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High prevalence of vertebral deformities in COPD patients: relationship to disease severity

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ABSTRACT: Bone mineral density decreases with advancing chronic obstructive pulmonary disease (COPD) severity, but it is not known whether this is reflected in higher fracture rates. The present authors wanted to compare the prevalence of vertebral deformities in COPD patients with those in a population-based reference group to determine whether the number of deformities was related to the severity of COPD and how far the use of oral corticosteroids (OCS) influenced the prevalence of deformities.

In the present cross-sectional study of 465 COPD patients and 462 controls, vertebral deformities were found in 31% of the COPD patients and 18% of the controls. In subjects who had never or sporadically used OCS, deformities were found in 29% of the COPD patients and 17% of the controls. In females, the average number of vertebral deformities was almost two-fold when COPD severity increased from Global Initiative of Chronic Obstructive Lung Disease stage II to III. In males, the use of OCS had a small but significant influence.

Prevalence of vertebral deformities was significantly higher in chronic obstructive pulmonary disease patients than in the controls. In females, the average number of deformities was related to chronic obstructive pulmonary disease severity even after adjustment for other known risk factors. The difference between patients and controls remained significant even in those who never or sporadically used oral corticosteroids.

KEYWORDS: Chronic obstructive pulmonary disease, prevalence, systemic steroid therapy, vertebral deformities, vertebral fractures

A higher fracture rate caused by osteoporosis may be a significant clinical problem in patients with advanced chronic obstructive pulmonary disease (COPD) [1]. Bone mineral density (BMD) is significantly lower in COPD patients than in healthy individuals, and decreases as the lung disease progresses [2, 3]. However, it is not known whether the decrease in BMD is reflected in higher fracture rates.

Many vertebral fractures are never brought to clinical attention [4–7], and valid estimates of the prevalence of these fractures must be based on a radiographical survey of the population. Use of the term ''vertebral deformity'' is now standard in morphometric studies performed without reference to clinical presentation. In the European Vertebral Osteoporosis Study (EVOS), the mean prevalence of radiographically defined vertebral deformities at the various centres was found to be 12%, using the McCloskey method, for both males and females. There was considerable geographical variation, with the highest rates in the Scandinavian countries. The prevalence increased with age in both sexes, although the gradient was steeper in females [4].

Although a prevalence of vertebral deformities as high as 63% has been reported in COPD patients [1], the relationship of COPD to vertebral deformities is difficult to assess in quantitative terms on the basis of previous studies. Prevalence figures vary widely between studies, possibly due to methodological or geographical differences, disease severity and the patients' use of oral corticosteroids (OCS) [1, 8]. Furthermore, COPD patients have rarely been compared with healthy controls or with a comparable general population. To the present authors' knowledge, there are no studies of the relationship between severity of COPD and number of vertebral deformities.

In the present cross-sectional study, the primary aim was to determine the prevalence of vertebral deformities among COPD patients and compare

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them with a population-based reference group. In addition, the present authors wanted to determine whether the severity of COPD had any impact on the average number of deformities and to what extent the use of OCS influenced the prevalence of deformities.

MATERIALS AND METHODS

The present study is part of a larger study on the consequences of vertebral deformities for lung function. A pilot study of deformities and lung function was performed prior to the main study in 50 consecutively admitted COPD patients in order to calculate the number needed to demonstrate a 12% difference in forced expiratory volume in one second (FEV_1) between patients with and without vertebral deformities. A significance level of 0.05 and a power of 0.80 required the inclusion of 462 COPD patients of both sexes.

Subjects

Glittreklinikken is situated in Hakadal (Norway) and is a rehabilitation centre that provides rehabilitation programmes for patients with pulmonary diseases with varying diagnoses and severity who are referred from all parts of the country. From September 2005 to October 2007, 1,004 consecutively admitted COPD patients attending a four-week rehabilitation programme were evaluated for inclusion in the study. Of these, 492 either had to be excluded or did not meet the inclusion criteria. Of the remaining 512, 47 dropped out, resulting in a study group of 465 COPD patients (fig. 1).

