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Correlates of osteoporosis in chronic obstructive pulmonary disease: An underestimated systemic component

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Summary
Rationale: Chronic obstructive pulmonary disease (COPD) patients are at increased risk of osteoporosis. Osteoporosis is under diagnosed and under treated in these patients and the underlying mechanisms remain unclear. To date, screening recommendations for osteoporosis in COPD patients are not available.

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Osteopenia;
Osteoporosis;
Screening advice

Objectives: To examine the prevalence of drug treatment of bone abnormalities as well as the clinical determinants of osteoporosis in COPD.
Methods: COPD patients ($n = 554$) consecutively entering pulmonary rehabilitation were included in this cross-sectional study. Medical history, current medication use, smoking status, lung function, bone mineral density, body composition and other clinical characteristics were assessed before entering pulmonary rehabilitation.

Univariate- and multivariate multinomial logistic regression analyses were used to determine correlates of osteoporosis.
Main results: Twenty-one percent of patients had osteoporosis and 41% had osteopenia. Osteoporosis was pharmacologically under treated (82% of osteoporotic patients were not receiving bone medication). Independent predictors of osteoporosis were cachexia (OR: 12.1; 95%CI: 4.5—32.7; $p < 0.001$), age between 55 and 65 years (OR: 6.0; 95%CI: 2.2—16.3; $p < 0.001$) and over 65 years (OR: 11.7; 95%CI: 4.1—33.1; $p = <0.001$). Overweight (OR: 0.1; 95%CI: 0.05—0.4; $p = 0.001$) and obesity (OR: 0.78; 95%CI: 0.02—0.4; $p = 0.002$) showed a substantial protective effect.
Conclusions: The majority of COPD patients with osteoporosis entering pulmonary rehabilitation did not receive pharmacological treatment for osteoporosis. Cachectic COPD patients should be screened for osteoporosis, especially when over 55 years of age.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by a usually progressive airflow limitation that is not fully reversible according to the Global Strategy for the Diagnosis, Management, and Prevention of COPD (GOLD).[1] COPD comprises a major health burden with an estimated global prevalence of 9—10% in adults of 40 years and older.[2,3]

The GOLD guidelines include ''significant extrapulmonary effects'' in the definition of COPD,[1] indicating that COPD can be considered a multicomponent disease with marked extra-pulmonary effects.[4—7] Examples of these effects are loss of muscle mass (with and without abnormal loss of body weight),[8] increased fat mass[9] and arterial stiffness.[10] Moreover, COPD patients have a higher risk of osteoporosis as compared to healthy subjects.[11] Indeed, COPD has been included in the male osteoporosis risk estimation score.[12]

Osteoporosis is a systemic skeletal disease characterized by low bone mineral density (BMD) and microarchitectural changes in bone tissue that increases the susceptibility to fractures.[13] In patients with established osteoporosis and patients at high risk of developing osteoporosis (e.g. in case of oral corticosteroid use of 7.5 mg prednisolone equivalent a day for at least 6 months), treatment aims at maintaining BMD and reducing the incidence of osteoporotic fractures.[13] In addition to behavioral intervention, treatment should include bisphosphonates in combination with calcium supplementation and vitamin D in case of vitamin D deficiency (''bone medication'').[13]

Recent studies have found an abnormal low BMD in COPD patients entering pulmonary rehabilitation.[14—16] Unfortunately, the external and internal validity of these studies is limited due to small sample sizes and various methodological issues. Indeed, the prevalence of pharmacological treatment of osteoporosis has not been investigated in COPD patients. Therefore, its prevalence remains currently unknown. Nevertheless, under diagnosis and, in turn, under treatment of osteoporosis in these patients in the clinical routine seems reasonable. Indeed, under treatment of osteoporosis has been reported in elderly subjects without airflow limitation and even in patients with fragility fracture.[17—20]

Previously, the increased prevalence of osteoporosis in COPD was attributed to the use of oral corticosteroids.[21—23] Later, attention was focused on the effects of inhaled steroids.[24—26] Several studies demonstrated that these drugs have no effect on BMD.[27—30] At present, the focus of investigation is more on factors besides corticosteroids to explain the increased prevalence of osteoporosis in COPD: low body mass index (BMI) and low fat free mass index (FFMI) are known risk factors for osteoporosis in COPD.[14,16,31] None of the aforementioned studies have taken into account the possible effects of factors such as an overweight or obese BMI,[32] cardiac drug therapies,[33—36] serotonin reuptake inhibitors (SSRIs)[37] and C-reactive protein (CRP)[38] on the prevalence of osteoporosis in COPD. Moreover, insight into these factors may help to explain the underlying mechanisms for the increased risk of osteoporosis in COPD patients.

Given the relative paucity in knowledge about osteoporosis in COPD, the present study aims to examine the prevalence of drug treatment of osteoporosis and to determine clinical correlates of osteoporosis and osteopenia in COPD patients.

