Prevalence of vertebral fractures in patients with Chronic Obstructive Pulmonary Disease admitted to a University Hospital

Correspondence: José Luis Pérez-Castrillón - Hospital Río Hortega - C/Dulzaina, 2 - 47013 Valladolid (Spain) e-mail: castrv@terra.es

Date of receipt: 01/05/2012
Date of acceptance: 30/05/2012

Summary
Objective: Chronic obstructive pulmonary disease (COPD) is a widely distributed disease with high morbimortality, associated with important pathologies, among which is included osteoporosis. The objective of this study was to evaluate the prevalence of vertebral fractures in those patients with chronic obstructive pulmonary disease and to determine some factors which heighten the risk of fracture in these patients, especially the severity of the COPD and the use and dosage of inhaled corticoids.

Material and method: Retrospective, observational transversal study, in which were included patients admitted to the Rio Hortega University Hospital during the year 2006 diagnosed with COPD who had a lateral thoracic X-ray. A control group was included, without COPD, of similar age and sex, admitted to the internal medicine service over the same period. The vertebral fracture was determined using Morphoxpress®.

Results: 115 patients with COPD and 87 control patients were included, with a higher prevalence of vertebral fractures in being observed in patients with COPD, although without there being a statistically significant difference with respect to the control group. However, if we consider only the moderate-severe fractures (Gennant Type II and III), there is a greater prevalence, which is related to the severity of the disease, measured by the decrease in FEV1 (Forced expiratory volume in one second). We found no relationship between the prevalence of fractures, the different types of treatment and the morbidity determined by the number of admissions.

Conclusions: Our study shows the tendency of patients with COPD to have an increased prevalence of vertebral fractures which are associated with the severity of the COPD and the seriousness of the fractures themselves. We found no relationship between the different inhaled corticoids, individually or grouped, and the presence of fractures. Nor did we find a relationship between the number of vertebral fractures and the number of flare-ups, treatment with broncodilators, corticoids, home oxygen therapy, or the diagnosis of, or previous treatment for, osteoporosis.

Key words: COPD, osteoporosis, vertebral fractures, Morphoxpress®.
Introduction

Chronic obstructive pulmonary disease (COPD) is a widely distributed disease and with high morbidity-mortality, principally associated with smoking, over and above the susceptibility of an individual to develop the disease. It is a chronic disease which brings with it significant comorbidities, among which is osteoporosis.

Both the age at which it develops, and the habit of smoking itself, and the systemic and inflammatory effects of the disease have an influence on the presence of a high risk of fracture, but it is, possibly, the use of corticoids in its treatment which is the most important factor in this association.

According to current guidelines, the treatment of COPD is based on the use of $\beta_2$-adrenergics of short and long duration and anticholinergics, which improve the quality of life and tolerance of exercise, and reduce exacerbations. The inhaled corticoids are added to the former in patients with moderate to severe COPD. They have been shown to reduce the frequency of exacerbations and to improve quality of life, above all combined with $\beta_2$-adrenergics, this being more effective than each of them separately. Oral corticoids are used in patients with severely exacerbated COPD, for a short period of time.

The presence of fractures in patients with COPD results in limitations to physical activity, sedentariness and the necessity for elderly nursing care. From the respiratory point of view, the thoracic vertebral fractures result in a reduction in lung volume which causes a restrictive ventilatory defect, with a reduction in forced vital capacity of up to 96%, an effect which is seen to be increased by the pain which accompanies it. However, although the role which oral corticoids play in osteoporosis and the risk of fracture in COPD has been widely demonstrated, it is not so clear to what extent the inhaled corticoids have similar effects on the bone.

The aim of this study was to evaluate the prevalence of vertebral fractures in those patients with chronic obstructive pulmonary disease, and to attempt to determine which factors cause the risk of fracture in these patients, especially the severity of the COPD and the use and dosage of inhaled corticoids.