Inclusion criteria

Patients with COPD in a stable phase whose diagnosis was based on clinical history and lung function values of post-bronchodilator FEV_1 <80% and post-bronchodilator FEV_1/forced vital capacity <70% were included in the study [9]. A stable phase was defined as no exacerbations involving decreased lung function and the need for antibiotics or additional OCS during the previous 4 weeks. Furthermore, the authors stipulated that the patients' general medical condition should not prevent them from participating in the study.

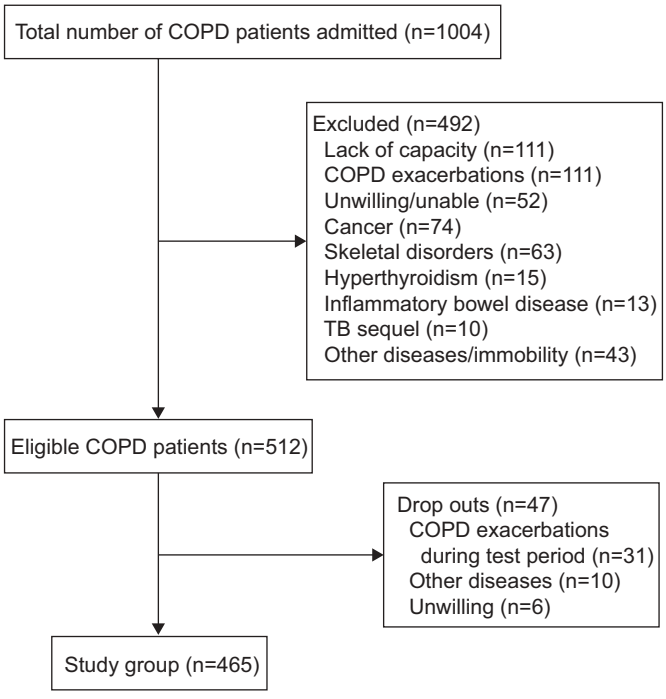

FIGURE 1. Flow chart of the patient selection. COPD: chronic obstructive pulmonary disease; TB: tuberculosis.

Exclusion criteria

Patients were excluded if they had cancer, inflammatory bowel disease, untreated hyperthyroidism, exacerbation of the lung disease during the previous 4 weeks, immobility or known kyphoscoliosis from adolescence. Written informed consent was obtained from all subjects, and the study was approved by the regional committee for medical research ethics (Oslo, Norway).

Control group

The control group consisted of 462 individuals randomly selected from the Oslo study group in EVOS, which consisted of 587 individuals aged 50–80 yrs [4]. The prevalence of COPD in this population was not reported, and EVOS did not include the lung function tests.

Measurements

Pulmonary function tests were carried out by trained operators in accordance with guidelines stipulated by the European Community for Steel and Coal [9] using MasterScreen equipment (Jaeger GmbH, Würzburg, Germany). Post-bronchodilator measurements were registered. The patients were classified into stages II–IV in accordance with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [10].

Arterial blood was obtained by a radial artery puncture after seated rest for 30 min. The samples were analysed for pH, arterial oxygen and carbon dioxide tension within 5 min of the puncture (Radiometer ABL 725, Copenhagen, Denmark). Height and weight were measured with the patients wearing light indoor clothing and no shoes, and body mass index (BMI) was calculated in terms of $kg \cdot m^{-2}$.

Information about smoking and treatment with corticosteroids, calcium and vitamin D, hormone replacement therapy (HRT) and bisphosphonates was obtained from patient interviews and medical records. Smoking exposure was estimated in terms of pack-yrs. Patients were classified as never-users or users of OCS. Patients with sporadic OCS use were classified as users if they had ever taken OCS for more than four 2-week periods. The present authors estimated that OCS use for four 2-week periods would be comparable to continuous use for 2 months. In EVOS, subjects were classified as OCS users if they had ever taken OCS daily for a period of $\geq$2 months. In the current study, patients taking less than this were classified as never-users. Prednisolone was the only type of OCS used, and the present authors estimated the cumulative dose for this drug. For those who only took OCS during exacerbations, the estimates were based on a cumulative dose of 0.3 g prednisolone per exacerbation period [10, 11]. The use of inhaled corticosteroids (ICS), bisphosphonates, calcium and vitamin D was recorded in terms of number of years' usage.