Materials and methods

Patient population and study design

COPD patients ($n = 554$) consecutively entering pulmonary rehabilitation were recruited between January 2005 and April 2007 from the Centre for Integrated Rehabilitation of Organ Failure (CIRO) in Horn, the Netherlands. All patients were clinically stable outpatients referred to CIRO by chest physicians working in respiratory departments of general

hospitals in the south-eastern part of the Netherlands. A cross-sectional design was used. Diagnosis of COPD was made according to the ATS guidelines,[4] severity classified according to the GOLD guidelines.[1] All assessments were made before entering a comprehensive pulmonary rehabilitation.[39] The institutional review board of the University Hospital of Maastricht approved the study protocol and written consent was obtained from all study participants.

Clinical characteristics

Medical history, current medication use and smoking status were assessed by reviewing the medical charts and by interviewing all patients. Age was divided into three categories: $\leq$55, 56–65 and $>$65 years.

Forced expiratory volume in the first second (FEV_1) and forced vital capacity (FVC) were assessed using the Jaeger MASTERLAB BODY® (VIASYS Healthcare) and FEV_1/FVC was determined. Arterial blood gases were collected to determine pH, arterial carbondioxide tension ($PaCO_2$) and arterial oxygen tension (PaO_2).

BMI was defined as low ($<$21 kg/m^2), normal (21–25 kg/m^2), overweight ($>$25–30 kg/m^2) and obese ($>$30 kg/m^2). Bio-impedance analysis was done using the BODYSTAT® 1500 medical, single frequency (Xitron Technologies). FFMI was defined as depleted (men $<$16 kg/m^2 and women $<$15 kg/m^2) or normal.[40] The combination of BMI and FFMI resulted into six categories: cachexia (low BMI and depleted FFMI), muscle atrophy (normal BMI and depleted FFMI), semi starvation (low BMI and normal FFMI), normal (normal BMI and normal FFMI), overweight (overweight BMI and normal FFMI) and obese (obese BMI and normal FFMI).[8] Whole-body BMD was determined using a DXA-scan (Lunar Prodigy® Ge-Lunar), with osteoporosis being defined by a *T*-score <-2.35, osteopenia: *T*-score between -2.35 and -0.9, normal BMD: *T*-score >-0.9.[41]

CRP was determined in duplicate by high-sensitivity particle enhanced immunoassay (LABAS micra, radiometer).

A six-minute walking distance test was conducted twice on 2 separate days. The longest distance was used in further analysis.[42]

Statistical analyses

Discrete variables were compared with the Chi-square test and presented as percentages. Continuous variables were compared with ANOVA and presented as means $\pm$ standard error of mean (SEM).

Univariate- and multivariate-multinomial logistic regression analyses (enter procedure) were performed to investigate determinants of osteoporosis and osteopenia in COPD patients without bone medication. Univariate analyses were used to test for the potentially confounding effect of biomedical and demographic factors. If significant at $p < 0.05$, the variables were included into the multivariate analyses. In addition, several covariates were selected based on the literature. Specific interactions were tested within the regression model. A posteriori, specificity of osteoporosis stratified by the two most important risk factors for osteoporosis as found in the current study was determined. A *p*-value $<$0.05 was used to indicate statistical significance. Odds ratio (OR) with 95% confidence intervals (CI) are reported. All statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 15.0.

Results

Patient characteristics

We included 554 patients with moderate to very severe COPD. Since only 16 patients (2.9%) were classified as mild COPD we merged patients with GOLD I and GOLD II into one category. BMI and/or FFMI were abnormal in 85% of the patients. The prevalence of osteoporosis was 21%, the prevalence of osteopenia 41% (Table 1).

Significant differences were found in gender, age, body composition and functional exercise capacity between patients with osteoporosis, osteopenia and/or normal BMD (Table 1).

Bone medication

Eighteen percent of the patients used bisphosphonates, calcium supplementation, vitamin D or a combination thereof. Surprisingly, patients with osteoporosis were not using significantly more bone medication as compared to patients with a normal BMD. Moreover, almost 82% of patients with osteoporosis were not treated with bone medication and almost 14% and 23% of patients with a normal BMD and osteopenia respectively did receive pharmacological treatment (Table 2). Of patients without osteoporosis treated with bone medication only 8.1% were using $\geq$7.5 mg prednisolone equivalents a day.

Determinants of osteoporosis in patients without bone medication ($n = 453$)

Univariate analysis showed an almost 3-fold increased risk of osteoporosis in patients between 55 and 65 years as compared to patients $\leq$55, increasing to an OR of 4.5 in patients over 65 years. To be sure this was not due to an interaction effect of age and GOLD-stage we repeated the analyses after stratification for GOLD. Indeed, in all GOLD-categories age $>$65 years significantly increased the OR for osteoporosis. In addition, in GOLD IV patients age between 55 and 65 increased the risk 4-fold (Table 3). Patients between 55 and 65 years had a 6-fold increased risk of osteoporosis as compared to patients $\leq$55 years, which even increased to a nearly 12-fold risk in patients over 65 years. Cachectic patients had a 12-fold increased risk of osteoporosis as compared to patients with a normal body composition, whereas overweight and obesity showed a substantial protective effect (Table 4). Specific testing for interactions within the regression model did not show any significant results. Cachectic patients over 55 years of age had an increased risk of osteoporosis as compared to patients $\leq$55 years and/or no cachexia (OR 28.2; 95%CI 10.4–76.9; $p < 0.0001$).