Material and methods

A retrospective, observational transverse study was carried out in which were included patients admitted to the Río Hortega University Hospital during the year 2006, diagnosed with COPD, older than 40 years of age, and who in the 4 months previous to their admission had had a baseline lateral thoracic X-ray and arterial gasometry. None of the patients were excluded due to the poor quality of the thoracic X-ray. The control group was obtained from patients admitted in the same year who had had a lateral thoracic X-ray in the previous 4 months, and who had not been diagnosed with COPD, or previously been in treatment with inhaled or oral corticoids. In both groups, those whose thoracic X-ray was not sufficiently clear for the measurement of vertebral crushing fractures, or who had degenerative disease or spinal deformities, were excluded.

The data evaluated in the patients and controls were: age, sex, smoking habit (non-smoker, ex-smoker, active smoker), previous diagnosis of osteoporosis and, in the case of the affirmative, the treatment followed, and the existence of earlier fractures. The patients with COPD were classified as a function of their FEV1 (forced expiratory volume in 1 second) as light (FEV1>80%), moderate (FEV1 60-80%) and severe (FEV1<60%), and the number of admissions due to the exacerbation of COPD over the 5 years up to 2006 was recorded. The treatments carried out at admission, especially bronchodilators and inhaled and oral corticoids were recorded, differentiating the different types of inhales corticoids (fluticasone, budesonide, beclamethasone), the daily dose of each of them and the number of courses of oral corticoids in the last year.

The presence of vertebral fractures was measured using the Morphoxpress® fracture detection programme, a software package which allows the detection of vertebral fractures through original digitised lateral X-rays. The analysis of the fractures is initiated manually, by marking up the upper and lower corners of the anterior and posterior walls of the vertebrae situated immediately above and below the vertebra to be evaluated.

Subsequently, the system analyses automatically the distances marked between these points and marks on the vertebra the evaluation of the corners of the anterior and posterior walls it has calculated. The marking of the points is carried out by the observer and by the system itself independently, subsequently comparing both measurements. The difference corresponds to the degree of crushing or fracture of the vertebra studied. The fractures found are classified according to the Genant classification as light or grade I (20-25%), moderate or grade II (25-30%) and severe or grade III (>40%).

Statistical analysis.

The database was established and its analysis carried out using the SPSS v15.0 statistical programme officially licensed to the University of Valladolid.

The continuous variables were described as mean ± ND (normal distribution), and the qualitative variables as frequencies and percentages. The Kolmogorov-Smirnov test was used to determine the normality of the distribution. To study the association between qualitative variables the Chi-squared test was used with the Fisher’s exact test or verisimilitude ratio when the conditions required it. To study the differences between the means, parametric or non-parametric statistical tests were used as required by the conditions which applied (Student’s t, Mann-Witney U, ANOVA with the Bonferroni post-hoc test, Kruskal-Wallis). The level of significance was considered to be at $p < 0.05$. 
Results
115 patients with COPD and 87 control patients were included, with comparable average ages (73 ± 11 years vs 74 ± 10 years, p>0.05) and with an age range of between 40 and 90 years. Of the 115 patients with COPD included, 8 (7%) were women, all postmenopausal, and 107 (93%) men. The controls had a similar distribution by sex. The majority (70%) were ex-smokers and only 8 (16%) continued to smoke. Only 5 (4.3%) had been diagnosed with osteoporosis, and 4 (3.5% of the total) had received treatment with calcium, vitamin D or bisphosphonates. The presence of previous fractures were found in the personal histories of 11 patients.

46 (40%) of the patients did not have a previous spirometry recorded, for whom it was not possible to determine the severity of their COPD. Of the remainder, 49 (43%) had a severe form, 10 (17.5%) moderate and 10 (17.5%) light. This admission was their first in the last 5 years for 48 (42%) patients, while 39 (34%) had been admitted due to exacerbation on 3 or more occasions over the same period of time.

