Correlates of osteoporosis in chronic obstructive pulmonary disease

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The aim of this study was to analyse the correlates of reduced bone mineral density in patients with chronic obstructive pulmonary disease (COPD), with special regard to a possible protective role of hypercapnia.

One hundred and four consecutive COPD inpatients in stabilized respiratory conditions underwent a comprehensive assessment of their health status. Bone mineral density was measured by X-ray absorptiometry at the lumbar site and at the femoral neck site. Differences in health-related variables between patients with (group O, n=62) and without (group N, n=42) lumbar and/or femoral neck osteoporosis were assessed first by univariate analysis and then by logistic regression analysis aimed to identify independent correlates of osteoporosis.

Group O was characterized by worse nutritional status, as reflected by indices exploring either lean or fat mass, and by a trend towards lower forced expiratory volume in 1 sec/forced vital capacity ratio. Arterial tension of carbon dioxide lacked any correlation with bone mineral density. According to the logistic regression analysis, body mass index \( \geq 22 \text{ kg m}^{-2} \) qualified as the only and positive independent correlate of osteoporosis (odds ratio \( \geq 4.18; 95\% \text{ confidence intervals} = 1.19–14.71 \)).

In conclusion, malnutrition characterizes COPD patients with osteoporosis, while mild to moderate hypercapnia lacks either a positive or negative effect on bone mineral density. Longitudinal studies are needed to identify predictors rather than correlates of bone mineral density.

Key words: osteoporosis; nutritional status; hypercapnia; chronic obstructive pulmonary disease.

Introduction

A well-defined association between chronic obstructive pulmonary disease (COPD) and osteoporosis has been reported (1,2). In these patients, inactivity, lower sunlight exposure, smoking, use of corticosteroids, nutritional impairment and hypercatabolic effects of recurrent inflammatory exacerbations probably contribute to accelerate the decline of bone mineral density (BMD) (3). Among nutritional parameters both body weight and body mass index (BMI) were reported to be inversely correlated with BMD (4,5). Interestingly, chronically inhaled and oral corticosteroids were found to have comparable negative effects on BMD (5). In advanced COPD, acidosis might favour progressive bone loss because bone hydroxyapatite buffers hydrogen ions (6). On the other hand, metabolic rather than respiratory acidosis has been found to negatively affect BMD in some experimental models (7).

Indeed, the retention of carbon dioxide (CO\(_2\)) and, then, the generation of bicarbonates (HCO\(_3\)\(^-\)) seems to exert some protective effect on bone mass (8–13). The few available clinical studies assessing the relationship between CO\(_2\) retention and BMD provide conflicting results (14,15). Differences in length of history of COPD and in the respective prevalence of the above-reported risk factors might partially account for this disagreement. Furthermore, lack of or incomplete quantification of health-related behaviours such as smoking habits and consumption of alcohol is likely to confound the results.

The present study aims to identify the main correlates of low BMD and to verify whether, and to what extent, the acid–base balance correlates with BMD in a COPD population carefully characterized with regard to variables affecting BMD.

Methods

SUBJECTS AND DATA COLLECTION

One hundred and four patients consecutively admitted to the respiratory ward of the University Hospital in a 9-
month period for an exacerbation of COPD were enrolled in a cross-sectional study. All but 25 of these patients regularly attended the outpatient respiratory department of the same hospital. Each patient gave his/her informed consent to participate in the study. The study protocol conformed to guidelines by the local Ethical Committee.

COPD was diagnosed according to criteria provided by the American Thoracic Society (ATS) (16). Patients were studied after the resolution of acute exacerbation provided that they were in stable conditions defined as follows: performance of activities of daily living (ADL) had to be comparable to that reported to be usual for the individual patient while at home; for subjects inhaling oxygen enriched air, an arterial oxygen saturation (SaO2) of at least 90% had to be maintained with the same inspired fraction of oxygen used for oxygen therapy at home.

Criteria of exclusion from the study were: premenopausal status; previous or actual post-menopausal hormone replacement therapy or any kind of therapy, e.g. diphosphonates, or co-morbid conditions such as chronic renal failure, known to affect bone turn over; cancer and/or near terminal illness. Use of steroids and/or diuretics, which affect bone turn over, did not qualify as exclusion criterion.