Table 1 Patients characteristics.

	Total group, $N = 554$	Normal BMD, $N = 212$	Osteopenia, $N = 227$	Osteoporosis, $N = 115$
Male/Female, %	62/38	60/40	59/41	70/30‡
Age, years	65.6 ± 0.4	61.3 ± 0.6	64.5 ± 0.6*	65.8 ± 0.9*
Age ≤55, %	45	30	19†	11*
Age >55 and ≤65, %	34	35	31	38
Age >65, %	21	35	50*	51*
FEV_1, %pred	42.1 ± 0.7	41.9 ± 1.0	43.6 ± 1.2	39.6 ± 1.5
GOLD I + II, %	22	24	23	16
GOLD III, %	34	36	34	30
GOLD IV, %	44	40	43	54†
Smoking				
Ex-smoker, %	73	74	75	80
Pack years	39.7 ± 0.8	40.3 ± 1.2	38.9 ± 1.2	40.1 ± 1.6
BMI, kg/m^2	24.7 ± 0.2	27.1 ± 0.3	24.3 ± 0.3*	21.2 ± 0.3*§
Low, %	24	9	25*	51*§
Normal, %	33	27	36†	37
High, %	29	41	29†	9*§
Obese, %	14	23	10*	3*‡
FFMI				
Male, kg/m^2	16.9 ± 0.1	17.9 ± 0.2	16.8 ± 0.2*	15.3 ± 0.2*§
Female, kg/m^2	14.9 ± 0.1	15.7 ± 0.2	14.7 ± 0.2*	13.7 ± 0.2*§
Low, %	43	24	46*	75*§
Normal, %	57	76	54*	25*§
Body composition				
Cachexia, %	23	9	23*	49*§
Muscle atrophy, %	18	13	20†	23†
Semi starvation, %	1	0	2	2
Normal, %	15	14	16	14
Overweight, %	29	41	29†	9*§
Obese, %	14	23	10*	3*‡
DXA-scan				
BMD, g/cm^2	1.081 ± 0.005	1.188 ± 0.005	1.055 ± 0.004*	0.933 ± 0.007*§
T-score	−1.29 ± 0.06	0.028 ± 0.05	−1.58 ± 0.03	−3.26 ± 0.07
CRP	8.4 ± 0.5	8.1 ± 0.7	9.0 ± 1.0	7.5 ± 0.9
6 MWD, m	421.4 ± 5.3	432.5 ± 8.5	419.8 ± 8.4	404.1 ± 11.7
6 MWD, % pred	64.8 ± 0.8	66.0 ± 1.2	65.3 ± 1.2	61.7 ± 1.7†

Values are expressed as mean ± standard error of mean, unless otherwise indicated. Abbreviations: FEV_1 = forced expiratory volume in the first second, BMI = body mass index, FFMI = fat free mass index, BMD = bone mineral density, Ca = calcium, CRP = C-reactive protein, 6 MWD = six minutes walking distance.
Post hoc tests: *$p < 0.01$ compared to normal BMD; †$p < 0.05$ compared to normal BMD; §$p < 0.01$ compared to osteopenia; ‡$p < 0.05$ compared to osteopenia.

The specificity of not having osteoporosis in low-risk COPD patients (non-cachectic and age ≤55) without bone medication was 91%.

Determinants of osteopenia in patients without bone medication ($n = 453$)

Patients over 65 years of age had a more than 3-fold increased risk of osteopenia as compared to patients ≤55 years (Table 5). In addition, cachectic patients had a more than 3-fold increased risk of osteopenia as compared to patients with a normal body composition, whereas obesity showed a substantial protective effect of osteopenia.

Discussion

In a large cohort of COPD patients entering pulmonary rehabilitation the prevalence of osteoporosis was 21% and of osteopenia 41%. Surprisingly, the majority of the osteoporotic patients was not treated with bone medication (82%). Older patients had an increased risk of osteoporosis as compared to younger patients. Additionally, cachectic

Table 2 Medication use.

	Total group, $N = 554$	Normal BMD, $N = 212$	Osteopenia, $N = 227$	Osteoporosis, $N = 115$
Bone medication, %	18	14	22*	18
Bisphosphonates, %	6	4	9*	5
Calcium, %	3	1	4	2
Vitamin D, %	0	1	0	0
Any Combination, %	9	8	9	11
Corticosteroids				
Oral, %	21	19	23	18
Inhalation, %	75	77	73	77
Beta mimetics (inh), %	72	72	70	74
Anticholinergics (inh), %	89	90	89	89
Diuretics				
Thiazide, %	9	11	8	6
Loop, %	19	21	18	16
K^+ saving, %	4	3	5	3
Statins	19	19	20	15
β-blockers, %	12	12	12	8
SSRIs, %	9	12	8	5*

Values are expressed as percentage of patients using medication. Abbreviations: Inh = inhaled; K^+ = potassium; SSRIs = selective serotonin reuptake inhibitors. Post hoc tests: *$p < 0.005$ compared to normal BMD.