Most of the patients were receiving treatment with beta-blockers and inhaled corticoids, 84 (73%) with beta-blockers and 81 (70%) with inhaled corticoids. Among the corticoids analysed only 2 patients (2%) were in treatment with beclamethasone, while 18 (16%) were taking budesonide, and 61 (53%) fluticasone. There were 54 patients (30%) who did not have, or could not recall having had, treatments with inhaled corticoids. With respect to the dosage, 11 (73%) were taking more than 400 µg daily of budesonide and 42 (70%), more than 500 µg of fluticasone. In the previous year, 43 (37%) received at least a course of oral corticoids and 32 (28%) had previously had domiciliary oxygenotherapy.

There were 50 patients with COPD with at least one fracture, as opposed to 29 in the control group (43.5% vs 33%), with no statistically significant differences (p=0.14), the total number of fractures being 79 (39%). 64% of those patients with COPD had a single fracture as opposed to 70% in the control group. In analysing the fractures as a function of their severity, significant differences were found between the two groups. The patients with COPD had a greater number of moderate or severe fractures, while light fracture predominated in the control group. The results appear in Table 1.

The severity of the COPD was a determining factor in the frequency of fractures; there was 1 fracture in patients with light COPD (2%), 6 in patients with moderate COPD (12%) and 24 in those patients with severe COPD (49%), the intergroup differences being statistically significant, p<0.05 (Figure 1). No differences were observed in the number of fractures with the taking of inhaled corticoids, their dosage, number of exacerbations, domiciliary oxygenotherapy and previous diagnosis of osteoporosis (Table 2).

Discussion
Our study shows a high prevalence of vertebral fractures in patients with COPD, although without seeing statistically significant differences with the control group made up of patients admitted to the internal medicine department without COPD. However, if we only consider moderate-severe fractures (Gennant Type II and III), there is a higher prevalence which is related to the severity of the disease, measured by the decrease in FEV1. We did not find a relationship between the prevalence of fractures, the various types of treatment and the morbidity determined by the number of admissions. The prevalence of vertebral fractures is higher than that observed in other recently published series8,9, although, if we exclusively consider moderate or severe COPD, it is similar. Recently, in a population of Spanish COPD patients the risk of fracture has been determined using the FRAX® tool. This study showed the risk of a major osteoporotic fracture at 10 years of 1.8% (CI 95% 0.9-3.6). Major osteoporotic fractures include vertebral fractures, and our data suggests a higher prevalence of this type of fracture, which probably means that in this population the FRAX® tool underestimates the risk of fracture, similar data to that observed in the Spanish osteoporotic population.

A greater prevalence of fractures in patients with COPD has been related to a variety of factors associated with the disease. Tobacco smoking is associated with a reduction in bone mineral density both in active smokers and in ex-smokers10,11. Given that women appear to be more susceptible to the negative effects of tobacco on the lungs2, the increase in the number of women smokers and their susceptibility to osteoporosis after menopause gives them a greater propensity to bone problems. Secondly, as happens with other chronic diseases, patients with COPD have higher levels of inactivity and weight loss, and a deficit in calcium and vitamin D, accentuated by a lack of exposure to sun, factors with which are associated a higher risk of osteoporosis and fractures12,13. Lastly, it has been suggested that the systemic effects of the disease itself may play a part in the bone damage which occurs in patients with COPD14.

These systemic effects would be related to pro-inflammatory cytokines and active inflammatory cells which would reach the bloodstream from the lungs and would intervene in bone turnover, either expressing or secreting the receptor activator of NF-κB ligand, either by producing cytokines (TNF-α and interleukins) which activate bone remodelling independently of the osteoblasts, or by the modification of the enzymes responsible intracellular metabolism of the corticoids, increasing their transformation into their active metabolites17,18.

It has been estimated that the prevalence of osteoporosis in patients with COPD who have not taken corticoids is twice as high as in healthy subjects and asthmatic patients19. This makes COPD a possible independent risk factor for a reduction in bone mineral density20, and for vertebral21 and hip22 fractures.
Although in our study we did not find a statistically significant relationship, a tendency was observed to a higher number of fractures in patients with COPD than in the controls. It is possible that the lack of statistical significance bears some relation to the high prevalence of fractures in the control group. However, this relationship becomes significant if the patients with COPD are grouped according to its severity. It was seen that the most severely affected patients had more fractures, a relationship which had been observed before23, this association being much higher among the men24. In addition, it was observed in our study that the severity of the fractures also increased with the severity of the COPD, such that the moderate and severe fractures are more frequent among those patients with COPD than in the control group, thus confirming other results25.

