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Effect of Inhaled Glucocorticoids and β_2 Agonists on Vertebral Fracture Risk in COPD Patients: The EOLO Study

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Abstract Although inhaled glucocorticoids (GCs) and β_2 agonists are being more frequently prescribed in the management of chronic obstructive pulmonary disease (COPD), their role in the impairment of bone status and in fracture risk remains controversial. This study aimed to evaluate whether the dose of inhaled GCs and β_2 agonists may independently influence bone status and vertebral fracture risk in COPD patients aged 50 years or over. COPD severity, presence of vertebral fractures on lateral chest X-ray, and bone status by quantitative ultrasound (QUS) at the calcaneus were evaluated. The risk of vertebral fractures was significantly increased in patients taking the highest daily dose (>1,500 μg) of inhaled GCs (OR = 1.4, CI 1.04–1.89). The highest dose of inhaled GCs was significantly associated with low values of stiffness index (OR = 1.74, CI 1.03–2.94). Inhaled β_2 agonists were not associated either with increased risk of vertebral fracture or with reduced values of stiffness. Moreover, the risk of fractures was markedly increased in patients with very severe or severe COPD (OR = 2.05, CI 1.28–3.28, and OR = 1.40, CI 1.06–1.82, respectively). In conclusion, in COPD patients high doses of inhaled GCs, but not β_2 agonists, are associated with an increased risk of vertebral fractures and a reduction of QUS at the calcaneus.

Keywords Vertebral fracture · Inhaled glucocorticoid · β_2 agonist · COPD · QUS

Chronic obstructive pulmonary disease (COPD) is, and will increasingly be, a major cause of morbidity and mortality worldwide. In the United States, COPD is the fourth leading cause of death in older adults and, by 2020, it is projected to be the third leading cause of death for both men and women [1]. COPD is now considered a multicomponent disease, and attention has focused on the role of comorbidities in determining disease severity in individual patients [2]. Among the comorbidities associated with COPD, osteoporosis is believed to affect 36–60% of patients who are suffering from this chronic lung disease [3–5]. Moreover, several studies have reported that in COPD patients the risk of osteoporosis is related to the severity of COPD [6, 7]. The occurrence of fractures as a consequence of osteoporosis can contribute to disability and mortality of patients with COPD and add to the economic burden associated with the disease [3, 8, 9].

It is unknown whether osteoporosis in COPD is due to its systemic nature, to physical limitations, or to pharmacological interventions. One of the most obvious causes of osteoporosis in COPD patients is treatment with glucocorticoids (GCs), both as systemic therapy and as inhaled GCs [3]. Many studies have reported that oral GCs represent a proven risk factor for osteoporosis and fractures [10]. Moreover, in a comprehensive meta-analysis van Staa et al. [11] found strong correlations between GC cumulative dose and bone loss and between GC daily dose and risk of fracture. Although inhaled GCs are being more frequently

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prescribed in the management of COPD, their role in the impairment of bone status and in fracture risk remains controversial [12, 13].

Observational, randomized, placebo-controlled, and systematic review studies have reported that inhaled GCs are associated with an increased risk of osteoporosis and fractures [14–17]. Another recent case–control study of people with COPD reported a small increase in fracture risk associated with the use of inhaled GCs, particularly at daily doses exceeding 1,600 μg [18]. However, this relationship has not been confirmed in all other studies [4, 19, 20]. In particular, a recent meta-analysis of 13 studies reported no association between use of inhaled GCs and fractures in older adults, even though a slight increase in risk was seen in those using high dosages [21]. The main reasons for these inconsistent data about the relationship between inhaled GCs and the risk of osteoporosis and fragility fracture risk in COPD patients may be due to the heterogeneity of the populations considered, to the large diversity in methods used for COPD severity assessment, and, above all, to the fact that in the majority of the above-mentioned studies fractures were self-reported. The aim of the present study was to evaluate whether the dose of inhaled GCs and β_2 agonists may influence bone status and vertebral fracture risk in a large and homogeneous cohort of Italian COPD patients who were participating in the Evaluation of Obstructive Lung Disease and Osteoporosis (EOLO) study.