Thoracic and lumbar spine radiographs were taken according to a standardised protocol [4], with the patient lying in the left lateral position. For the thoracic radiographs, a breathing technique was used that allowed blurring of the overlying ribs and lung details by motion. The film was centred at Th7 for the thoracic and L2 for the lumbar radiographs. All radiographs from COPD patients and controls were evaluated at the Center for Muscle and Bone Research (Benjamin Franklin Hospital, Berlin, Germany).

A semi-quantitative approach was used to assess vertebral deformities. Anterior (a), mid (m) and posterior (p) heights and corresponding height ratios a:p, m:p, p:p_{up}, p:p_{low} were estimated. Height p_{up} and p_{low} are the posterior heights of the vertebrae one level above and one below the assessed vertebra, respectively. A vertebra was considered to have a deformity if any height ratio at baseline was below the threshold of 0.80 [12].

As the original evaluation of the EVOS population was performed morphometrically at the Center for Muscle and Bone Research, and as the prevalence of vertebral deformities was obtained by both the Eastell and the McCloskey algorithms, the EVOS images were re-evaluated using the previously mentioned method to ensure comparability between the COPD patients and control groups. The re-evaluation was expected to result in different figures for the prevalence of vertebral deformities between the original EVOS evaluation from the Oslo material and the evaluation in the present study.

As the hospital changed radiography equipment during the study, 255 of the radiographs were obtained with a Diagnost 88 (Philips, Paris, France) and the remainder with a ddR Formula Plus (Swissray, Hochdorf, Switzerland).

Statistical analysis

Categorical variables were analysed by Chi-squared tests. Pearson or Spearman correlations were used to estimate the associations between two continuous variables. Differences between two independent groups were tested by two sample unpaired t-tests or Mann–Whitney U-tests, as appropriate. Univariate and multivariate Poisson regression models were used to estimate the relative changes (95% confidence interval (CI)) in the average number of deformities.

To test whether the effect of the GOLD stage on the average number of vertebral deformities was the same for both sexes, the interaction term GOLD multiplied by sex was tested by a likelihood ratio test. Two-sided p-values $\leqslant 0.05$ were considered statistically significant.

The curve for the relative change in the average number of deformities (95% CI) to patient age was estimated by generalised additive regression GAM with the LOG link in statistical software R, version 2.6.0 for Windows (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Sex distribution did not differ significantly between the excluded and included COPD patients; however, age and FEV_1 (%) differed slightly, but significantly, between the two groups (table 1).

Sex and age did not differ significantly between the study group and the group of drop-outs. Lung function tests were not reported for the drop-outs. The study group and the control group had the same distribution with regard to sex, BMI and use of HRT by females. The mean age was 2 yrs higher in the control group ($p=0.002$). Significant differences between COPD patients and controls were also found for pack-yrs and use of calcium/vitamin D and OCS. For the control group, bisphosphonates were not available at the time of the EVOS study, thus the present authors have no data on the use of ICS or cumulative doses of OCS (table 2).

Vertebral deformities were found in 143 (31%) of the COPD patients and 82 (18%) of the controls ($p<0.0001$). In those who had never or only sporadically used OCS, deformities were found in 29% of the COPD patients and 17% of the controls ($p<0.0001$). In OCS users, the difference in prevalence of vertebral deformities between patients and controls was not significant (fig. 2).

The mean numbers of vertebral deformities were 0.8 in the patients and 0.4 in the controls ($p<0.0001$; table 2). In the 143 patients with deformities, the range of deformities was 1–13. The mean numbers of vertebral deformities in patients with GOLD stages II, III and IV were 0.5, 0.7 and 1.1, respectively, in males and 0.6, 1.1 and 0.5, respectively, in females (table 3).

Due to the nonlinear effect of age on the average number of deformities (fig. 3), patient age was categorised into two groups: above and below the median age (63 yrs) in the univariate and multivariate Poisson regression models. This resulted in 257 patients aged $\leqslant 63$ yrs and 208 patients aged >63 yrs. A highly significant interaction effect was found between sex and GOLD stage ($p<0.001$). Therefore, stratified analyses for sex were performed for the univariate and multivariate Poisson regression models.