COPD patients had a higher risk of osteoporosis whereas overweight and obese COPD patients had a decreased risk of osteoporosis as compared to their normal weight peers. This risk increased even more in cachectic patients >55 years of age irrespective of the severity of COPD. In low-risk patients (non-cachectic and age ≤55) only a very small percentage of osteoporosis (9%) will be missed when not referred for a DXA-scan.

Table 3 Age effects on osteoporosis after stratification for GOLD-stage.

	N	OR	95%CI	*p*-value
GOLD I and II	114			
<55 years[a]	27			
55–65 years	31	2.353	0.398–13.900	.345
>65 years	56	5.500	1.047–28.879	**.044**
GOLD III	166			
<55 years[a]	38			
55–65 years	57	2.173	0.514–9.183	.291
>65 years	71	5.739	1.481–22.245	**.011**
GOLD IV	173			
<55 years[a]	37			
55–65 years	59	3.789	1.173–12.247	**.026**
>65 years	77	3.168	1.009–9.951	**.048**
Total group	453			
<55 years[a]	102			
55–65 years	147	2.933	1.326–6.488	**.008**
>65 years	205	4.463	2.073–9.608	**<.0001**

Analysis was done in patients without bone medication.
[a] Reference category.

Prevalence

The prevalence of osteoporosis of 21% in this study is in line with previous studies. In brief, prevalence of osteoporosis is higher in COPD patients as compared to healthy subjects (24–32% in COPD versus 0–13% in healthy subjects).[10,14,43] Moreover, in COPD patients entering pulmonary rehabilitation a prevalence of osteoporosis of about 23% was found.[14] In the latter study DXA of the hip and lumbar spine was used whereas we used whole-body DXA-scan. However, this difference in methodology was corrected for by defining osteoporosis according to Boyanov in order to have a good sensitivity-to-specificity ratio in the diagnosis of osteoporosis.[41] Prevalence of osteoporosis of the current study differed from two other studies investigating COPD patients starting pulmonary rehabilitation.[15,16] Vrieze and colleagues found a prevalence ranging from 0% to 18%, however they used quantitative ultrasound, which is not the gold standard to measure BMD, and in addition, is hard to compare to studies using DXA-scanning.[16] Engelen and colleagues used *Z*-scores, instead of *T*-scores as recommended by the WHO.[13] They found 36% of patients with a *Z*-score of <−2, and 56% with a *Z*-score of <−1.[15]

Pharmacological treatment

This is the first study to determine proportion of osteoporotic COPD patients who were treated with bone medication. In fact, most studies *a priori* excluded patients using bone medication[15,31,44] or did not report on the prevalence of bone medication.[14,16,45] In the present study, a majority of COPD patients with osteoporosis were not treated with bone medication, indicating that these patients were not recognized as osteoporotic patients by the referring chest physicians. In the elderly, a high prevalence of under

Table 4 Correlates of osteoporosis in patients without bone medication (results of multivariate analysis) ($n = 453$).

	N	OR	95%CI	*p*-value
Male	290	1.732	0.850–3.529	.130
Age				
<55 years[a]	102			
55–65 years	147	6.020	2.226–16.281	**<.0001**[†]
>65 years	204	11.703	4.140–33.082	**<.0001**[†]
GOLD I and II[a]	114			
GOLD III	166	1.086	0.464–2.542	.850
GOLD IV	173	1.864	0.738–4.707	.188
Pack years	453	0.992	0.973–1.011	.393
Body composition				
Normal[a]	69			
Cachexia	109	12.088	4.469–32.697	**<.0001**[†]
Muscle atrophy	81	2.112	0.808–5.524	.127
Semi starvation	6	5.399	0.406–71.874	.202
Overweight	127	0.145	0.047–0.440	**0.001**[†]
Obese	61	0.078	0.015–0.399	**0.002**[†]
hs-CRP	453	0.979	0.952–1.008	.148
6 MWD	452	0.999	0.996–1.002	.388
Corticosteroids				
Oral	59	0.901	0.331–2.457	.839
Inhaled	337	1.133	0.553–2.320	.732
Diuretics	110	1.410	0.618–3.217	.414
Statins	83	0.609	0.252–1.473	.271
β-blocking agents	53	0.784	0.264–2.329	.661
SSRIs	39	0.746	0.215–2.584	.644

[†] p-value < 0.05.
Abbreviations: COPD = chronic obstructive pulmonary disease, hs-CRP = high-sensitivity C-reactive protein, 6 MWD = six minutes walking distance, SSRIs = selective serotonin reuptake inhibitors.
[a] Reference category.