Materials and Methods

Study Population

The EOLO study has been described in detail elsewhere [7]. Briefly, EOLO is a multicenter, observational epidemiological study, carried out in 57 Italian outpatient pneumological centers. The centers were located in both academic and nonacademic general hospitals equipped with facilities for the diagnosis of osteoporosis. In each center, between January and December 2005, experienced clinicians recruited up to 80 consecutive ambulatory outpatients (males and postmenopausal females), aged 50 years or over, referred by their family physicians for a programmed evaluation of their COPD.

Patients were included if they had a forced expiratory volume of 1 second (FEV_1)/forced vital capacity (FVC) ratio <70%, no changes in COPD treatment during the previous 2 months, and a lateral chest X-ray taken at the moment of the inclusion visit or during the preceding 2 months. Patients were excluded if their chest X-ray was prompted by physical trauma or if they had known or suspected malignancy, severe hepatic or renal disease, marked scoliosis, or moderate–severe cognitive impairment. Other exclusion criteria were surgical menopause, history of alcohol abuse (>400 g/week), and intake of drugs known to interfere with calcium metabolism such as anticonvulsants, heparin, anabolic steroids, gonadic hormones, and vitamin D and its metabolites. Patients who had taken bisphosphonates, strontium ranelate, or teriparatide were also excluded. Each patient underwent a structured medical interview (including detailed questions on any drugs taken for the treatment of COPD, smoking history, concomitant diseases, etc.), weight and height measurement, and pulmonary function evaluation. Information about GC therapy (dosages, route of administration, years of use) was collected from patient interviews and medical records.

A total of 3,030 eligible COPD patients, 1,768 men and 1,262 women (mean age 69.9 ± 8.8 years), were analyzed. Of COPD patients, 68.5% were treated with glucocorticoids (55.1% inhaled GCs, 3.9% oral GCs, and 9.5% oral + inhaled GCs), 16.7% were not treated with specific COPD medications, and the remaining 14.8% were treated with short- or long-acting β_2 agonists, xanthines, and antimuscarinics but not with GCs. In order to standardize the inhaled GC dose, all inhaled GCs were expressed as beclometasone equivalents [22, 23]. Accordingly, the equivalent doses for inhaled GCs are beclomethasone 100 μg, budesonide 80 μg, fluticasone 50 μg, and triamcinolone 200 μg [23]. The short-acting β_2 agonists (albuterol, fenoterol) and the long-acting β_2 agonists (salmeterol and formeterol) were considered separately. Then, we expressed the daily dosage of β_2 agonists in each individual patient as albuterol equivalents. All patients gave written informed consent to participate, and approval for the study was obtained from the local ethics committee.

Methods

COPD patients were classified into stages I–IV in accordance with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [1]. The classification is based on postbronchodilator FEV_1. In stage I (mild COPD) FEV_1 is ≥80% of predicted values. In stage II (moderate COPD) FEV_1 is 50–80% of predicted values. In stage III (severe COPD) FEV_1 is 30–50% of predicted values. In stage IV (very severe COPD) FEV_1 is <30% or <50% plus chronic respiratory failure [1].

Vertebral fractures on lateral chest X-ray were assessed by the physicians of the osteoporosis center of each hospital using dedicated software for quantitative morphometry (MorphoXpress, Egham, UK). The characteristics and performances of MorphoXpress have been reported in detail by one of the authors (G. G.) [24].

In 41 of the 57 centers it was possible to carry out an evaluation of bone status using quantitative ultrasonography (QUS; Achilles Apparatus; GE-Lunar, Madison, WI).

Broadband ultrasound attenuation (BUA) and speed of sound (SOS) were measured. Stiffness index (SI), a composite parameter obtained by a mathematical combination of BUA and SOS, was calculated by the software of the device and expressed as a percentage of values for young subjects. Because no universally accepted thresholds exist for stiffness, we used the thresholds indicated in the official positions of the International Society of Clinical Densitometry [25]. Therefore, patients were divided into three groups: low risk of having osteoporosis (stiffness $\geq$ 78%), high risk of having osteoporosis (stiffness $<$ 57%), and moderate risk of having osteoporosis (stiffness 57–77%). The mean coefficient of variation for SI was 1.7% (range 1.2–2.1%).