TABLE 1 Excluded *versus* included chronic obstructive pulmonary disease patients

	Excluded	Patients included	p-value
Subjects n	492	465	
Males/females	234 (47)/259 (53)	231 (50)/234 (50)	0.514
Age yrs	66±9	63±8	<0.0001
Post-bronchodilator FEV_1 % pred	43±15[#]	45±14	0.020

Data are presented as n (%) or mean±SD, unless otherwise stated. FEV_1: forced expiratory volume in one second; % pred: % predicted. [#]: 12 missing values.

TABLE 2 Subject characteristics for the study group and the control group

	Patients	Controls	p-value
Subjects n	465	462	
Males/females	231 (50)/234 (50)	228 (49)/234 (51)	0.973
Subjects with deformities	143 (31)	82 (18)	<0.0001
Males/females with deformities	74 (52)/69 (48)	39 (48)/43 (52)	0.641
Number of vertebral deformities	0.8 (0.6–0.9)	0.4 (0.3–0.5)	<0.0001
Age yrs	63 (32–83)	65 (50–80)	0.002
BMI kg·m^{-2}	25 (14–54)	25 (15–46)	0.063
Pack-yrs	30 (0–114)	10 (0–150)	<0.0001
OCS	201 (43)$^{+,\S}$	31 (7)$^{+}$	<0.0001
Cumulative dose OCS g	0.9 (0.0–180.0)		
ICS$^{\#}$	430 (93)		
HRT¶	86 (37)	68 (29)	0.157
Calcium/vitamin D	73 (16)	27 (6)	<0.0001
Bisphosphonate	44 (10)	0	

Data are presented as n (%) or median (range), unless otherwise stated. The numbers of vertebral deformities are presented as mean (95% confidence interval). BMI: body mass index; OCS: oral corticosteroids; ICS: inhaled corticosteroids; HRT: hormone replacement therapy. $^{\#}$: patients who have used ICS; ¶: females who currently or previously have used HRT; $^{+}$: patients who have used OCS daily for >2 months; §: patients who have used OCS sporadically for more than four periods of 2 weeks.

In the female patients (table 4), the average number of vertebral deformities was significantly associated with GOLD stage, age group and current use of HRT, but not with BMI, number of years of ICS usage, cumulative OCS dose, use of bisphosphonates or previous use of HRT. Females in GOLD stage III had a 97% higher average number of deformities than females in GOLD stage II ($p<0.0001$). There was no significant difference in the average number of deformities between GOLD II and IV. For current use of HRT, the relative change in the average number of deformities was 0.42 ($p=0.020$). Patients aged >63 yrs had a 2.44 ($p<0.0001$) times higher average number of deformities than the age group <63 yrs.

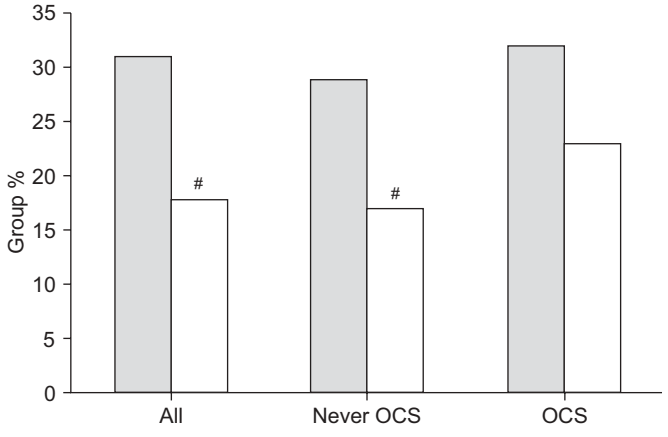

FIGURE 2. Vertebral deformities in chronic obstructive pulmonary disease patients (■) *versus* controls (□). All: all patients and controls; never OCS: never used oral corticosteroids (OCS) daily for >2 months or sporadically for more than four 2-week periods; OCS: used OCS daily for >2 months or sporadically for more than four 2-week periods. Data are presented as the percentage of affected subjects out of the actual group. $^{\#}$: $p<0.0001$.