Table 5 Correlates of osteopenia in patients without bone medication (results of multivariate analysis) ($n = 453$).

	N	OR	95%CI	*p*-value
Male	290	1.080	0.636–1.836	.775
Age				
<55 years[a]	102			
55–65 years	147	1.694	0.886–3.238	.111
>65 years	204	3.398	1.695–6.811	**.001**[†]
GOLD I and II[a]	114			
GOLD III	166	0.938	0.518–1.696	.831
GOLD IV	173	1.127	0.578–2.199	.725
Pack years	453	0.991	0.978–1.004	.175
Body composition				
Normal[a]	69			
Cachexia	109	3.247	1.392–7.572	**.006**[†]
Muscle atrophy	81	1.321	0.609–2.862	.481
Semi starvation	6	2.852	0.264–30.842	.388
Overweight	127	0.522	0.266–1.024	.059
Obese	61	0.364	0.158–0.842	**.018**[†]
hs-CRP	453	0.995	0.976–1.015	.631
6 MWD	452	0.999	0.997–1.002	.539
Corticosteroids				
Oral	59	1.065	0.520–2.180	.863
Inhaled	337	0.915	0.540–1.552	.742
Diuretics	110	0.691	0.382–1.251	.222
Statins	83	1.162	0.633–2.134	.629
β-blocking agents	53	1.044	0.503–2.166	.908
SSRIs	39	0.780	0.338–1.800	.560

[†] p-value < 0.05.
Abbreviations: COPD = chronic obstructive pulmonary disease, hs-CRP = high-sensitivity C-reactive protein, 6 MWD = six minutes walking distance, SSRIs = selective serotonin reuptake inhibitors.
[a] Reference category.

treatment of osteoporosis has been found, ranging between 59 and 91%.[20,46] Additionally, screening for and/or treatment of osteoporosis is low in men,[18] and even in patients with fragility fractures diagnosis and/or treatment is often inadequate.[17,19] Therefore, under diagnosis and under treatment of osteoporosis seem to be a general health problem rather than a COPD-related issue.

More than 18% of 439 COPD patients without osteoporosis were treated with bone medication. A possible explanation could be that these patients with former osteoporosis were successfully treated with bone medication and continued their treatment. Another explanation could be daily use of oral corticosteroids for at least 6 months with 7.5 mg prednisolone equivalents a day or more, since the WHO advises to treat these patients with bone medication.[13] In the current study, only 8.1% of 80 patients without osteoporosis treated with bone medication used ≥7.5 mg prednisolone. Since osteonecrosis of the jaw is one of the potential side effects of treatment with bisphosphonates[47,48] we recommend a DXA-scan to confirm diagnosis of osteoporosis before starting treatment with bone medication. In addition, we had no information on previous fragility fractures in the patients or their parents, therefore we do not know whether or not these patients met criteria for treatment based on the WHO FRAX 10-year fracture risk calculator.[49]

Correlates of osteopenia

No previous studies have focused on risk factors for osteopenia in COPD. We found age >65 years and cachexia to be independent correlates. In addition, obesity was protective of osteopenia. More longitudinal studies are needed investigating potential risk factors for osteopenia in order to identify these patients and perform regular DXA-scanning in order to detect progression to osteoporosis in an early stage.

Correlates of osteoporosis

The WHO indicates that the onset of substantial bone loss starts at 65 years in men and 50 years in women.[13] In the present study, patients between 55 and 65 years had

a 6-fold increased risk of osteoporosis compared to younger peers, which even increased to a more than 11-fold risk in patients over 65 years. This is the first study to find age to be a significant, independent risk factor for osteoporosis in COPD. In addition, cachectic patients had an increased risk of osteoporosis. This is in line with other studies.[16,31,44,50] In the current study we combined FFMI with BMI in order to make a more precise risk estimation of osteoporosis in COPD patients. Indeed, Bolton and colleagues found the highest prevalence of osteoporosis (50%) and osteopenia (50%) in cachectic COPD patients.[14] Unfortunately, they did not investigate the influence of overweight or obesity on osteoporosis. In the present study, overweight and obese COPD patients had a decreased risk of osteoporosis, as compared to normal weight peers. At first this finding seems somewhat surprising, since obesity has been linked to an increased production of inflammatory cytokines which may impair bone formation.[51] However, an increased daily physiological mechanical loading of the cortical skeleton may prevent an abnormal loss of BMD in obese subject.[52]

No previous study investigated the combined effect of age and body composition on BMD in COPD patients. In the present study the combination of cachexia and age >55 increased the risk of osteoporosis even more than either of the two variables separately.