The patient underwent a multi-dimensional assessment exploring the following domains:

(i) Sociodemographic: age, sex, education, occupational role before retirement defined according to Featherman and Hauser (17). (ii) Behavioural variables: previous smokers, i.e. patients who stopped smoking at least 6 months before were distinguished from actual smokers; the average number of daily smoked cigarettes was recorded and pack-years were calculated. The daily consumption of wine was rated as follows: none, less than 0.5 l, 0.5–1 l, 1 l. The number of daily smoked cigarettes was recorded. The daily consumption of wine was rated as follows: none, less than 0.5 l, 0.5–1 l, 1 l. The composition of the diet was estimated by a food-frequency questionnaire and the average daily calcium intake was assessed according to the calcium content of servings (18).

(iii) Physical function was categorized according to the Barthel scale of disability (19). This scale takes into account nine indices of self-care and six of mobility. The final score ranges between 0 and 100 (19). (iv) Cognitive function was rated by the mini-mental status (MMS) test (20). The final score ranges between 0 and 30. The cut-off value of 24 has been reported to distinguish normal from abnormal performance (20). However, in older and less educated subjects a cut-off of 21 is frequently used (21). (v) Affective status was assessed by the short form of the geriatric depression scale (GDS). This simplified form of the original scale includes 15 items; a final score greater than seven is considered to be consistent with a depressive trait (22). (vi) Co-morbid diseases were diagnosed by the assessing physician according to the International Classification of Diseases (23). A standardized index of co-morbidity was computed according to the method of Charlson et al. (24). (vii) The number and duration of courses of systemic steroid therapy and of diuretics during the last year was approximately estimated by interviewing the patient and his/her relatives or care-givers and by reviewing drug prescriptions, when available. For the 79 patients regularly attending the outpatient respiratory department information was primarily gathered from individual sheets. Patients who were administered systemic steroids and diuretics for at least 4 and 7 months, respectively, were considered to be frequent users of such drugs. (viii) Length of history of COPD was estimated by an account of historical data provided by the patient and of the available medical documentation. Given that 79 patients regularly attended the outpatient respiratory department of the same hospital, detailed historical information was available for most of the patients. (ix) Respiratory function: the patient performed a forced expiratory manoeuvre with a water-sealed computerized Baires system (Biomedin, Padova, Italy) fulfilling the ATS recommendations for diagnostic spirometry (25). Inability to meet the ATS criteria for acceptability and reproducibility was criterion for exclusion from the study. Arterial blood gases were measured with the patient breathing room air or oxygen-enriched air through a facial mask, if needed. The acid–base balance reflecting the usual condition of the patient on continuous oxygen therapy was considered to be a more reliable correlate of BMD than acid–base balance measured without oxygen supplementation. (x) Anthropometric data: weight and height were measured according to guidelines by de Groot and van Staveren and body mass index (BMI) was obtained as follows: weight (kg)/height (M)² (26). Mid-arm circumference (MAC) and triceps skin-fold (TSF) were measured with a centimeter and a John Bull skinfold caliper (British Indicator Ltd), according to Tanner (27). Mid-arm muscle circumference (MAMC) was obtained as follows: MAMC=MAC−(3.14×0.1×TSF) (28). Serum albumin and haemoglobin concentrations were measured. (xi) BMD was assessed at lumbar and femoral neck sites by double energy X-ray absorptiometry (DXA) using a Hologic Dextra QDR 2000 (Hologic, Walthman, MA, U.S.A.). In order to exclude the confounding effect of osteophytes, lateral scan of the spine was systematically performed (29).

STATISTICAL ANALYSIS

Patients were grouped according to whether they had (group O) or did not have (group N) a BMD value at the lumbar column and/or the femoral neck more than 2.5 SD below the young adult mean value. We remind the reader that this level of BMD is considered to represent the threshold for the diagnosis of osteoporosis (30). Differences between groups were assessed by a χ²-test for dichotomous variables and by a Student’s t-test or Mann–Whitney test for continuous variables according to whether the variable did, or did not have, both normal distribution and homogeneous variance, respectively (31).

