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ORIGINAL RESEARCH

Lower Prevalence of Osteoporosis in Patients with COPD Taking Anti-Inflammatory Compounds for the Treatment of Diabetes: Results from COSYCONET

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Background: Patients with chronic obstructive pulmonary disease (COPD) often have osteoporosis and diabetes as comorbid conditions. Anti-diabetic medication, including metformin, has protective effects on osteoporosis in experimental studies. We therefore studied whether patients with COPD receiving anti-diabetic medication had a lower osteoporosis prevalence in a large COPD cohort, COSYCONET.

Methods: Assessment of osteoporosis was based on patients' reports of physician-based diagnoses and the presence of disease-specific medication. The predictive value of physical characteristics, lung function, comorbidities, cardiovascular medication, and the use of anti-inflammatory diabetes medication, including metformin, sulfonylureas, glinides or DPP4I, was evaluated using logistic regression analysis. ClinicalTrials.gov: NCT01245933.

Results: In total, 2222 patients were eligible for analysis (863 [39%] female, mean age 65 y), 515 of whom had higher symptoms and exacerbations (Global Initiative for Chronic Obstructive Lung Disease group D). Osteoporosis was present in 15.8% of the overall cohort, and in 24.1% of GOLD D patients. Regression analyses identified the following as associated with osteoporosis ($p < 0.05$): female sex, higher age, lower body-mass index, asthma, higher air trapping, oral steroids, and cardiovascular medication. Although oral anti-diabetic medication was overall not associated with a lower prevalence of osteoporosis ($p = 0.131$), anti-inflammatory anti-diabetic medication ($p = 0.009$) and metformin-containing therapy ($p = 0.039$) were. This was driven by GOLD D patients.

Conclusion: In a large COPD cohort, anti-inflammatory diabetes therapy, including metformin, was associated with a lower prevalence of osteoporosis, especially in patients with higher symptoms and exacerbations. These findings suggest a protective effect of common anti-diabetic medication on osteoporosis, possibly as a result of attenuated systemic inflammation.

Keywords: chronic obstructive pulmonary disease, oral corticosteroids, inhaled corticosteroids, anti-inflammatory, metformin, diabetes

Introduction

Osteoporosis is a major comorbidity of chronic obstructive pulmonary disease (COPD).[1–7] In addition to generic osteoporosis risk factors, such as female sex, higher age, smoking, cachexia and reduced physical capacity, a range of COPD-related risk factors are known to also increase osteoporosis risk, including the severity of pulmonary impairment, vitamin D deficiency, or systemic inflammation,[8,9] with systemic

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inflammation also an independent predictor of low bone mineral density (BMD) in patients with stable COPD.[10] Diabetes mellitus is also a common comorbidity in COPD,[11] and there is evidence that inflammatory pathways are involved in the pathogenesis of this disease.[12] Besides decreased BMD, more frequently observed in type 1 diabetes, decreased bone quality is associated with increased fragility, especially in type 2 diabetes.[13] This suggests that in patients with comorbid COPD and diabetes, systemic inflammation related to both diseases may contribute to the development of osteoporosis. Conversely, anti-inflammatory medication with systemic action, in particular anti-diabetic medication containing metformin, sulfonylureas, glinides or DPP4I,[11,14,15] could have the potential to reduce the risk of osteoporosis.[13,16]

A further contributing factor in COPD may be the fact that many patients are treated with inhaled corticosteroids (ICS),[17] with a significant proportion receiving oral corticosteroids (OCS).[18] OCS use clearly promotes the development and progression of osteoporosis,[19] whereas findings for ICS use are equivocal in patients with COPD – although there is an increased risk of osteoporosis in patients with asthma, especially when receiving high-dose ICS.[20]

Recent in-vitro and animal studies have evaluated the role of metformin in bone turnover independent of the presence of diabetes.[21–24] Anti-diabetic drugs, especially metformin, have the potential to prevent corticosteroid-induced bone loss, including via mechanisms to suppress bone resorption and stimulate bone formation.[25] Taken together, this suggests that patients with COPD could be appropriate to examine potential effects of anti-diabetic medication on the development of osteoporosis. This could be particularly true for patients with a high disease burden[18] as is the case for those classified by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) as "group D",[26] who would therefore be expected to more frequently use ICS and/or OCS therapy. Based on this, data from the German COPD and Systemic Consequences - Comorbidities Network (COSYCONET) cohort were analyzed to evaluate whether the use of anti-diabetic medication is associated with a lower adjusted prevalence of osteoporosis.[4]