Statistical Analysis

The descriptive analysis of the study population and of the study parameters was carried out by considering mean and standard deviation (SD) or frequency.

For data not normally distributed, the nonparametric Kruskal–Wallis procedure was used to test the hypothesis that the means of quantitative variables were not significantly different across the different groups, while the extended Mantel–Haenszel Chi-squared test was used to test for trends in proportions.

The extent to which inhaled GC treatment and β_2 agonists were independently associated with SI and vertebral fractures, respectively, was evaluated by separate multiple logistic regression analyses. We assumed the dose of inhaled GCs and β_2 agonists as independent exposures and age, sex, BMI, and COPD severity as control variables. The odds ratio (OR) estimates for each variable and their confidence intervals (95% CIs), along with the P value and corresponding degree of freedom (Wald Chi-squared test statistics), were given for the two outcomes. $P < 0.05$ (two-sided) was considered statistically significant. Analyses were carried out in SPSS 16.00 (SPSS, Inc., Chicago, IL).

Results

Table 1 shows the clinical characteristics of those COPD patients treated with inhaled GCs (n = 1,664), not treated with specific COPD medications (n = 509), or treated with other COPD medication but not with GCs (n = 449). COPD patients treated with oral GCs and oral + inhaled GCs were not considered in this study. No differences in gender distribution and in BMI values were observed, whereas COPD patients not treated with specific medications were significantly younger. As reported in Table 1, the SI values were significantly different in the three treatment groups, with the lowest value in COPD patients treated with inhaled GCs (=75%) and the highest in those not treated with specific medications for COPD (=78.9%).

Table 1 Demographic and clinical features of the study population

	No treatment	Inhaled GCs	Other treatment[a]
n (M/F)	509 (274/235)	1,664 (954/710)	449 (270/179)
Age (years)*	68.0 ± 8.5	70.4 ± 8.1	71.5 ± 7.8
BMI (kg/m^2)	27.4 ± 4.7	27.3 ± 4.8	27.2 ± 4.5
Stiffness (%)*	78.9 ± 18.2	75.0 ± 18.6	76.6 ± 17.7
Fractures			
No	67.7	57.4	58.2
Yes	32.3	42.6	41.8
COPD severity			
Mild	40.3	19.0	19.4
Moderate	45.6	48.5	52.6
Severe	12.4	27.2	25.8
Very severe	1.8	5.3	2.2
COPD duration			
≤1 year	23.6	8.9	24.8
1–5 years	44.2	32.6	31.2
>5 years	32.2	58.4	44.0
Smoking status			
Nonsmokers	35.4	29.3	31.6
Smokers	23.2	14.0	17.4
Ex-smokers	41.5	56.7	51.0

Values are expressed as mean ± SD or prevalence rate (%) by treatment group

[a] Includes subjects treated with short- or long-acting β_2 agonists, xanthines, and antimuscarinics but not with GCs

* Kruskal–Wallis nonparametric test: age $P < 0.001$, stiffness $P = 0.006$

In Table 2, COPD patients treated with inhaled GCs were categorized into the following daily dose groups of beclometasone or equivalent: ≤750 μg (group 1), 751–1,500 μg (group 2), and >1,500 μg (group 3). The prevalence rates of vertebral fractures increased in patients taking higher daily doses of inhaled GCs. As expected, the mean daily dose of β_2 agonists was lower in group 1 (371.2 ± 164.6 μg) than in groups 2 and 3 (402.9 ± 159.9 μg and 410.2 ± 146.8 μg, respectively). Concerning the evaluation of bone status by QUS at the calcaneus, stiffness was higher in the patients of group 1 (76.0%) with respect to those of groups 2 and 3 (74.4 % and 73.9%, respectively) (Table 2).