Variables significantly or near significantly different between groups at the univariate analysis were entered in a logistic regression model having the presence of osteoporosis as dependent variable and adjusted for age and gender. Arterial CO₂ tension (PaCO₂) was forced into the model in order to evaluate the effect of hypercapnia on BMD. The independent variable was considered to be significantly associated with the outcome if one was not enclosed between the 95% confidence intervals (95% CI) of the odds ratio (OR) (32).
Results

Differences between groups O and N are shown in Tables 1 and 2. Groups were comparable with regard to age, gender, health-related behaviours, neuropsychological and functional status characteristics. Group N had significantly better nutritional status, as reflected by average nutritional indices such as BMI and MAC and, to a lesser extent, by indices selectively reflecting fat-free (MAMC) and fat mass (TSF). Haemoglobin and albumin concentrations were not significantly different between groups. Dynamic lung volumes and arterial blood gases did not distinguish significantly different between groups. Forced expiratory volume in 1 sec/forced vital capacity (FEV1/FVC) ratio in group N was evident. Groups also had comparable duration of COPD history, prevalence of co-morbid diseases and frequent user of steroids for any route and diuretics.

Table 3 summarizes the results of the logistic regression analysis. BMI ≤22 kg m⁻², which corresponds to the lowest quartile of BMI distribution, was identified as the only independent correlate of the outcome osteoporosis. PaCO₂ > 6·93 kPa, which selects the highest quartile of PaCO₂ distribution, lacked predictability. Both MAC and TSF, which were significantly lower in the osteoporotic group, were not entered into the logistic regression analysis in order to prevent their collinearity with BMI. Indeed, it seemed logical to test the correlative role of MAMC besides that of BMI because MAMC was the only available index of fat-free mass.

Discussion

No relationship between hypercapnia and osteoporosis was observed. This finding should be interpreted in the light of the effects that CO₂ exerts on the bone matrix and of its role as a marker of COPD severity. Indeed, increased formation of carbonated apatite has been observed in the bone exposed to a medium having high PaCO₂ (8,13). The concentration of HCO₃⁻ is a direct function of PaCO₂ and it is known that HCO₃⁻ exerts an important protective effect on the bone by preventing the release of calcium (10). Thus, increasing HCO₃⁻ concentration at constant pH results in decreased calcium efflux from the bone (10). Collaterally, chronic respiratory acidosis has been shown to enhance gut calcium absorption in the rat (13). Furthermore, several studies on cultured mouse calvarie have shown that the homeostatic role of the bone changes as a function of the metabolic or respiratory type of acidosis (8–13): chronic metabolic acidosis promotes a dramatic calcium efflux from the bone of the live calvariae, whereas

Table 1. Differences in sociodemographic, nutritional and neuropsychologic characteristics and in the level of physical independence between patients with (group O) and without (group N) osteoporosis