Materials and Methods

Study Population

The present study used baseline data (visit 1) from the COSYCONET COPD cohort, a multi-center study investigating the role of comorbidities in patients with COPD (ClinicalTrials.gov: NCT01245933). COSYCONET was conducted in accordance with the Declaration of Helsinki, has been approved by the ethics committees of all study centers, and all patients gave their written informed consent. Detailed information on the recruitment process, inclusion/exclusion criteria and assessments can be found elsewhere.[4]

Assessments

All measurements were performed when patients had stable disease, defined as the absence of moderate or severe exacerbations within the last four weeks.[4] Post-bronchodilator[4] lung function data included forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC), each as percent predicted,[27] and the ratio of residual volume to total lung capacity (RV/TLC), as a measure of air trapping/hyperinflation. Patients were classified as GOLD grades 1–4 based on FEV_1 categories,[26] and GOLD groups A-D on symptoms and exacerbation history according to GOLD 2017 criteria,[26] using the modified Medical Research Council dyspnea scale (mMRC). Smoking was categorized as current smoking versus former or never-smoking. These analyses only included patients of GOLD grades 1–4,[26,28] who had complete data for age, sex, body-mass index (BMI), smoking status, FEV1, FVC, RV, TLC and GOLD grouping.

Comorbidities and Medication

Patients were asked to bring all their medication to the study visit.[29] The presence of comorbidities, including osteoporosis and diabetes, was assessed in a structured interview from patient reports of physician-based diagnoses[4] and supplemented by disease-specific medication.[29] Coronary artery disease, cardiac failure and myocardial infarction were analyzed individually and were also summarized into a combined "cardiac disease" variable. Cardiovascular medication included beta-blockers, renin-angiotensin-aldosterone system inhibitors, angiotensin-receptor antagonists, angiotensin II receptor blockers, calcium-channel blockers and diuretics. Anti-diabetes medication comprised metformin, sulfonylureas, glinides, dipeptidyl peptidase 4 inhibitors (DPP4I), incretin mimetics and insulin. Medication containing metformin, sulfonylureas, glinides or DPP4I was considered anti-inflammatory.[14,15] We also evaluated the category of metformin-containing medication,[25] alone or in combination with other anti-diabetes drugs, as well as that of oral anti-diabetes drugs in general.

Data Analysis

Groups with and without osteoporosis were compared using either unpaired *t*-tests or chi-square statistics as appropriate. Binary logistic regression analysis was employed to assess the dependence of osteoporosis on risk factors. For this purpose, sets of variables were successively added, until the final set of predictors was reached. This process started with the set of demographic data, then lung function, then comorbidities, then medication. We retained all variables that were significant ($p < 0.05$, two-sided) and also any non-significant variables that were considered relevant confounders from a clinical perspective. The analyses were performed for the total data set and also for single GOLD groups or combinations of groups. To reveal whether groups of COPD patients with different disease severity showed a different association with diabetes medication, we performed analyses stratified according to GOLD groups. This approach was chosen, as the introduction of an indicator variable for these categories implicitly assumes a linear effect, while it may be that the degree of association is affected not the mean level. To properly account for this would have needed the introduction of several interaction terms, thereby complicating the analysis. All analyses were performed using SPSS (Version 27.0.0.0, Armonk, NY, US). We additionally checked the results of the regression analyses by propensity score matching, using the method of full matching, as done previously for the effects of respiratory medication on the heart.[30]

Results

Baseline Characteristics

The study population comprised 2222 patients, 351 (15.8%) of whom had a diagnosis of osteoporosis, with osteoporosis prevalence across GOLD groups A/B/C/D of 11.1/16.0/14.5/24.1%. Further characteristics stratified by presence or absence of osteoporosis are given in Table 1. There were significant differences between the two groups

Table 1 Patient Characteristics Including Demographics, Lung Function, COPD Categories, Major Comorbidities and Medication

