was estimated from deuterium dilution space (6). In the late evening, each subject consumed a preweighted oral dose of ²H₂O (12) (99.84 atom percent excess) of 1 g/L predicted TBW (based on height, weight, age, and sex). This dose was mixed into 70 mL deionized water. Just before and ≈10 h later a urine sample was collected; the latter sample was obtained after complete voiding of the bladder.

An isotope ratio mass spectrometer was used to analyze ²H₂O concentration in the urine according to the standard Maastricht protocol (13). After complete equilibration, deuterium dilution space was calculated from the quantity of ²H₂O administered and the urinary ²H₂O concentrations (14). In calculating TBW, it was assumed that deuterium dilution space was a factor of 1.04 times greater than TBW, owing to the estimated 4% nonaqueous hydrogen exchange and isotope fractionation (15). TBW was used to estimate deuterium-based FFM with the assumption that water represents a fixed proportion of the FFM (hydration factor of 0.73) and that fat is anhydrous. A 2-compartment model was used to derive FFM: FFMDex = TBW × (1.04 × 0.73). Fat mass was calculated by subtracting FFM from body weight and expressed as a percentage of body weight.

Pulmonary function tests

All subjects underwent spirometry with determination of FEV₁ and forced vital capacity (FVC) with the highest value from ≥3 technically acceptable assessments being used. Static and dynamic lung volumes (total lung capacity, residual volume, and airway resistance) were assessed by whole-body plethysmography (Masterlab; Jaeger, Würzburg, Germany). Diffusing capacity for carbon monoxide was measured by using the single-breath method (Masterlab). All values obtained were related to a reference value and expressed as percentage of the predicted value (16).

Statistical analysis

Results are expressed as means ± SDs. The paired t test was used for pairwise comparisons between measures of FFM, and linear regression analysis was performed to determine the relation between estimates of FFM for the 2 methods. The limits of agreement between the different methods were calculated as the mean intermethod difference ± 2 SD according to the method described by Bland and Altman (17). Intermethod FFM and BMD differences between men and women or between COPD patients and healthy, age-matched volunteers were assessed by using independent-sample t tests. Significance of difference was assessed at P < 0.05.

RESULTS

In 79 patients with moderate to severe airflow obstruction and in 23 healthy volunteers (16 men and 7 women), body composition was measured by DXA and Deu. Age, weight, and height did not differ significantly between the COPD and healthy volunteer groups (Table 1). COPD patients had significantly lower values for FFMDXA, FFMDex, TBW, FEV₁, diffusing capacity for carbon monoxide, and FVC, and higher values for total lung capacity, residual volume, and airway resistance.

There was a strong relation between mean FFMDXA and FFMDex in all subjects combined (R² = 0.94, P < 0.001) and when the study group was divided into men (Figure 1) and women (Figure 2). A Bland-Altman plot of the intermethod difference in FFM against the mean value of FFM by DXA and Deu (FFMDxa-
TABLE 1
General characteristics of patients with chronic obstructive pulmonary disease (COPD) and healthy, age-matched volunteers

<table>
<thead>
<tr>
<th></th>
<th>COPD patients (n = 64 M, 15 W)</th>
<th>Healthy volunteers (n = 16 M, 7 W)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>65.0 ± 8.1</td>
<td>65.0 ± 3.3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>69.0 ± 13.7</td>
<td>72.2 ± 11.4</td>
</tr>
<tr>
<td>TBW (L)</td>
<td>34.2 ± 6.2</td>
<td>37.8 ± 6.4^2</td>
</tr>
<tr>
<td>FFM_{DXA} (kg)</td>
<td>50.2 ± 8.7</td>
<td>53.9 ± 10.5^2</td>
</tr>
<tr>
<td>FFM_{Deu} (kg)</td>
<td>46.8 ± 8.5</td>
<td>51.8 ± 8.8^2</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168.0 ± 9.3</td>
<td>168.9 ± 8.2</td>
</tr>
<tr>
<td>FEV1 (% of predicted)</td>
<td>39.7 ± 14.1</td>
<td>109.9 ± 17.1^f</td>
</tr>
<tr>
<td>DLco (% of predicted)</td>
<td>61.1 ± 21.7</td>
<td>116.7 ± 21.4^f</td>
</tr>
<tr>
<td>FVC (% of predicted)</td>
<td>86.0 ± 18.8</td>
<td>119.7 ± 15.0^f</td>
</tr>
<tr>
<td>TLC (% of predicted)</td>
<td>121.2 ± 18.0</td>
<td>115.2 ± 10.2^2</td>
</tr>
<tr>
<td>Residual volume (% of predicted)</td>
<td>185.9 ± 55.9</td>
<td>113.2 ± 15.4^f</td>
</tr>
<tr>
<td>Airway resistance (% of predicted)</td>
<td>242.4 ± 96.3</td>
<td>92.7 ± 42.8^f</td>
</tr>
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</table>

^2 P < 0.05; ^f P < 0.001.