<table>
<thead>
<tr>
<th></th>
<th>Group O</th>
<th>Group N</th>
<th>P-value (*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>62</td>
<td>42</td>
<td>0·137</td>
</tr>
<tr>
<td>Males</td>
<td>37 (59·7)</td>
<td>31 (73·8)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>71·31 ± 7·55</td>
<td>70·24 ± 6·92</td>
<td>0·527</td>
</tr>
<tr>
<td>Years of formal education</td>
<td>7·25 ± 4·19</td>
<td>6·34 ± 3·55</td>
<td>0·671</td>
</tr>
<tr>
<td>Actual smokers</td>
<td>35 (56·4)</td>
<td>22 (52·3)</td>
<td>0·459</td>
</tr>
<tr>
<td>Pack-years of smoking</td>
<td>51·52 ± 29·27</td>
<td>56·24 ± 35·5</td>
<td>0·548</td>
</tr>
<tr>
<td>Daily wine intake</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>18 (37·5)</td>
<td>9 (32·1)</td>
<td></td>
</tr>
<tr>
<td>≤ 1/2 l</td>
<td>26 (54·2)</td>
<td>17 (60·7)</td>
<td>0·857</td>
</tr>
<tr>
<td>&gt; 1/2 l</td>
<td>4 (8·3)</td>
<td>2 (7·1)</td>
<td></td>
</tr>
<tr>
<td>Daily calcium intake (mg)</td>
<td>886·42 ± 354·14</td>
<td>731·48 ± 190·08</td>
<td>0·134</td>
</tr>
<tr>
<td>BMI (kg m⁻²)</td>
<td>24·46 ± 4·11</td>
<td>28·94 ± 4·61</td>
<td>&lt;0·0001</td>
</tr>
<tr>
<td>MAC (mm)</td>
<td>248·00 ± 30·55</td>
<td>281·52 ± 32·73</td>
<td>&lt;0·0001</td>
</tr>
<tr>
<td>MAMC (mm)</td>
<td>210·29 ± 21·03</td>
<td>228·98 ± 28·81</td>
<td>0·0037</td>
</tr>
<tr>
<td>TSF (mm)</td>
<td>13·03 ± 6·71</td>
<td>17·62 ± 9·17</td>
<td>0·0203</td>
</tr>
<tr>
<td>Serum albumin (g L⁻¹)</td>
<td>41·43 ± 3·97</td>
<td>42·77 ± 3·65</td>
<td>0·142</td>
</tr>
<tr>
<td>Hemoglobin (g L⁻¹)</td>
<td>134·36 ± 19·31</td>
<td>139·55 ± 15·48</td>
<td>0·174</td>
</tr>
<tr>
<td>GDS</td>
<td>6·17 ± 3·31</td>
<td>5·43 ± 3·42</td>
<td>0·315</td>
</tr>
<tr>
<td>MMS</td>
<td>26·84 ± 3·26</td>
<td>27·34 ± 2·23</td>
<td>0·559</td>
</tr>
<tr>
<td>Barthel index</td>
<td>80·92 ± 19·59</td>
<td>83·00 ± 20·74</td>
<td>0·641</td>
</tr>
</tbody>
</table>

Values are presented as mean ± sd or as absolute number with percentage in parentheses. BMI: body mass index; MAC: mid-arm circumference; MAMC: mid-arm muscle circumference; TSF: triceps skin-fold; GDS: geriatric depression scale; MMS: mini-mental status.

*By χ²-test for dichotomous variables and by unpaired t-test or Mann-Whitney test, as appropriate, for continuous variables.
Frequent users of systemic steroids 28 (45

Frequent users of diuretics

Abbreviations as in Tables 1 and 2.

Corresponding to the highest quartile of the distribution of BMI, FEV1/FVC and MAMC.

By \( \chi^2 \)-test for dichotomous variables and by unpaired \( t \)-test or Mann–Whitney test, as appropriate, for continuous variables.

Table 3. Logistic regression analysis having osteoporosis as outcome

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds ratio</th>
<th>95% Confidence intervals</th>
<th>Coefficient</th>
<th>Standard error</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI ( \leq 22 \text{ kg} \cdot \text{m}^{-2} )</td>
<td>4.18</td>
<td>1.19–14.71</td>
<td>1.43</td>
<td>0.64</td>
<td>0.026</td>
</tr>
<tr>
<td>( P_{aCO2} &gt; 6.93 \text{kPa} )</td>
<td>0.60</td>
<td>0.23–1.61</td>
<td>−0.50</td>
<td>0.49</td>
<td>0.313</td>
</tr>
<tr>
<td>FEV1/FVC &lt; 34%*</td>
<td>1.65</td>
<td>0.62–4.37</td>
<td>0.49</td>
<td>0.49</td>
<td>0.318</td>
</tr>
<tr>
<td>MAMC &lt; 201–34 mm*</td>
<td>1.34</td>
<td>0.55–3.26</td>
<td>0.29</td>
<td>0.45</td>
<td>0.512</td>
</tr>
<tr>
<td>Age</td>
<td>1.01</td>
<td>0.95–1.08</td>
<td>0.01</td>
<td>0.03</td>
<td>0.679</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.54</td>
<td>0.21–1.38</td>
<td>−0.61</td>
<td>0.47</td>
<td>0.199</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or as absolute number with percentage in parentheses. FVC, forced vital capacity; FEV1, forced expiratory volume in 1 sec; \( P_{aO2} \), arterial oxygen tension; \( P_{aCO2} \), arterial carbon dioxide tension; \( P_{A–aCO2} \), alveolar–arterial oxygen difference; \( \text{FiO2} \), inspired fraction of oxygen.