Variable	All	No Osteoporosis	Osteoporosis	p value
	N = 2222	N = 1871	N = 351	
Demographics				
Age (y)	65.0 ± 8.4	64.8 ± 8.6	66.2 ± 7.5	0.005
Sex m/f	1359 (61.2%)/863 (38.8%)	1225 (65.5%)/646 (34.5%)	134 (38.2%)/217 (61.8%)	<0.001
BMI (kg/m^2)	26.6 ± 5.2	26.9 ± 5.2	25.2 ± 4.9	<0.001
Smoking status (active)	552 (24.8%)	481 (25.7%)	71 (20.2%)	0.029
Lung function				
FEV_1 (% predicted)	52.8 ± 18.4	53.4 ± 18.4	49.5 ± 18.4	<0.001
FVC (% predicted)	78.5 ± 18.9	79.2 ± 19.0	75.1 ± 18.2	<0.001
RV/TLC (%)	54.4 ± 11.0	53.6 ± 10.9	58.4 ± 10.6	<0.001
GOLD grades 1/2/3/4	200/945/852/225	174/821/702/174	26/124/150/51	0.001
GOLD groups A/B/C/D	861/556/290/515	765/467/248/391	96/89/42/124	<0.001
Comorbidities				
Asthma	425 (19.1%)	325 (17.4%)	100 (28.5%)	<0.001
Diabetes	288 (13.0%)	253 (13.5%)	35 (10.0%)	0.069
Arterial hypertension	1254 (56.4%)	1042 (55.7%)	212 (60.4%)	0.103
Cardiac disease	461 (20.7%)	383 (20.5%)	78 (22.2%)	0.458
Medication				
ICS	1460 (65.7%)	1200 (64.1%)	260 (74.1%)	<0.001
OCS	280 (12.6%)	200 (10.7%)	80 (22.8%)	<0.001
Cardiac medication	1327 (59.7%)	1087 (58.1%)	240 (68.4%)	<0.001
Oral anti-diabetes medication	222 (10.0%)	199 (10.6%)	23 (6.6%)	0.019
All anti-inflammatory diabetes medication	175 (7.9%)	162 (8.7%)	13 (3.7%)	0.002
Any metformin-containing medication	140 (6.3%)	131 (7.0%)	9 (2.6%)	0.002

Note: Data are mean ± standard deviation or number (percent).

Abbreviations: FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; RV/TLC, ratio of residual volume to total lung capacity determined by body plethysmography; BMI, body mass index; ICS, inhaled corticosteroids; OCS, oral corticosteroids.

for sex, age, BMI, smoking status, GOLD grades and groups, FEV_1, FVC, RV/TLC, and the presence of asthma (all $p < 0.05$), but not the presence of diabetes or cardiac disease (either as a summary score or the single items; not shown). As we performed a separate analysis for patients of GOLD group D, baseline characteristics were compared between group D patients and the pooled groups ABC (Supplemental Table 1).

Medication

Of 351 patients with osteoporosis, 105 (29.9%) received osteoporosis-specific medication; in 15 (4.3%) patients the osteoporosis diagnosis was based solely on the presence of this disease-specific medication. ICS use was reported overall by 1460 (65.7%) patients, with use higher in those with osteoporosis compared to those without (74.1% versus 64.1%, $p < 0.001$, Table 1). OCS therapy was used by 280 (12.6%) patients, again with use higher in the osteoporosis group (22.8% versus 10.7%, $p < 0.001$), overlapping with ICS use. Overall, 1327 patients (59.7%) were receiving any type of cardiac medication (including diuretics), with yet again use higher in those with osteoporosis (68.4% versus 58.1%, $p < 0.001$). Oral anti-diabetic medication was being used by 222 (77.1%) of the 288 patients with diabetes: anti-inflammatory diabetes medication (defined as above) in 175 patients (60.8%), and specifically metformin-containing therapy in 140 patients (48.6%). The percentages of patients receiving anti-inflammatory (3.7% versus 8.7%, $p = 0.002$) or specifically metformin-containing therapy (2.6% versus 7.0%, $p = 0.002$) were lower in the osteoporosis group. Comparisons between GOLD group D and groups ABC are shown in Supplemental Table 1, illustrating the higher percentage of ICS, OCS and cardiac medication use by patients in group D.