Deu versus FFM_{DXA-Deu}/2) showed a high degree of agreement for men (Figure 1) and women (Figure 2). There was no relation between the 2 measures in the 2 sexes or in the COPD or healthy volunteer group. Mean FFM_{DXA} in men was 3.6 kg above mean FFM_{Deu}, the difference in FFM values being between −0.5 and 7.8 kg of the mean of the 2 values. Mean FFM_{DXA-Deu} in women was 1.4 kg and the limits of agreement were −6.2 to 5.3 kg.

FFM_{Deu} was significantly higher than FFM_{DXA} in the COPD group (mean difference: 3.4 ± 2.2 kg; P < 0.001) as well as in the healthy volunteer group (mean difference: 2.1 ± 2.1 kg; P < 0.001). Moreover, this intermethod difference in FFM was significantly higher in the COPD group than in the healthy volunteers (P < 0.05). Stratification by sex showed that there were higher values for FFM_{DXA} than FFM_{Deu} in men in particular. In men, there was a higher intermethod difference in FFM in the COPD group (P < 0.05) and in the healthy volunteer group (P < 0.001) than in women (Figure 3).

The intermethod difference in FFM correlated significantly with sex (r = 0.40, P < 0.001), health status (0 = no COPD, 1 = COPD; r = 0.24, P < 0.05), height (r = 0.35, P < 0.001), and FFM of the trunk (r = 0.29, P < 0.01). However, in linear regression analysis, only sex, COPD, and height remained as significant predictors and explained 24% of the variance in FFM_{DXA-Deu}.

Whole-body BMD (in g/cm²) was significantly lower in COPD patients than in the group of 23 healthy, age-matched volunteers (P < 0.001; Table 2). In the COPD group, significantly lower values were also found for BMD of the arms (P < 0.05), legs (P < 0.01), and trunk (P < 0.01). Compared with age-, sex-, weight-, and ethnicity-matched reference population data provided by Lunar software, 56% of the COPD patients studied had indications of bone mineral loss (z score < −1); 9% of the healthy volunteer group had these indications. In 36% of the total COPD group, BMD was > 2 SDs below that of the reference population (z score < −2); 19% of the COPD patients had a BMD between 1 and 2 SDs below that of the reference population (−2 < z score < −1). Mean BMDs of the latter 2 groups were 0.94 ± 0.07 and 0.99 ± 0.07 g/cm² (NS), respectively, which corresponds to 83 ± 4% and 88 ± 3% of predicted BMD (P < 0.01). The BMD of the COPD group with no indications of bone mineral loss (z score > −1; BMD: 1.12 ± 0.08 g/cm²; 99 ± 5% of predicted) was significantly higher than that of the 2 COPD groups with bone mineral loss (P < 0.001). The percentage of patients using corticosteroids was not significantly different between the COPD groups with and without bone mineral loss (inhaled corticosteroids: 84% compared with 85%; oral corticosteroids: 49% compared with 36%).

FIGURE 1. Estimates of fat-free mass (FFM) by dual-energy X-ray absorptiometry (DXA) and deuterium dilution (Deu) in 64 male patients with chronic obstructive pulmonary disease (●) and in 16 healthy male volunteers (○). R² = 0.93 (P < 0.001); FFM_{DXA} = (0.97 × FFM_{Deu}) + 5.34; SEE = 2.11 kg. Line of identity is included. Difference in FFM between DXA and Deu for the 80 men studied versus the mean FFM between the 2 methods. The intermethod difference in FFM (dotted line) is 3.6 kg; the limits of agreement (dashed lines) are −0.5 to 7.8 kg; R² < 0.001.

DISCUSSION
This study showed a high level of agreement between DXA and Deu in the estimation of FFM, although systematically higher values for FFM were given by DXA, particularly in men, regardless of health status. Furthermore, DXA provided BMD values that were lower in COPD patients than standardized reference values.

We found highly significant correlation coefficients in COPD patients and in healthy volunteers when we compared FFM_{DXA} and FFM_{Deu} and these estimates were as good as those reported...
In healthy volunteers ($r = 0.74–0.92$, $P < 0.001$) (7, 18–20). Intermethod differences in FFM in male and female COPD patients and healthy volunteers were randomly distributed in relation to the means of the 2 estimates for FFM, according to Bland-Altman–type analyses. SEEs from comparisons of FFM were lower than or similar to SEEs reported by Pierson et al (21) and Wellens et al (22) in healthy adults. Therefore, we suggest that DXA and Deu are interchangeable when assessing FFM in healthy persons and those with COPD.