In the male patients (table 4), the average number of vertebral deformities was significantly associated with cumulative dose of OCS, number of years of ICS usage and BMI, but not by GOLD stage, age group or use of bisphosphonates. For every additional gram of cumulative OCS dose, the average number of deformities increased by 3% ($p<0.0001$). Patients using ICS had a reduction of 7% ($p<0.001$) for every additional year of ICS usage. The average number of deformities was reduced by 5% ($p<0.004$) when the patient's BMI increased by 1 kg·m^{-2}.

The average number of vertebral deformities was not significantly associated with partial pressure of oxygen, partial pressure of carbon dioxide, pH or pack-yrs in any of the previous groups in either the univariate or the multivariate analyses. In both COPD patients and controls, deformities

TABLE 3 Subject characteristics for males and females in the study group

	Males	Females	p-value
Subjects n	231	234	
GOLD II	73 (32)	92 (39)	
GOLD III	114 (49)	98 (42)	0.195
GOLD IV	44 (19)	44 (19)	
Age yrs	63 (42–83)	63 (32–81)	0.694
BMI kg·m^{-2}	26 (16–46)	24 (14–54)	0.002
Cumulative dose OCS g	0.6 (0.0–74.2)	1.2 (0.0–180.0)	<0.0001
ICS usage yrs	6 (0–25)	5 (0–25)	0.804
Bisphosphonate use	22 (10)	22 (9)	0.964

Data are presented as n (%) or median (range), unless otherwise stated. GOLD: Global Initiative for Chronic Obstructive Lung Disease; BMI: body mass index; OCS: oral corticosteroids; ICS: inhaled corticosteroids.

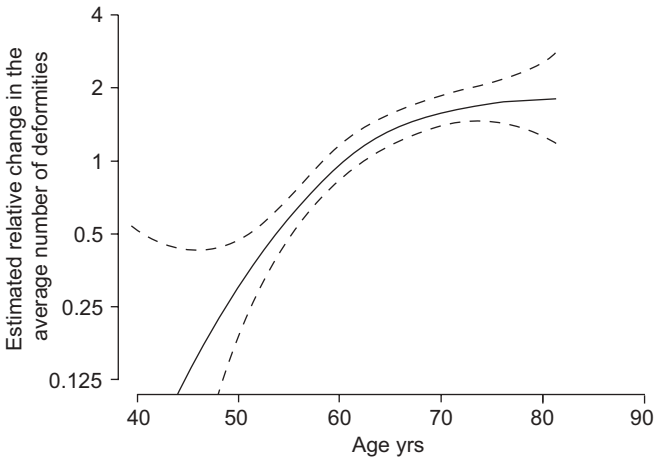

FIGURE 3. Estimated relative change in the average number of deformities (——) with 95% confidence intervals (- - - -) related to patient age.

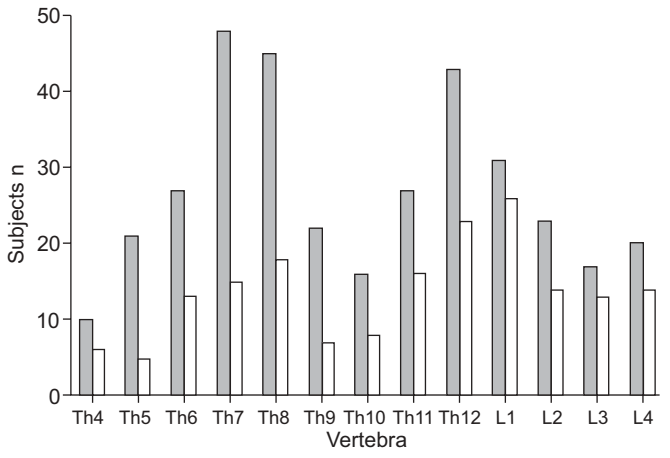

FIGURE 4. Number of chronic obstructive pulmonary disease patients (■) and controls (□) with deformities in vertebrae Th4–12 and L1–4.

were more frequent in the mid-thoracic region and at the thoracic–lumbar junction. For all vertebral levels, a larger number of patients than controls had deformities (fig. 4).