As reported in Table 3, the risk of vertebral fractures was significantly increased in patients taking the highest dose (>1,500 μg) of inhaled GCs (OR = 1.4, CI 1.04–1.89). The use of inhaled GCs at doses ranging from 751 to 1,500 μg was associated with a positive, but not significant, increase in vertebral fracture risk. On the contrary, different daily doses of β_2 agonists were not associated with an

Table 2 Demographic and clinical features of COPD patients treated with inhaled GCs by average daily dose

	Inhaled GCs ≤ 750 μg	750 < Inhaled GCs ≤ 1,500 μg	Inhaled GCs > 1,500 μg
n (M/F)[a]	392 (219/173)	560 (318/242)	651 (381/270)
Age (years)	69.8 ± 8.5	70.8 ± 8.0	70.4 ± 7.9
BMI (kg/m^2)	27.4 ± 5.1	26.9 ± 4.7	26.9 ± 4.7
β_2 agonists (μg/day)*	371.2 ± 164.6	402.9 ± 159.9	410.2 ± 146.8
Stiffness (%)	76.0 ± 19.7	74.4 ± 18.1	73.9 ± 18.4
Fractures**			
No	60.1	58.1	54.0
Yes	39.9	41.9	46.0
COPD severity			
Mild	21.2	20.9	16.3
Moderate	47.2	46.6	50.2
Severe	24.7	28.0	28.3
Very severe	6.9	4.5	5.2
COPD duration**			
≤1 year	11.3	6.4	9.9
1–5 years	35.2	34.9	29.6
>5 years	53.5	58.7	60.6
Smoking status			
Nonsmokers	32.7	28.7	27.4
Smokers	15.3	15.3	12.2
Ex-smokers	51.9	56.0	60.40

Values are expressed as mean ± SD or prevalence rate (%) by inhaled GC dose

[a] Analysis was carried out on 1,603 patients; 61 subjects were discharged for inadequate chest X-ray quality or incomplete reporting of the treatment

* Kruskal–Wallis nonparametric test β_2 agonists $P = 0.003$

** Chi-square for trend: fractures ("No" as reference category, $P = 0.048$); COPD duration ("≤5 years" as reference category, $P = 0.033$)

increased risk of vertebral fractures. Moreover, the risk of vertebral fractures was markedly increased in patients with very severe or severe COPD (OR = 2.05, CI 1.28–3.28, and OR = 1.40, CI 1.06–1.82, respectively) (Table 3).

Only the highest dose of inhaled GCs was significantly associated with low values of SI (OR = 1.74, CI 1.03–2.94), while no significant associations were found between β_2 agonists and high risk of osteoporosis (Table 4). Moreover, both age and female gender were significantly associated with a high risk of osteoporosis. Patients with very severe COPD were about three times more likely to have a high risk of osteoporosis (OR = 3.08, CI 1.50–6.33), whereas the association of severe COPD with high risk of osteoporosis was positive but not significant (Table 4).

Discussion

Our findings add to the evidence that in COPD patients the use of inhaled GCs is associated with an increase in vertebral fracture risk, particularly at higher doses. Previous long-term trials evaluating the effects of inhaled GCs on BMD have produced conflicting results. In the Lung Health Study the use of inhaled triamcinolone was associated with a 2% reduction of BMD at the femoral neck over 3 years compared with placebo [15]. On the other hand, no significant differences in femoral or lumbar BMD were found following 3 years of inhaled budesonide [19]. In the TORCH study, inhaled GC therapy alone or in combination with long-acting β_2 agonists had no significant impact on BMD over a 3-year period compared with placebo [4]. In addition, a recent Dutch study by Graat-Verboom et al. [5] did not find GC treatment to be a risk factor for osteoporosis after correcting for several confounders. The fact that many studies have included both asthmatic and COPD patients seems to be the main reason for these inconsistent findings; in fact, in COPD patients the doses of inhaled GCs are generally markedly higher than those used in asthma. Moreover, in COPD patients there is a higher prevalence of osteoporosis with respect to asthmatic patients, which may be due to the fact that in COPD lung function remains continuously decreased [2]. Other factors, such as higher cigarette smoking, hypercapnia, and lower BMI in patients with COPD than in those with asthma, may