Female gender was not a significant risk factor for osteoporosis although in the overall population women are at increased risk of osteoporosis as compared to their male peers.[13] This may in part be explained by the fact that female patients were significantly younger than male patients (mean age: 59 versus 66 years). In addition we did not find an independent effect of CRP, cardiac medication and SSRIs on osteoporosis in the present sample. There are no studies in COPD patients that included the previously mentioned covariates in their analyses. However, in patients without COPD, circulating levels of high-sensitivity CRP (hs-CRP) were found to be significantly higher in healthy women with the lowest BMD.[38] Possibly, this higher hs-CRP was not found in COPD patients with osteoporosis since hs-CRP levels are already elevated as compared to healthy subjects due to chronic low-grade systemic inflammation in COPD. In addition, thiazide diuretics, beta-blocking agents and statins decrease the risk of osteoporosis,[33–36] whereas SSRIs[37] increase this risk in subjects without COPD. We found no significant influence of corticosteroids on osteoporosis. This could be due to the fact that we corrected for several other covariates including degree of airflow obstruction. Indeed, de Vries and colleagues found the influence of inhaled corticosteroids to disappear after correcting for airflow obstruction.[27] In addition, the duration of treatment with oral corticosteroids, the number of courses and the cumulative dose were unknown, and different corticosteroid regimens had different effects on BMD.[21] Further (longitudinal) research regarding these potential confounders of osteoporosis in COPD patients is needed.

Clinical considerations

In the integrated care of COPD patients the importance of recognizing and treating extrapulmonary features is stressed.[1,53] Based on the present results, it seems reasonable to conclude that the awareness regarding diagnosis and/or pharmacological treatment of osteoporosis in COPD patients entering pulmonary rehabilitation is rather low amongst referring chest physicians. An extensive phenotyping of complex and (mostly) extra-pulmonary features in COPD patients entering pulmonary rehabilitation seems necessary.[39] Recently, Shepherd and colleagues advised to screen for osteoporosis in men with COPD over 55 years of age and/or having a body weight <80 kg.[12] Based on the current results, we would advise chest physicians to screen for osteoporosis in cachectic COPD patients older than 55 years, irrespective of gender or GOLD classification.

Methodological considerations

Some limitations of the current study should be noted. First, the external validity may be limited to COPD patients entering pulmonary rehabilitation. However, a comparable prevalence of osteoporosis has been found in COPD patients in primary care settings as well as in outpatients.[43,45] Whether or not COPD patients entering rehabilitation are representative for the whole population remains currently unknown. At least the patients starting pulmonary rehabilitation form a representative sample of COPD patients referred to chest physicians. The included patients represent different stages of COPD severity as reflected by the GOLD stages. Second, a control group was lacking. Nevertheless, previous studies did already find an increased prevalence of osteoporosis as compared to healthy subjects.[11] The third limitation is that we did not have information on duration of treatment with oral corticosteroids and treatment courses in the past. However, no differences were found in prevalence of patients on maintenance oral corticosteroids between normal BMD, osteopenia and osteoporosis (Table 2). Moreover, not all current oral steroid users had osteoporosis and not all osteoporotic patients used oral steroids at the time of the study. Therefore, it seems reasonable to conclude that oral steroid use may partially explain the presence of osteoporosis in patients with COPD. Then again, the pathophysiology of osteoporosis in COPD is clearly multi-factorial.

Another limitation is that we did not gather information about previous fractures in patients and their parents; important known risk factors in the general population for fractures and incorporated in the FRAX fracture calculation tool of the WHO.[49] However, the aim of the study was not to estimate 10-year fracture risk but to investigate prevalence, prevalence of treatment and correlates of osteoporosis as defined by DXA. More studies are needed investigating this 10-year fracture risk in COPD patients. On the other hand, more research has to be done to investigate whether or not COPD in itself should be incorporated in the FRAX scoring system like rheumatoid arthritis. Indeed, in the male osteoporosis risk estimation score COPD was included as a risk factor.[12] Furthermore, we did not measure daily physical (in)activity in COPD. We did use the 6 min walking distance in our analyses which can be used as a surrogate marker of daily physical activity, particularly in COPD patients with a walking distance of about 400 m.[42] Finally, we used whole-body DXA instead of DXA at lumbar spine or hip and the diagnosis of osteoporosis according to

the WHO is based on *T*-scores measured at the hip or lumbar spine.[13] Therefore, we used recently determined cut-off values by Boyanov in order to have a good sensitivity-to-specificity ratio in the diagnosis of lumbar spine osteoporosis and low bone mass.[41]

In conclusion, more than 1 out of every 5 COPD patients entering pulmonary rehabilitation have osteoporosis. However, most of these osteoporotic COPD patients do not receive WHO-advised treatment to prevent fractures. Higher age and cachexia increase the risk of osteoporosis in COPD patients, irrespective of other clinically relevant factors. In contrast, overweight and obese COPD patients have a decreased risk of osteoporosis. Based on our findings we advise chest physicians to refer cachectic COPD patients for a DXA-scan, especially when they are older than 55 years of age irrespective of gender or COPD severity.

Conflicts of interest

All authors have no conflicts of interests.