Associations Between Osteoporosis and Predictors

Analysis of the Total Study Cohort

The process of variable selection is shown in Table 2. Using the demographic data as predictors, osteoporosis

Table 2 Results of Logistic Regression Analyses During Several Steps, Leading to Final Step 8

Predictor	Step 1	Step 2	Step 3	Step 4	Step 5	Step 6	Step 7	Step 8
Demographics								
Age (per 10 y)	1.307***		1.252**	1.247**	1.215*	1.215*	1.179*	1.182*
Sex (female vs male)	3.087***		2.797***	3.178***	2.771***	2.848***	2.827***	2.829***
BMI (kg/m^2)	0.942***		0.951***	0.931***	0.946***	0.945***	0.941***	0.942 ***
Smoking status (active)	0.699*		0.729*	0.733*	0.756[a]	0.810	0.841	0.850
Lung function								
FEV_1 (% predicted)		1.007						
FVC (% predicted)		1.009						
RV/TLC (%)		1.063***	1.028***		1.029***	1.023***	1.022***	1.022***
Comorbidities								
Asthma				1.650***	1.746***	1.576**	1.620***	1.643***
Sleep apnea				1.157				
Diabetes				0.870[a]	0.857	0.837	0.828	1.371
Arterial hypertension				1.342*	1.319*	1.278	0.902	0.912
Cardiac disease				1.363[a]	1.359*	1.383*	1.257[a]	1.259
Hyperuricemia				1.202				
Hyperlipidemia				1.073				
Medication								
ICS						1.222[a]	1.198	1.199
OCS						1.956***	1.863***	1.818***
Cardiac medication							1.742**	1.723**
Diabetes medication[b]								0.358**

Notes: Odds ratios (Exp [B]) values are shown. Predictors revealed as statistically significant were kept in the subsequent steps of analyses. Significance is denoted as follows: *p<0.05, **p<0.01, ***p<0.001. [a]These predictors were included in the following steps, even when not being statistically significant, as they were rated as of potential clinical relevance. [b]In the final analysis we used either any oral anti-diabetes medication, or any anti-inflammatory anti-diabetes medication, or any metformin-containing medication (see Results); the table shows the results for any anti-inflammatory anti-diabetes medication (see Table 2 for details).

Abbreviations: BMI, body mass index; ICS, inhaled corticosteroids; OCS, oral corticosteroids.

was associated with older age, female sex, lower BMI and active smoking status. Using lung function parameters as predictors, it was linked only to higher RV/TLC. When combining the two sets of variables, a higher RV/TLC, older age, female sex, lower BMI and active smoking status remained significant. Regarding comorbidities as predictors (Table 2), only asthma and hypertension were significantly linked to osteoporosis, with a tendency for cardiac disease. When further combining comorbidities with both demographic characteristics and RV/TLC, older age, female sex, higher BMI, asthma, hypertension and higher RV/TLC remained significant. We thus kept asthma and hypertension in the further analyses as robust predictors but also smoking status, diabetes and cardiac disease despite being not significant to account for their presence when analyzing the effects of diabetes and cardiac medication.

In the next step, ICS and OCS use were added as predictors. Only OCS use was significantly related to osteoporosis. Despite this, we kept ICS in the further analyses since they might be relevant in subgroups. Cardiovascular medication was introduced as the next predictor; it was significantly associated with an increased prevalence of osteoporosis. In the final step, we added anti-diabetic medication as predictor (Table 2). There was no significant relationship between osteoporosis and the presence of any oral anti-diabetic medication ($p = 0.131$). However, anti-inflammatory anti-diabetic medication ($p = 0.009$) was associated with a reduction in the prevalence of osteoporosis ($p = 0.008$), as was metformin-containing medication ($p = 0.039$) (Table 3 and Figure 1). As can be seen in Table 3, the detrimental effect of cardiac medication remained significant.