DISCUSSION

The prevalence of vertebral deformities was 72% higher in COPD patients than in a general population sample from the same geographical region. The difference remained almost the same when the patients and controls that never or only sporadically used systemic steroids were compared. The use of HRT did not differ significantly between the study and the control group.

Previous studies of vertebral deformities in COPD patients have shown a prevalence range of 27% [13] to 63% [1], both of which are higher than in the general population in EVOS. In two studies that reported a prevalence of >60%, all the patients had been continuous users of OCS [1, 14]. In one of the studies, COPD patients who had never used OCS were compared with COPD patients who were continuous users, and the never-users had a prevalence of 49% [1]. Neither of the studies included controls without lung disease, and neither contained information about the prevalence of vertebral deformities in the general population in the same geographical region.

TABLE 4 Relative change of average number of vertebral deformities related to risk factors for osteoporosis

	Unadjusted relative change	p-value	Adjusted relative change	p-value
Males				
GOLD III#	1.23 (0.76–1.99)	0.398	1.18 (0.79–1.77)	0.413
GOLD IV#	1.69 (0.92–3.12)	0.093	1.51 (0.95–2.41)	0.084
BMI	0.97 (0.93–1.01)	0.132	0.95 (0.92– 0.98)	0.004
ICS¶	0.96 (0.92–1.00)	0.038	0.93 (0.90–0.97)	<0.0001
Cumulative dose of OCS	1.02 (1.01–1.03)	0.001	1.03 (1.01–1.05)	<0.0001
Bisphosphonates	0.78 (0.38–1.61)	0.504	0.70 (0.38–1.29)	0.251
Age >63 yrs+	1.24 (0.81–1.90)	0.323	1.28 (0.94–1.75)	0.123
Females				
GOLD III#	1.64 (0.96–2.78)	0.068	1.97 (1.42–2.73)	<0.0001
GOLD IV#	0.84 (0.43–1.64)	0.606	0.76 (0.45–1.28)	0.301
BMI	1.00 (0.96–1.04)	0.809	1.00 (0.98–1.03)	0.833
ICS¶	0.99 (0.94–1.03)	0.537	0.98 (0.95–1.01)	0.257
Cumulative dose of OCS	1.01 (1.00–1.01)	0.111	1.00 (0.99–1.01)	0.835
Bisphosphonates	0.87 (0.38–2.00)	0.750	0.70 (0.41–1.19)	0.184
Age >63 yrs+	2.02 (1.26–3.25)	0.004	2.44 (1.78–3.33)	<0.0001
Taking HRT currently§	0.57 (0.26–1.24)	0.157	0.42 (0.20–0.87)	0.020
Taken HRT previously§	0.98 (0.56–1.72)	0.940	0.97 (0.70–1.36)	0.873

Data are presented as relative change (95% confidence interval), unless otherwise stated. Univariate and multivariate Poisson regression analyses were performed separately for males and females. GOLD: Global Initiative for Chronic Obstructive Lung Disease; BMI: body mass index; ICS: inhaled corticosteroids; OCS: oral corticosteroids; HRT: hormone replacement therapy. #: compared with GOLD II; ¶: number of years used ICS; +: compared with age ⩽63yrs; §: compared with never having taken HRT.

In contrast to the present findings, two previous studies have reported no difference in the prevalence of vertebral fractures between COPD patients and controls [13, 15]. However, the study by RIANCHO *et al.* [15] only included males and the control group, of 27 healthy males, was small. The study by PAPAIOANNOU *et al.* [13] consisted of 127 COPD patients, and patients admitted to hospital without a diagnosis of COPD or asthma were used as controls. Neither study contained information about the prevalence of vertebral deformities in the general population.

The differences in reported prevalence are not unexpected as the studies used different methodologies and inclusion and exclusion criteria. Moreover, EVOS revealed a substantial geographical variation in the prevalence of vertebral deformities in Europe, and a similar geographical variation could be expected for COPD patients.