The factors which influence these results, leaving aside the systemic and inflammatory effects of the disease itself, which will be more intense the greater the severity of the COPD, could be related to the corticoid treatment. This supposes that those patients included with the most severe degree of the disease have required treatment with inhaled and oral corticoids more frequently in response to a higher number of exacerbations.

Our study tried to demonstrate a relationship between the taking of inhaled corticoids and the prevalence of vertebral fractures, independently of the severity of the disease and, above all, of the taking of oral corticoids. This relationship is a current cause of concern, given that the use of inhaled corticoids in COPD has become widespread since it has been demonstrated to improve the quality of life and reduce the frequency of exacerbations, and even more if it is associated with β-adrenergics and used as an underlying treatment. There are numerous studies on this subject in which it is not clear that the taking of inhaled corticoids significantly increases the risk of fracture, or increases the likelihood of osteoporosis. On the one hand, most studies do not hold that inhaled corticoids have an effect on osteoporosis, or on the risk of fractures. In 2003, Rich et al.26 made a systematic review of studies carried out of this relationship to date. Firstly, they found that there was a significant relationship between the pharmacological dose of inhaled corticoids and a reduction in bone mineral density in the lumbar region and the femoral neck in studies lasting at least two years, and that this relationship was much stronger with high doses of inhaled corticoids and with greater periods of exposure. However, the same study concluded that, generally, there were no data which related the taking of inhaled corticoids and the risk of fracture, giving greater significance to other associated factors, such as the presence of previous fractures.

Table 1. Prevalence of fractures in COPD and control

<table>
<thead>
<tr>
<th></th>
<th>COPD</th>
<th>Control</th>
<th>Signification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total fractures</td>
<td>50 (56.5%)</td>
<td>29 (66.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>Minor fractures</td>
<td>17 (34%)</td>
<td>22 (33%)</td>
<td>NS</td>
</tr>
<tr>
<td>Moderate-severe fractures</td>
<td>27 (54%)</td>
<td>6 (21%)</td>
<td>p&lt;0.05</td>
</tr>
</tbody>
</table>

Table 2. Prevalence of fractures according to treatment

<table>
<thead>
<tr>
<th></th>
<th>No Fracture</th>
<th>Fracture</th>
<th>Signification</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Oxygenotherapy</td>
<td>51 (61.4%)</td>
<td>32 (38.6%)</td>
<td>NS</td>
</tr>
<tr>
<td>Oxygenotherapy</td>
<td>14 (43.8%)</td>
<td>18 (56.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>No 2-inhaled</td>
<td>20 (64.5%)</td>
<td>11 (35.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>2-inhaled</td>
<td>45 (53.6%)</td>
<td>39 (46.4%)</td>
<td>NS</td>
</tr>
<tr>
<td>No budesonide inhaled</td>
<td>56 (57.7%)</td>
<td>41 (42.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Budesonide inhaled</td>
<td>9 (50%)</td>
<td>9 (50%)</td>
<td>NS</td>
</tr>
<tr>
<td>No Fluticasone inhaled</td>
<td>32 (59.3%)</td>
<td>22 (40.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>Fluticasone inhaled</td>
<td>33 (54.1%)</td>
<td>28 (45.9%)</td>
<td>NS</td>
</tr>
<tr>
<td>No Oral Corticosteroids</td>
<td>43 (59.7%)</td>
<td>29 (40.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Oral Corticosteroids</td>
<td>22 (51.2%)</td>
<td>21 (48.8%)</td>
<td>NS</td>
</tr>
</tbody>
</table>
the earlier diagnosis of osteoporosis and advanced age. In terms of the classes of inhaled corticoids studied, the meta-analysis indicates that triamcinolone is the one which is most associated with bone mineral loss, followed by beclamethasone and budesonide, with no data in this study for fluticasone. Other studies have confirmed these data. Johannes et al. found no relationship between the taking of inhaled corticoids and the presence on non-vertebral fractures, independently of the corticoid inhaled and the dose used. Nor did Nuti et al. find any relationship between the taking of inhaled corticoids and the risk of vertebral or non-vertebral fractures. However, not all the data are uniform; other studies affirm that there is a relationship, and that it occurs at high doses inhaled corticoids. Hubbard et al. describe an association between the taking of inhaled corticoids and the risk of fracture, independently of other factors, such as the taking of oral corticoids, the severity of the COPD, the use of bronchodilators and daily physical activity, but dependent on the dosage. And Pujade et al. found small increases (not significant) in the risk of fracture associated with high doses of corticoids which were independent of the degree of COPD and the taking of oral corticoids. However, this relationship does not always appear to be dose dependent, or this is lost when the data are adjusted for other confusion factors such as the severity of the COPD and the class of bronchodilator. In addition, the clinical significance of the effect of high doses of inhaled corticoids on the prevalence of vertebral fractures does not appear to be much higher than that of other risk factors such as the taking of antipsychotic or hypnotic medication, low body mass index, cerebrovascular disease and active tobacco smoking.