Analysis Stratified According to GOLD Groups

The associations with anti-inflammatory diabetes medication and with metformin found in the total population of patients were significant only in GOLD group D ($p = 0.006$), and not in groups A, B or C. We therefore pooled these groups in the analysis. In this pooled group, the associations were still not

Table 3 Results of Logistic Regression Analyses in Either the Total Population of Patients or Those in GOLD Group D, Demonstrating the Significant Effect of Anti-Inflammatory Diabetes Medication in Both

Predictor	All Patients (N = 2222)				GOLD Group D (N = 515)			
	OR	95% CI of OR		p value	OR	95% CI of OR		p value
		Lower	Upper			Lower	Upper	
Demographics								
Age (per 10 y)	1.182	1.012	1.380	0.035	1.386	1.037	1.852	0.028
Sex (female vs male)	2.829	2.184	3.663	<0.001	2.523	1.583	4.020	<0.001
BMI (kg/m^2)	0.942	0.917	0.967	<0.001	0.942	0.899	0.986	0.011
Smoking status (active)	0.850	0.625	1.156	0.300	0.794	0.410	1.538	0.494
Lung function								
RV/TLC (%)	1.022	1.010	1.035	<0.001	1.013	0.989	1.036	0.286
Comorbidities								
Asthma	1.643	1.232	2.190	0.001	1.309	0.782	2.190	0.306
Diabetes	1.371	0.813	2.311	0.237	2.158	0.979	4.760	0.057
Arterial hypertension	0.912	0.643	1.293	0.605	0.741	0.409	1.342	0.323
Cardiac disease	1.259	0.921	1.721	0.148	1.271	0.751	2.151	0.371
Medication								
ICS	1.199	0.905	1.590	0.206	2.789	1.340	5.808	0.006
OCS	1.818	1.323	2.498	<0.001	1.857	1.141	3.024	0.013
Cardiac medication	1.723	1.173	2.531	0.006	1.546	0.784	3.049	0.208
Anti-inflammatory diabetes medication	0.358	0.166	0.773	0.009	0.183	0.054	0.619	0.006

Notes: Results for metformin were similar ($p<0.05$), while those for any oral anti-diabetes medication did not indicate a significant relationship to this medication (see Figure 1). In GOLD groups A, B, C and the pooled group ABC there were no significant relationships to any of the anti-diabetes medications.

Abbreviations: OR, odds ratio (= EXP[B]); 95% CI, respective 95% confidence interval; RV/TLC, ratio of residual volume to total lung capacity determined by body plethysmography; ICS, inhaled corticosteroids; OCS, oral corticosteroids.

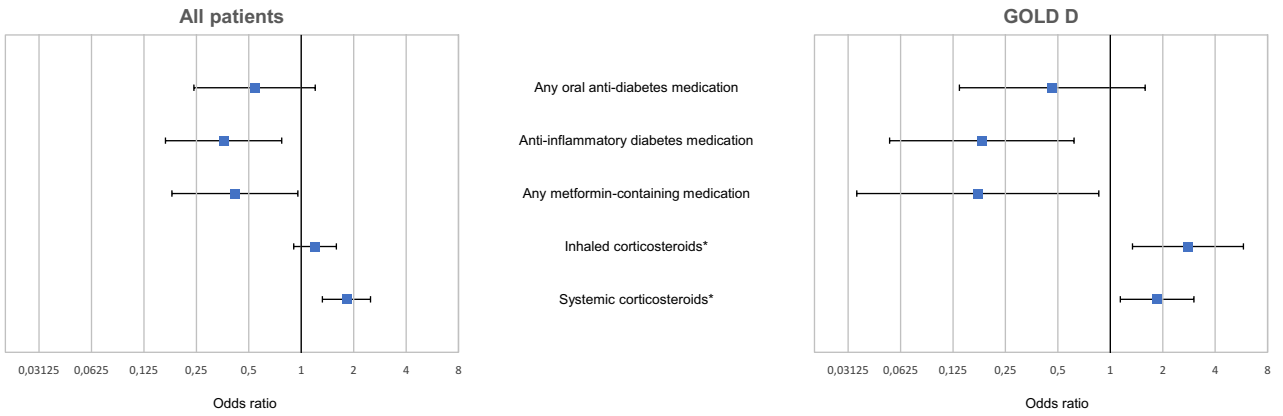

Figure 1 Results of logistic regression analyses in either the total population of patients or those in GOLD group D, demonstrating the significant effect of anti-inflammatory diabetes medication in both.

significant (p = 0.389), despite the increase in sample size. Results for GOLD group D are given in Table 3 and Figure 1.