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References

1. Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2007;**176**:532—55.
2. Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. *Lancet* 1997;**349**:1436—42.
3. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet* 2006; **367**:1747—57.
4. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. American Thoracic Society. *Am J Respir Crit Care Med* 1995;**152**:S77—121.
5. Agusti AG. Systemic effects of chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2005;**2**:367—70.
6. Andreassen H, Vestbo J. Chronic obstructive pulmonary disease as a systemic disease: an epidemiological perspective. *Eur Respir J Suppl* 2003;**46**:2s—4s.
7. Wouters EF. Introduction: systemic effects in chronic obstructive pulmonary disease. *Eur Respir J Suppl* 2003;**46**:1s.
8. Schols AM, Broekhuizen R, Weling-Scheepers CA, Wouters EF. Body composition and mortality in chronic obstructive pulmonary disease. *Am J Clin Nutr* 2005;**82**:53—9.
9. Vestbo J, Prescott E, Almdal T, et al. Body mass, fat-free body mass, and prognosis in patients with chronic obstructive pulmonary disease from a random population sample: findings from the Copenhagen City Heart Study. *Am J Respir Crit Care Med* 2006;**173**:79—83.
10. Sabit R, Bolton CE, Edwards PH, et al. Arterial stiffness and osteoporosis in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007;**175**:1259—65.
11. Graat-Verboom L, Wouters EF, Smeenk FW, Borne van den BE, Lunde R, Spruit MA. Current status of research on osteoporosis in COPD: a systematic review. Eur Respir J, in press.
12. Shepherd AJ, Cass AR, Carlson CA, Ray L. Development and internal validation of the male osteoporosis risk estimation score. *Ann Fam Med* 2007;**5**:540—6.
13. WHO Scientific Group on the Prevention and Management of Osteoporosis. Prevention and management of osteoporosis: report of a WHO scientific group [WHO technical report series; 921], http://whqlibdoc who int/trs/WHO_TRS_921 pdf; 2007.
14. Bolton CE, Ionescu AA, Shiels KM, et al. Associated loss of fat-free mass and bone mineral density in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004;**170**:1286—93.
15. Engelen MP, Schols AM, Heidendal GA, Wouters EF. Dual-energy X-ray absorptiometry in the clinical evaluation of body composition and bone mineral density in patients with chronic obstructive pulmonary disease. *Am J Clin Nutr* 1998;**68**: 1298—303.
16. Vrieze A, de Greef MH, Wijkstra PJ, Wempe JB. Low bone mineral density in COPD patients related to worse lung function, low weight and decreased fat-free mass. *Osteoporos Int* 2007;**18**:1197—202.
17. Freedman BA, Potter BK, Nesti LJ, Cho T, Kuklo TR. Missed opportunities in patients with osteoporosis and distal radius fractures. *Clin Orthop Relat Res* 2007;**454**:202—6.
18. Gruntmanis U. Male osteoporosis: deadly, but ignored. *Am J Med Sci* 2007;**333**:85—92.
19. Hajcsar EE, Hawker G, Bogoch ER. Investigation and treatment of osteoporosis in patients with fragility fractures. *CMAJ* 2000; **163**:819—22.
20. Wright RM. Use of osteoporosis medications in older nursing facility residents. *J Am Med Dir Assoc* 2007;**8**:453—7.
21. Dubois EF, Roder E, Dekhuijzen PN, Zwinderman AE, Schweitzer DH. Dual energy X-ray absorptiometry outcomes in male COPD patients after treatment with different glucocorticoid regimens. *Chest* 2002;**121**:1456—63.
22. Gluck O, Colice G. Recognizing and treating glucocorticoid-induced osteoporosis in patients with pulmonary diseases. *Chest* 2004;**125**:1859—76.
23. Goldstein MF, Fallon Jr JJ, Harning R. Chronic glucocorticoid therapy-induced osteoporosis in patients with obstructive lung disease. *Chest* 1999;**116**:1733—49.
24. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. *N Engl J Med* 2000;**343**:1902—9.
25. Israel E, Banerjee TR, Fitzmaurice GM, Kotlov TV, LaHive K, LeBoff MS. Effects of inhaled glucocorticoids on bone density in premenopausal women. *N Engl J Med* 2001;**345**:941—7.
26. Wong CA, Walsh LJ, Smith CJ, et al. Inhaled corticosteroid use and bone-mineral density in patients with asthma. *Lancet* 2000;**355**:1399—403.
27. de Vries F, van Staa TP, Bracke MS, Cooper C, Leufkens HG, Lammers JW. Severity of obstructive airway disease and risk of osteoporotic fracture. *Eur Respir J* 2005;**25**:879—84.
28. Elmstahl S, Ekstrom H, Galvard H, Johnell O, Gerhardsson DV, Norjavaara E. Is there an association between inhaled corticosteroids and bone density in postmenopausal women? *J Allergy Clin Immunol* 2003;**111**:91—6.
29. Li JT, Ford LB, Chervinsky P, et al. Fluticasone propionate powder and lack of clinically significant effects on hypothalamic-pituitary-adrenal axis and bone mineral density over 2 years in adults with mild asthma. *J Allergy Clin Immunol* 1999; **103**:1062—8.
30. Pauwels RA, Lofdahl CG, Laitinen LA, et al. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. European Respiratory Society Study on Chronic Obstructive Pulmonary Disease. *N Engl J Med* 1999;**340**:1948—53.