*Corresponding to the lowest quartile of the distribution of BMI, FEV1/FVC and MAMC.

†Corresponding to the highest quartile of the distribution of \( P_{aCO2} \).

chronic respiratory acidosis only marginally affects the calcium content of bone (6). On the other hand, hypercapnia is considered a marker of severity of COPD (33). Thus, hypercapnic patients are expected to have a longer history of COPD and of exposure to risk factors for osteoporosis clustering in COPD. The theoretical opposite effects on bone mass of \( P_{CO2} \) per se and as a marker of disease severity likely result in lack of a prevalent effect.

The direct relationship between nutritional indices and BMD confirms findings pertaining to normal populations as well as to a Japanese and an American COPD population (4,5,34,35). It is worth observing that BMI is an index of the average nutritional status, MAMC reflects lean body mass, MAC partially depends upon the width of the humeral bone and TSF is an index of fat mass. These four indices exploring different aspects of anthropometric and nutritional status were correlated with BMD. Indeed, fat tissue might benefit BMD of post-menopausal women by a direct mechanical effect and by converting androstenedione to estrone, whereas lean body mass partially depends upon testosterone levels which also increase bone mass in men (36,37). On the contrary, health outcomes could not distinguish patients with and without osteoporosis as if loss of BMD did not in parallel decline in disease-related health status (38). It should be considered that health outcomes can be considered the end result of a complex interaction among clinical, respiratory function, behavioural, psychological and social variables in conditioning quality of life. Accordingly, health outcomes do not qualify as direct indicators of disease severity, but as
'summary indicators' of the health status. This limits our understanding of their meaning and, thus, of their relationship to BMD.

The lack of independent correlates of osteoporosis besides low BMI might reflect some limitation of the retrospective assessment of health-related behaviours and/or a prevailing pathogenetic role of presently unexplored determinants of osteoporosis such as inadequate peak bone mass and genetic factors (39). A recent report on the risk of osteoporosis in asthmatic women shows that the duration of use of inhaled steroids, expressed in years, is inversely correlated with spinal BMD (40). We could not test such a relationship because information on pharmacological treatment was limited to the year prior to the study.

Furthermore, the level of physical independence, quantified by the Barthel index, does not necessarily reflect the daily physical activity, a well-recognized protective factor against loss of BMD. The recently reported lack of differences in BMD between COPD patients who were chronically administered oral or topic steroids contributes to explain BMD between COPD patients who were chronically losing BMD. The recently reported lack of differences in BMD between COPD patients who were chronically administered oral or topic steroids contributes to explain the present findings (5): the very low prevalence (15-4%) of patients free from steroid therapy through any route limits the possibility of disclosing any relationship between steroid use and BMD. These limitations might have concealed other potential correlates of BMD, but cannot throw any doubt upon the observed correlation with nutritional status.

In conclusion, poor nutritional status is a strong correlate of low BMD in COPD patients. Further research is needed to verify whether malnutrition qualifies as a generic indicator of COPD severity and/or marks a population suffering from an hypercatabolic status also involving the bone. Indeed, a well-defined pattern of cytokine production inducing hypercatabolism has been found to characterize a consistent proportion of COPD patients (41). Present results also allow us to exclude that slight to moderate hypercapnia has any effect on BMD. Attempts should be made to better define both determinants and prognostic relevance of mineral bone loss in COPD. Indeed, subjects with lumbar or femoral fractures are frequently found to suffer from COPD (42,43). However, this might reflect the higher prevalence of COPD in the elderly and the relatively old age of COPD patients rather than a causal link between COPD and fractures. The possibility that osteoporosis affects respiratory function either by increasing dorsal kyphosis or by limiting the inspiratory effort to prevent costal and vertebral pain also deserves consideration (44). Thus, the present study opens some perspective of research in a field where it is quite difficult to disentangle the complex interaction of several factors conditioning the loss of BMD.

References

31. Mann HB, Whitney DR. On a test of whether one of two variables is stochastically larger than the other. *Ann Mathem Stat* 1947; 18: 50–60.