Propensity Score Matching Regarding Diabetes Medication

In the total group, the results for ICS (p = 0.097) and OCS (p = 0.014) were in accordance with those of the conventional regression analysis, as was the case for any oral anti-diabetic medication (p = 0.171) and for anti-inflammatory anti-diabetic medication (p = 0.016); the result for metformin only showed a tendency (p = 0.058). In patients in GOLD group D, results were also consistent with the conventional regression analysis, since ICS (p = 0.022), OCS (p = 0.0007), anti-inflammatory anti-diabetic medication (p = 0.004), and metformin-containing medication (p = 0.004) were linked to osteoporosis, whereas any oral anti-diabetic medication was not (p = 0.917).

Discussion

In the present cross-sectional study of patients with stable COPD, the use of anti-inflammatory compounds for the treatment of diabetes was associated with a lower prevalence of osteoporosis. This result was obtained while taking into account known osteoporosis risk factors and was robust, as it was observed with two statistical approaches. The beneficial effect of anti-diabetic medication was driven by patients from GOLD group D, ie, patients with high symptoms and exacerbations, in whom OCS and ICS use were most prevalent, and both OCS and ICS were significantly associated with osteoporosis. Our findings suggest benefits from the treatment of diabetes in patients with COPD that extend beyond diabetes itself. This could be clinically relevant, as patients with COPD are more than twice as likely as those without COPD to have osteoporosis (OR, 2.83), with an estimated global osteoporosis prevalence of 38% in COPD.[31] In our study cohort, the prevalence was lower than this (16%), probably due to the fact that our population comprised more males than females and the prevalence of osteoporosis was higher in females (25.6%) than males (9.9%). The development of osteoporosis is known to depend on generic risk factors including female sex, older age and low BMI,[32–35] as well as COPD-related factors including smoking,[36] OCS use,[3,37] ICS use,[38] cardiac disease[39] and diabetes.[40] We confirmed these associations, although, when taking into account a broad panel of risk factors, cardiac disease (20.8% of patients) was not significantly associated with osteoporosis. It was, however, indirectly related to an increased prevalence of osteoporosis via the intake of cardiac medication including diuretics, known risk factors for osteoporosis.[41,42] Although in the total study population there was no significant link between ICS use and osteoporosis, this link was clearly present in GOLD group D. It was not detectable in any of the other GOLD groups, confirming the adequacy of a stratified analysis. For this stratification, we selected GOLD groups based on the assumption that risk factors of osteoporosis including systemic inflammation would be most pronounced in patients of GOLD group D.

Systemic inflammation is not only involved in the pathophysiology of COPD, but is also relevant in diabetes and osteoporosis.[43] Our observations are consistent with experimental data on the effects of anti-inflammatory anti-diabetes medication, including metformin, on the risk for osteoporosis especially in the presence of corticosteroids.

Studies demonstrated anti-inflammatory effects of anti-diabetes treatment on vascular disorders,[44] via inhibition of adenosine monophosphate-activated protein kinase (AMPK), production of reactive oxygen species, inhibition of interleukin (IL)-1β activation in macrophages, peroxisome proliferator–activated receptor (PPAR)γ, expression of pro-inflammatory cytokines and increased adiponectin levels.[15,44,45] As some of these mechanisms could also be involved in the development of osteoporosis, it is reasonable to expect beneficial effects of medication with anti-inflammatory action, as observed in our study. Indeed, from health insurance data there are hints that the prevalence of osteoporosis in diabetes is lower in patients receiving metformin therapy than in patients with diabetes not receiving metformin.[46,47] Metformin use was also associated with a lower risk of osteoporosis regardless of the presence of diabetes or obesity.[48] Indeed in a Phase 2 trial, non-diabetic patients receiving systemic glucocorticoids due to inflammatory disease were randomized to receive metformin or placebo; in the metformin arm, an improved bone metabolism was observed.[24]