31. Incalzi RA, Caradonna P, Ranieri P, et al. Correlates of osteoporosis in chronic obstructive pulmonary disease. *Respir Med* 2000;**94**:1079—84.
32. Looker AC, Flegal KM, Melton III LJ. Impact of increased overweight on the projected prevalence of osteoporosis in older women. *Osteoporos Int* 2007;**18**:307—13.
33. Bonnet N, Gadois C, McCloskey E, et al. Protective effect of â blockers in postmenopausal women: influence on fracures, bone density, micro and macroarchitecture. *Bone* 2007;**40**:1209—16.
34. Pasco JA, Henry MJ, Sanders KM, Kotowicz MA, Seeman E, Nicholson GC. Beta-adrenergic blockers reduce the risk of fracture partly by increasing bone mineral density: Geelong Osteoporosis Study. *J Bone Miner Res* 2004;**19**:19—24.
35. Schoofs MW, van der Klift M, Hofman A, et al. Thiazide diuretics and the risk for hip fracture. *Ann Intern Med* 2003; **139**:476—82.
36. Schoofs MW, Sturkenboom MC, van der KM, Hofman A, Pols HA, Stricker BH. HMG-CoA reductase inhibitors and the risk of vertebral fracture. *J Bone Miner Res* 2004;**19**:1525—30.
37. Haney EM, Chan BK, Diem SJ, et al. Association of low bone mineral density with selective serotonin reuptake inhibitor use by older men. *Arch Intern Med* 2007;**167**:1246—51.
38. Koh JM, Khang YH, Jung CH, et al. Higher circulating hsCRP levels are associated with lower bone mineral density in healthy pre- and postmenopausal women: evidence for a link between systemic inflammation and osteoporosis. *Osteoporos Int* 2005;**16**:1263—71.
39. Spruit MA, Vanderhoven-Augustin I, Janssen PP, Wouters EF. Integration of pulmonary rehabilitation in COPD. *Lancet* 2008; **371**:12—3.
40. Baarends EM, Schols AM, Mostert R, Wouters EF. Peak exercise response in relation to tissue depletion in patients with chronic obstructive pulmonary disease. *Eur Respir J* 1997;**10**:2807—13.
41. Boyanov M. Estimation of lumbar spine bone mineral density by dual-energy X-ray absorptiometry: standard anteroposterior scans vs sub-regional analyses of whole-body scans. *Br J Radiol* 2008;**81**:637—42.
42. Pitta F, Troosters T, Spruit MA, Probst VS, Decramer M, Gosselink R. Characteristics of physical activities in daily life in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005;**171**:972—7.
43. Dimai HP, Domej W, Leb G, Lau KH. Bone loss in patients with untreated chronic obstructive pulmonary disease is mediated by an increase in bone resorption associated with hypercapnia. *J Bone Miner Res* 2001;**16**:2132—41.
44. Iqbal F, Michaelson J, Thaler L, Rubin J, Roman J, Nanes MS. Declining bone mass in men with chronic pulmonary disease: contribution of glucocorticoid treatment, body mass index, and gonadal function. *Chest* 1999;**116**:1616—24.
45. Sin DD, Man JP, Man SF. The risk of osteoporosis in Caucasian men and women with obstructive airways disease. *Am J Med* 2003;**114**:10—4.
46. Vik SA, Jantzi M, Poss J, et al. Factors associated with pharmacologic treatment of osteoporosis in an older home care population. *J Gerontol A Biol Sci Med Sci* 2007;**62**:872—8.
47. Pazianas M, Miller P, Blumentals WA, Bernal M, Kothawala P. A review of the literature on osteonecrosis of the jaw in patients with osteoporosis treated with oral bisphosphonates: prevalence, risk factors, and clinical characteristics. *Clin Ther* 2007; **29**:1548—58.
48. Reid IR, Bolland MJ, Grey AB. Is bisphosphonate-associated osteonecrosis of the jaw caused by soft tissue toxicity? *Bone* 2007;**41**:318—20.
49. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. FRAX and the assessment of fracture probability in men and women from the UK. *Osteoporos Int* 2008;**19**:385—97.
50. Engelen MP, Schols AM, Lamers RJ, Wouters EF. Different patterns of chronic tissue wasting among patients with chronic obstructive pulmonary disease. *Clin Nutr* 1999;**18**:275—80.
51. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante Jr AW. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest* 2003;**112**: 1796—808.
52. Reid IR. Obesity and osteoporosis. *Ann Endocrinol (Paris)* 2006; **67**:125—9.
53. Nici L, Donner C, Wouters E, et al. American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. *Am J Respir Crit Care Med* 2006;**173**:1390—413.