In the present study, mean FFM$_{\text{DXA}}$ was significantly higher than FFM$_{\text{Deu}}$ in COPD patients and in healthy volunteers. In the past, contradictory results were observed for FFM—higher (19, 22) as well as lower (7) estimates of FFM were found by DXA than by Deu. FFM$_{\text{DXA}}$ was lower than FFM determined by skinfold-thickness measurements (23) and hydrodensitometry (20, 22), although most of these studies were carried out in healthy research volunteers. Intermethod differences in FFM were noted in all COPD patients and in healthy male volunteers but not in healthy female volunteers. This observation contrasts with the findings of an earlier study in which FFM$_{\text{DXA}}$ was significantly higher than FFM$_{\text{Deu}}$ in healthy men and women (22). The discrepancy may have been due to the small number of healthy female subjects participating in the current study ($n = 7$). Furthermore, a higher intermethod difference in FFM was measured in the COPD group than in the healthy volunteers, suggesting a COPD-related effect. This intermethod difference was entirely sex-specific because it was higher in female COPD patients than in female volunteers, but was not different between male COPD patients and male volunteers ($P = 0.26$). More studies are needed to evaluate whether there actually is a COPD-related effect on intermethod differences in FFM.

In both COPD patients and healthy volunteers, the overestimation of FFM by DXA compared with FFM by Deu was significantly greater in men than in women, confirming a sex-related intermethod difference in FFM, as reported earlier in healthy adults. The systemic overestimation of FFM by DXA compared with Deu might be related to systematic errors in the DXA or Deu method used. To avoid adjustment for potential overestimation of TBW, Deu uses a correction factor of 4% for potential error due to the exchange of nonaqueous protein hydrogen. However, when the extremes of isotopic exchange factors of 2% and 5% (24) were used in the current study, the intermethod difference in FFM did not change significantly. Furthermore, the Deu method assumes uniform hydration of FFM (TBW = 0.73 FFM$_{\text{Deu}}$), although extensive interindividual variation exists (67–78%) (25). Particularly in hospitalized patients and very old people, this hydration...
coefficient (0.73 L/kg) might not be accurate (26). The attenuation coefficient of FFM used in DXA assumes constant hydration, but in practice physiologic changes in hydration have a minimal effect on the measured FFM. Earlier studies found that DXA accurately assesses small manipulations in hydration in vivo as changes in lean tissue mass (27–29). In the present study, the hydration coefficient calculated as the ratio of TBW to FFM_{DXA} was lower in the COPD group than in the healthy volunteers (0.68 ± 0.03 compared with 0.71 ± 0.03 L/kg; P < 0.001). These values were lower than the hydration coefficient of 0.73 L/kg reported by others (30). If DXA indeed measures FFM hydration more accurately than the constant of 0.73 L/kg, then body composition in this study population may not be estimated accurately by Deu. However, it is still uncertain whether this analysis was confounded by the potential influence of hydration itself on DXA.

What might the clinical consequences be of this systematic difference between Deu and DXA in measuring FFM? In general, when a systematic difference is found between 2 indirect measures of body composition, and neither method is a gold standard, it is difficult to determine which of the methods is responsible for the difference and which is providing an accurate assessment. Comparison of DXA with more sophisticated body-composition measures might shed light on this conundrum. In clinical longitudinal studies in COPD patients, the consequences of a systematic difference are not important because the evaluation of the effect of time-related interventions on body composition is not influenced by a systematic difference. Differences between methods might only be a problem when absolute values of FFM are compared among different studies in COPD patients. However, the intermethod difference in the present study was relatively small and therefore no real problems are expected when studies are compared. Patients with moderate to severe COPD participated in the present study, and although our study group did not represent COPD patients in general, it represented the population of interest in most metabolic studies of COPD. Because FFM_{DXA} and FFM_{Deu} values were nearly equal in COPD patients and in healthy control subjects, we think that DXA can also be used in patients with mild COPD.

BMD, as assessed by DXA, is the key clinical indicator of the patient’s skeletal status and varies with age, sex, menopausal state, ethnicity, and physical activity. BMD values below the age-matched SD indicate that additional factors may be affecting the patient’s BMD (secondary factors, ie, those not age-related or osteoporosis). In the present study, whole-body and subregional BMD were lower in the COPD group than in the healthy volunteers. When compared with matched reference population data provided by the Lunar software, 36% of the studied COPD patients had a BMD < 2 SDs of the reference population and 19% had a BMD between 1 and 2 SDs. The exact cause of this high prevalence of bone mineral loss in COPD is still open for discussion. Although the percentage of corticosteroid users was not different between the COPD groups with and without bone mineral loss, no information was available about the history of duration and dose of corticosteroid intake.

In the present study, highly significant correlations in the estimate of FFM were found between DXA and Deu, suggesting that DXA is an alternative method to Deu for assessing body composition. However, DXA gives systematically higher values for FFM than does Deu, particularly in men, regardless of health status. DXA makes it possible to identify the relatively high percentage of COPD patients with indications of bone mineral loss. We therefore conclude that DXA is an informative, well-suited, and easily applicable method for clinically evaluating body composition and BMD in patients with COPD.

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