In our study, the anti-inflammatory treatment was predominantly metformin, a drug with pleiotropic, anti-inflammatory effects with the potential to prevent osteoporosis.[13,16,49] This is relevant as diabetes is linked to secondary bone loss, possibly from impaired osteoblastic function,[50] and cohort studies indicated an increased risk of fracture in patients with diabetes.[51] Conversely, experimental studies in animals have shown positive effects of metformin on bone loss,[23,24] and treatment with oral anti-diabetic medication seems to be associated with increased density bone mineral density, in contrast to insulin, for which lower intestinal absorption and increased urinary excretion of calcium,[16] as well as vitamin D regulation, might play a detrimental role. In cell cultures, osteogenic effects of metformin have been shown,[7,8] involving AMPK, mTOR (mechanistic target of rapamycin) complexes 1 and 2 and SIRT6 (sirtuin 6), with effects on NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells), a key pro-inflammatory transcription factor. It also increased OPG (osteoprotegerin) and decreased RANKL (receptor activator of NF-κB ligand) that is associated with osteoclastic activity and bone resorption.[52,53] Thus, there are multiple pathways by which anti-inflammatory anti-diabetic medication,[44] including metformin, could reduce the risk of osteoporosis. It was not the aim of the present study to identify a specific compound as protective but the results suggest that metformin played a role. These mechanisms could be especially important in patients with COPD, a large percentage of whom are treated with corticosteroids.[18] Effects of corticosteroids on the development of osteoporosis are probably to be most pronounced in patients with the highest intensity of this treatment and the highest degree of systemic inflammation. From this perspective, it does not seem surprising that the beneficial effect of diabetes medication that we observed was driven by patients in GOLD group D, although this represented only about one quarter of our population.

Impaired lung function has been reported to be linked to osteoporosis;[54] this was confirmed in our study, in which RV/TLC, as a marker of trapped air and hyperinflation, was the most robust lung function predictor. RV/TLC is associated with airway obstruction,[55] but its predictive value dominated over that of FEV_1 and FVC. Low BMI was also a risk factor for osteoporosis, although interestingly it is commonly linked to a lower, not a higher value of RV/TLC.[56] These results highlight that BMI and RV/TLC had independent predictive values. As an indicator of air trapping, RV/TLC is associated with lung emphysema, which is known to be linked to lower BMI. The fact that RV/TLC was positively related to the prevalence of osteoporosis confirmed that lung emphysema is among the risk factors of osteoporosis.[57] We additionally observed a trend for lower prevalence of diabetes among patients with osteoporosis. A potential reason for this could be the fact that COPD patients with osteoporosis had a lower BMI and thus a lower risk of developing type 2 diabetes, which was the pre-dominant type of diabetes in the cohort.

In the total group of patients, the intake of anti-inflammatory anti-diabetic medication was associated with a reduction in the prevalence of osteoporosis of approximately 3-fold, while in patients of GOLD group D the reduction was approximately 5-fold; for metformin the reductions were approximately 2.5-fold. These numbers indicate a marked reduction in the prevalence of osteoporosis, and should be compared with other influencing factors. The increase in prevalence associated with female sex was at least 2.5-fold, while that for OCS use was about 2-fold. In patients of GOLD group D, ICS use was linked to a close to 3-fold increase in prevalence, whereas cardiac medication was significant only in the total group, with a 1.7-fold increased osteoporosis prevalence. These numbers indicate that the benefit from anti-inflammatory anti-diabetic medication was at least as great as the detrimental effect of a number of risk factors. Our

observations suggest that future studies should carefully observe whether such tremendous effects can be substantiated.

Limitations and Strengths

Our analyses were based on cross-sectional data. Although the results are plausible from clinical and pathophysiological points of view, this does not allow us to infer causal relationships. Further, data on daily dosages, duration of treatment and adherence to medication were not collected, although from a previous analysis of COSYCONET we know that adherence to medication is very high.[58] The multiple influencing factors on osteoporosis required multiple adjustments, but the results were robust in the sense that standard multiple logistic regression analysis and propensity score matching essentially yielded the same results. Finally, no measurements on bone density were available, and thus we had to rely on the patients' reports of physician-based diagnoses of osteoporosis. The same was true for other comorbidities, but those other comorbidities could be largely confirmed by analysis of disease-specific medication.[29] Still, the potential bias from a potentially sex-dependent under-diagnosis of osteoporosis has to be considered. In our study cohort, the prevalence of treatment with ICS and OCS was high as previously described.[17,18] As animal data suggest a particular effectiveness against metformin-induced corticosteroid induced osteoporosis,[13] it might be speculated that the beneficial effect observed by us was linked to the high level of corticosteroid treatment. We did not test whether in the GOLD group D the beneficial effect was also present in patients without corticosteroids, as the number of these patients was too small and they probably represented a highly biased sub-population. We also believe with the introduction of triple-therapy the corticosteroid-associated problems will remain in the future.