Table 3 Association of selected clinical variables with vertebral fractures: Wald chi-squared statistics (degrees of freedom [DF] and *P* values)

	Fractures vs. no fractures			
	OR	95% CI	*P*	DF
Age (years)	1.03	1.02–1.05	<0.001	1
Gender (M/F)	0.93	0.78–1.13	n.s.	1
BMI (<26.7 kg/m^2)	1.28	1.07–1.54	0.008	1
COPD severity				
Very severe	2.05	1.28–3.28	0.003	
Severe	1.40	1.06–1.82	0.017	
Moderate	1.29	1.01–1.62	0.03	
Mild	1.00			3
lnhaled GCs (μg/day)				
GCs > 1,500	1.40	1.04–1.89	0.03	
750 < GCs ≤ 1,500	1.36	0.93–1.72	n.s.	
GCs ≤ 750	1.26	0.98–1.89	n.s.	
No treatment	1.00			3
Inhaled β_2 agonists (μg/day)				
>400	0.93	0.69–1.25	n.s.	
≤400	1.00			1

This model includes 2,073 patients

Multiple logistic model adjusted for age, gender, BMI, and COPD severity

Table 4 Association of selected clinical variables with SI: Wald chi-squared statistics (degrees of freedom [DF] and *P* values)

	High risk vs. low/moderate risk[a]			
	OR	95% CI	*P*	DF
Age (years)	1.06	1.04–1.08	<0.001	1
Gender (M/F)	0.55	0.39–078	<0.001	1
BMI (<26.7 kg/m^2)	1.17	0.85–1.61	n.s.	1
COPD severity				
Very severe	3.08	1.50–6.33	0.002	
Severe	1.45	0.91–2.31	n.s.	
Moderate	1.13	0.76–1.69	n.s.	
Mild	1.00			3
Inhaled GCs (μg/day)				
GCs > 1,500	1.74	1.03–2.94	0.041	
750 < GCs ≤ 1,500	1.32	0.75–2.33	n.s.	
GCs < 750	1.40	0.81–2.48	n.s.	
No treatment	1.00			3
Inhaled β_2 agonists (μg/day)				
>400	1.27	0.75–2.14	n.s.	
≤400	1.00			1

This model includes COPD patients treated with inhaled GCs or on no specific treatment who underwent QUS evaluation ($n = 1{,}538$). Multiple logistic model adjusted for age, gender, BMI, and COPD severity

[a] Reference: high risk (stiffness < 57%) vs. low/moderate risk (stiffness ≥ 57%)

also contribute [26]. To date, also the association between inhaled GCs and fracture risk remains unclear. Van Staa et al. [12] reported that the risk of hip fracture was significantly associated with the use of inhaled GCs at doses >1,600 μg/daily. In a Canadian case–control study, there was a dose–response relationship between inhaled GC use and fractures but there were concurrent contributions by both oral GC exposure and inhaled β_2 agonists [23]. Recently, data from the TORCH study showed no significant increase in the incidence of fractures with inhaled GC use, either alone or in combination with LABA [4]. However, in the study by Ferguson et al. [4] no systematic radiological assessments were carried out, and this could have impeded the diagnosis of the majority of vertebral fractures.

Our data seem to be in agreement with a recent systematic review of both observational and controlled trials which specifically quantified the risk of fracture in patients treated with inhaled GCs [21]. In general, this meta-analysis does not confirm a positive association between inhaled GC use and risk of fractures. However, when the analysis was stratified by dose, a slight increase in the risk of fractures was found among high-dose inhaled GC users [21]. Also, Pujades-Rodríguez et al. [18] provided evidence of a small increase in any fracture risk associated with inhaled GCs at doses exceeding 1,600 μg/daily.

A recent meta-analysis by Weatherall et al. [17] reported that in older adults with asthma or COPD the relative risk of nonvertebral fractures increases by about 12% for each 1,000-μg increase in the daily dose of beclometasone or equivalent. Indeed, the fact that the relationship between inhaled GCs and both bone status and fracture risk is dose-dependent is not surprising when we consider that inhaled GCs seem to have a systemic effect only at doses >800–1,000 μg/daily [15, 23].