In the present study, the average number of vertebral deformities was only significantly associated with the severity of COPD in females. An increase in severity from GOLD stage II to stage III was associated with an almost two-fold increase in the average number of vertebral deformities. Adjusting for confounding variables did not substantially change the relationship between GOLD stage and number of deformities. There was an unexpected, but not statistically significant, reduction in relative change (0.76) in the average number of deformities with an increase in severity from GOLD II to IV compared with that from GOLD II to III. This result should be interpreted with caution, considering that GOLD stage IV represents patients with FEV_1 <30% or FEV_1 <50% of predicted and chronic respiratory failure. The patients in the lower half of this category can hardly be represented, and probably only a few of the patients in the upper half attend a rehabilitation programme. This is supported by the fact that, in the present study, the number of GOLD stage IV patients was only 50% that of GOLD stage III patients, and the average FEV_1 for GOLD stage IV is 30% pred, while for GOLD stage III it is ~39%.

In females, the average number of vertebral deformities was also significantly associated with age, probably owing to postmenopausal bone loss. Current use of HRT gave a significant reduction of almost 60% in the average number of vertebral deformities, while previous use of HRT did not. This is in accordance with a Swedish study [16], which showed that recent use of HRT is required for optimal fracture protection.

In males no effects of COPD severity were found on the average number of vertebral deformities. This sex difference may be related to the generally higher propensity of females for developing osteoporosis. As BMI increased there was a significant reduction in the average number of vertebral deformities. Although the effect was weak, it is consistent with previously published results [17].

According to a recent review by YANG *et al.* [18], the effect of prolonged ICS use on fracture rates and BMD is not clear. In the current study, ICS use was associated with a small but statistically significant reduction in the average number of vertebral deformities for males, but not for females. The present authors also found a small, but significantly greater, number of vertebral deformities with a rise in cumulative dose of OCS in males but not in females. There is no explanation for this sex difference, but an effect of OCS in females could possibly have been masked by other factors in this group, such as differences in use of bisphosphonates and HRT. However, this is entirely speculative.

The present method of recording OCS use was adjusted to the method used in EVOS (see the Measurements section). When the patients and controls that never or only sporadically used systemic steroids were compared, a significant difference was still found between the groups with regard to vertebral deformities. This could indicate that the effect of COPD on vertebral deformities does not depend on OCS use alone.

The current study has several strengths. One is that all the COPD patients admitted during the study period were evaluated for inclusion. Furthermore, by using the GOLD classification the authors were able to relate vertebral deformities to COPD severity. The patients admitted for rehabilitation may be those with more severe disease, but this was taken into account by the use of GOLD staging. It is not known whether the patients admitted are representative of COPD patients in general in Norway. Patients who apply for rehabilitation may be more motivated to take care of their health than the general population. However, the clinical impression of patients admitted to the clinic in general are that many of them are smokers, have not participated in physical training for several years prior to admission, and do not seem to know what to expect from a rehabilitation programme. Thus, the external validity is probably sufficient for COPD patients in GOLD stage II and worse. Furthermore, all radiographs from patients and controls were evaluated at a single centre, which excludes between-centre variations in the evaluation of deformities.

However, the present study was conducted almost 15 yrs after EVOS. If secular changes have occurred in the prevalence of vertebral deformities in the general population, this could have had consequences for the use of EVOS material as a control group.

The presence of vertebral deformities has been shown to predict subsequent deformities [19, 20]. Vertebral deformities may reduce lung function [13, 21], cause pain and anxiety and reduce physical capacity [22], and are therefore a burden on the individual and society. Early identification and targeted interventions for the growing number of COPD patients with a high risk of deformities could reduce this burden.

In conclusion, the current results show a significantly higher prevalence of vertebral deformities in chronic obstructive pulmonary disease patients than in a population-based cohort. In females, the number of deformities was related to the severity of chronic obstructive pulmonary disease even when adjustment was made for other known risk factors. The difference between patients and controls remained significant even for individuals who had never or only sporadically used systemic steroids, which suggests that the lung disease itself has a specific effect.

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