Conclusion

The present analyses indicate a beneficial effect of anti-inflammatory anti-diabetic medication on the prevalence of osteoporosis in patients with COPD. This effect was especially notable in patients with frequent exacerbations and high symptoms scores, known as GOLD group D, who also had the highest exposure to ICS and OCS. The findings are consistent with experimental data regarding anti-diabetes medication, especially metformin, and highlight the pleiotropic potential of systemic medication to exert beneficial effects on other comorbidities in patients with COPD.

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The study was based on data from 2741 patients recruited within the COSYCONET framework (ClinicalTrials.gov, Identifier: NCT01245933). For further information see Karch A, Vogelmeier C, Welte T, Bals R, Kauczor HU, Biederer J, Heinrich J, Schulz H, Glaser S, Holle R et al. The German COPD cohort COSYCONET: Aims, methods and descriptive analysis of the study population at baseline. *Respir Med*. 2016;114:27–37.

Data Sharing Statement

The basic data are part of the German COPD cohort COSYCONET (www.asconet.net) and available upon

request. The website of the network provides a detailed procedure for respective applications. The data can be obtained after submission of a proposal that is evaluated by the steering committee. All results to which the manuscript refers, are documented appropriately in the text, figures or tables.

Ethics Approval and Consent to Participate

All assessments were approved by the central (Marburg (Ethikkommission FB Medizin Marburg) and local (Bad Reichenhall (Ethikkommission bayerische Landesärztekammer); Berlin (Ethikkommission Ärztekammer Berlin); Bochum (Ethikkommission Medizinische Fakultät der RUB); Borstel (Ethikkommission Universität Lübeck); Coswig (Ethikkommission TU Dresden); Donaustauf (Ethikkommission Universitätsklinikum Regensburg); Essen (Ethikkommission Medizinische Fakultät Duisburg-Essen); Gießen (Ethikkommission Fachbereich Medizin); Greifswald (Ethikkommission Universitätsmedizin Greifswald); Großhansdorf (Ethikkommission Ärztekammer Schleswig-Holstein); Hamburg (Ethikkommission Ärztekammer Hamburg); MHH Hannover/Coppenbrügge (MHH Ethikkommission); Heidelberg Thorax/Uniklinik (Ethikkommission Universität Heidelberg); Homburg (Ethikkommission Saarbrücken); Immenhausen (Ethikkommission Landesärztekammer Hessen); Kiel (Ethikkommission Christian-Albrechts-Universität zu Kiel); Leipzig (Ethikkommission Universität Leipzig); Löwenstein (Ethikkommission Landesärztekammer Baden-Württemberg); Mainz (Ethikkommission Landesärztekammer Rheinland-Pfalz); München LMU/Gauting (Ethikkommission Klinikum Universität München); Nürnberg (Ethikkommission Friedrich-Alexander-Universität Erlangen Nürnberg); Rostock (Ethikkommission Universität Rostock); Berchtesgadener Land (Ethikkommission Land Salzburg); Schmallenberg (Ethikkommission Ärztekammer Westfalen-Lippe); Solingen (Ethikkommission Universität Witten-Herdecke); Ulm (Ethikkommission Universität Ulm); Würzburg (Ethikkommission Universität Würzburg)) Ethical Committees, and written informed consent was obtained from all patients.

Consent for Publication

Within the ethical approval of COSYCONET, the participants of the study gave their consent to publish the data collected without reference to their person.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

Professor Joachim H Ficker reports personal fees from Boehringer-Ingelheim, AstraZeneca, and GSK; personal fees, non-financial support from CSL Behring and Novartis, outside the submitted work. Professor Jürgen Behr reports personal fees from Boehringer-Ingelheim, AstraZeneca, and Novartis, outside the submitted work. Professor Robert Bals reports COSYCONET is supported by the German Centre for Lung Research (DZL), grant number 82DZLI05A2 (COSYCONET), the BMBF, grant number 01GI0881 and also received unrestricted grants from AstraZeneca GmbH, Boehringer Ingelheim Pharma GmbH & Co. KG, GlaxoSmithKline GmbH&Co. KG,

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