De Vries et al. [27], by studying the Dutch PHARMO-RLS database, found that 1,600 μg/daily of beclometasone or equivalent was associated with hip fractures; but the relationship disappeared after adjustment for β_2 and other indicators of COPD severity. Thus, it has been reported that the increase in fracture risk may not be due to the inhaled GCs but, rather, to the severity of the lung disease for which they were prescribed.

Our study has shown that inhaled β_2 agonists are not associated either with increased risk of vertebral fracture or with reduced values of stiffness. In the literature, inhaled β_2 agonists have at times been associated with an increased fracture risk. However, it is unknown which doses could be associated with an increased fracture risk and whether differences exist between short-acting and long-acting inhaled

β_2 agonists. Osteoblasts possess β_2-adrenergic receptors, and moreover some recent in vitro and in vivo experimental studies have reported that the noradrenergic activation of β_2 receptors on osteoblasts leads to increased osteoclastogenesis and reduced bone mineral density [28]. Corresponding to these results, a meta-analysis of studies assessing fracture risk in patients using β-blockers showed a 14% reduction in the risk of any fracture [29]. Two recent large case–control studies have evaluated the relationship between β_2 agonists and fracture risk [26, 27]. De Vries et al. [27] found an increased risk of hip fracture in patients treated with high-dose β_2 agonists, whereas Vestergaard et al. [26] found that inhaled short-acting β_2 agonists, but not LABA, were associated with an increased risk of any fractures, which was not dose-dependent. In both of these latter studies, the associations between β_2 agonists and fracture were no longer significant after adjustment for indicators of underlying disease severity. The fact that in the study by Vestergaard et al. [26] an increase in fracture risk was seen only with short-acting β_2 agonists points against a pharmacological effect of the β_2 agonists. In fact, short-acting β_2 agonists are most often used to control the acute phases of COPD disease and in patients having poor lung function.

The findings of this study represent one of the first indications that high-dose inhaled GCs are associated with reduced values of QUS at the calcaneus. At present, the evaluation of BMD by DXA is considered not satisfactory in evaluating the changes induced by GCs in bone. This has stimulated interest in QUS, which is thought to reflect not only bone density but also some structural properties of bone, such as elasticity and connectivity [30]. Therefore, at least in theory, QUS evaluation could express GC-induced alterations in bone architecture and structure not captured by BMD. However, at present, no sufficient data are present in the literature to recommend routine evaluation of QUS in the management of COPD patients.

This study has several limitations. First, the cross-sectional design of the study does not allow the assessment of any causal association. Second, the past GC exposure information was mainly collected from patient interviews, and this could have determined underregistration and imprecision; moreover, hypoxia and hypercapnia were not taken into consideration for the assessment of COPD severity. Third, the evaluation of bone status was made only with a QUS device. Indeed, even though there is general agreement that the gold standard for the diagnosis of osteoporosis is central DXA, numerous studies have clearly reported that the SI by Achilles is able to predict fragility fractures as well as axial BMD by DXA [25]. Fourth, the exclusion of COPD patients treated with anti-osteoporotic drugs may have led to an underestimation of the prevalence of vertebral fracture; indeed, at the time of the study the use of antiosteoporotic treatments in ambulatory outpatients of pneumological centers was marginal. Finally, use of chest X-rays allows an adequate assessment of vertebral fractures almost exclusively for the thoracic part of the spine. This study also has several strengths. Mainly, it is a large epidemiological study based on a representative sample of Italian patients with COPD. Moreover, the homogeneity in the evaluation of the vertebral fractures was assured by the use of a reproducible semiautomatic method. Finally, the standardized definition of COPD severity was based on a spirometry test carried out on the same day of the inclusion visit.

In conclusion, this study, carried out on a large and homogeneous population, provides further evidence that the more severe stages of COPD are the main determinant of both impaired bone status and increased fracture risk. Inhaled GCs, particularly at doses exceeding 1,500 μg/day, are associated with a small increase in vertebral fracture risk, which remains significant after adjusting for confounding factors.

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