In our study we also observed no association between the taking of inhaled corticoids and the prevalence of vertebral fractures, a fact that remains when the corticosteroids are grouped by class or dose. In terms of the other treatments which may have an influence on the higher presence of vertebral fractures in patients with COPD, what is notable is the absence of an association between the taking of oral corticoids and the incidence of fractures, a fact widely illustrated in the literature. This may be due principally to the short time period over which the data has been collected, which means a lack of knowledge about the quality of corticoids taken previously.

It should also be highlighted that no association was found between the taking of β-adrenergics and the incidence of fractures. It has been found that the overstimulation of the adrenergic system is related to a low level of bone mineral density and greater bone fragility, which is produced by the activation of the β-adrenergic receptors in the osteoblasts, which increase the production of the receptor activator of NF-κB ligand and encourage the activation of the osteoclasts, above all salbutamol. On the other hand, two recent studies have concluded that the risk of fracture associated with the β-adrenergics diminishes when adjusted for the use of oral corticoids and the severity of the disease, and that, in any case, this risk is higher for the oral β-adrenergics, and at low doses.

There are various limiting factors which may also influence the results. Firstly, the fact that the population selected has a wide spread of ages (of between 40 and 90 years, with an average of 77 years). Secondly, the absence of more complete information from the data collected. There is little data related to the style and quality of life of the subjects, such as daily physical activity, nutrition and exposure to sun. The lack of more exhaustive data in relation to the quantity of inhaled or oral corticoids taken previously, and the loss of subjects due to missing data, mainly regarding the severity of the COPD and due to the lack of knowledge of any treatments at the time of their inclusion in the study, reduced the sample size. This would explain why no association was found between the prevalence of vertebral fractures and oral corticoids, or between the prevalence of vertebral fractures and domiciliary oxygenotherapy, which is usually associated with the severity of the COPD. The control group is not a healthy group, but is formed of patients admitted to the internal medicine service for other reasons, which may explain its high prevalence of vertebral fractures. Finally, the fact that the vertebral fractures were quantified using the Morphoxpress® system gives the study greater objectivity, but it does not rule out the fact that the diagnosis is still dependent on the skill of the observer.

In conclusion, our study shows the tendency of patients with COPD to have an increased prevalence of vertebral fractures, these being associated with the severity of the COPD and the seriousness of the vertebral fractures themselves. We found no relationship between the different inhaled corticoids, individually or grouped, and the presence of fractures. Nor did we find a relationship between the number of vertebral fractures and the number of exacerbations, treatment with bronchodila-
tors, corticoids, long term domiciliary oxygenotherapy or the earlier diagnosis and treatment of osteoporosis. Given the consequences of these fractures on the morbimortality of the COPD, a more aggressive approach on the part of the clinician to the diagnosis and treatment of osteoporosis in this population is necessary.

Bibliography


