

**Bone imaging and strength in
chronic obstructive pulmonary disease**

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COLOFON

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PROEFSCHRIFT

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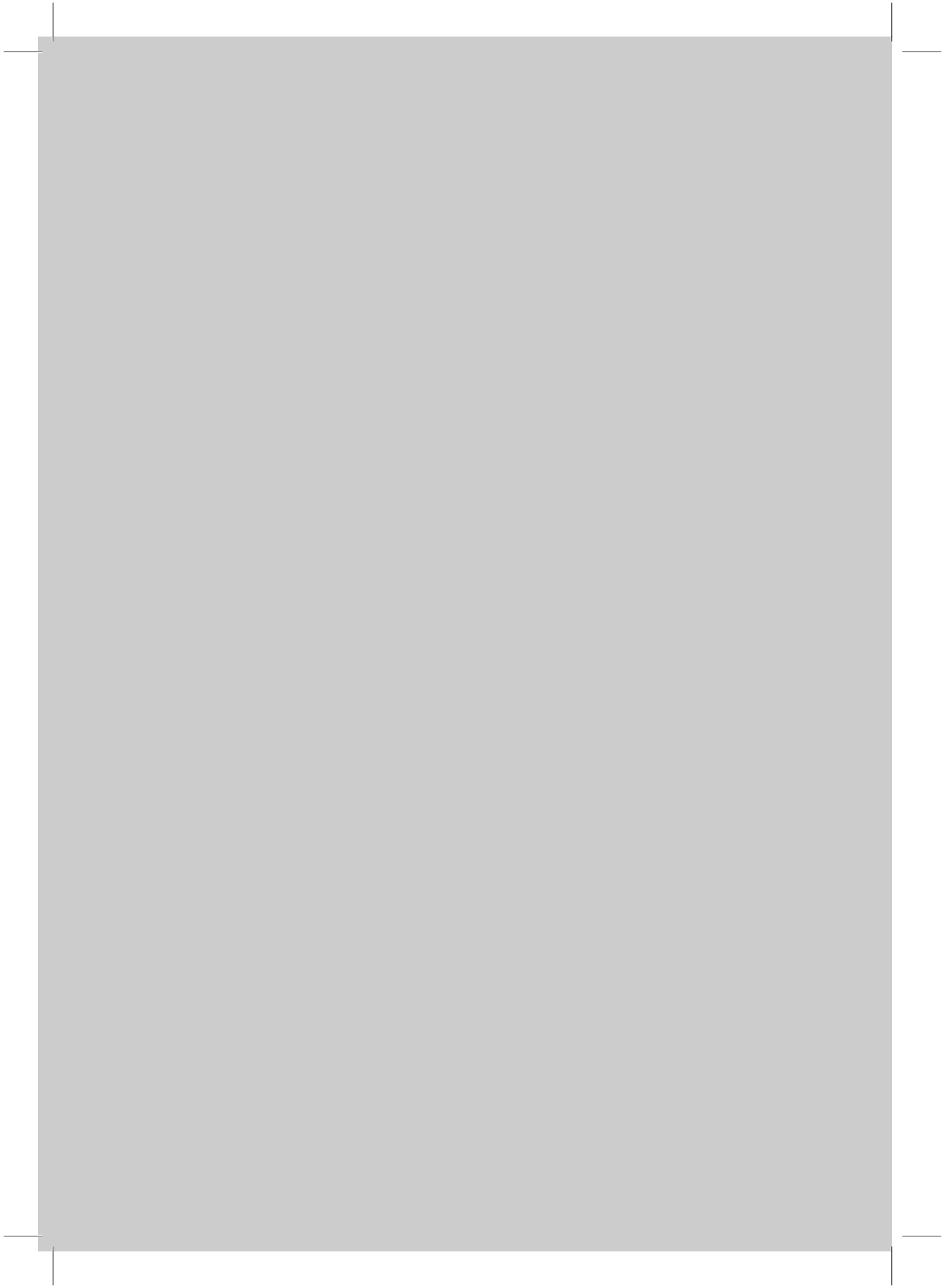
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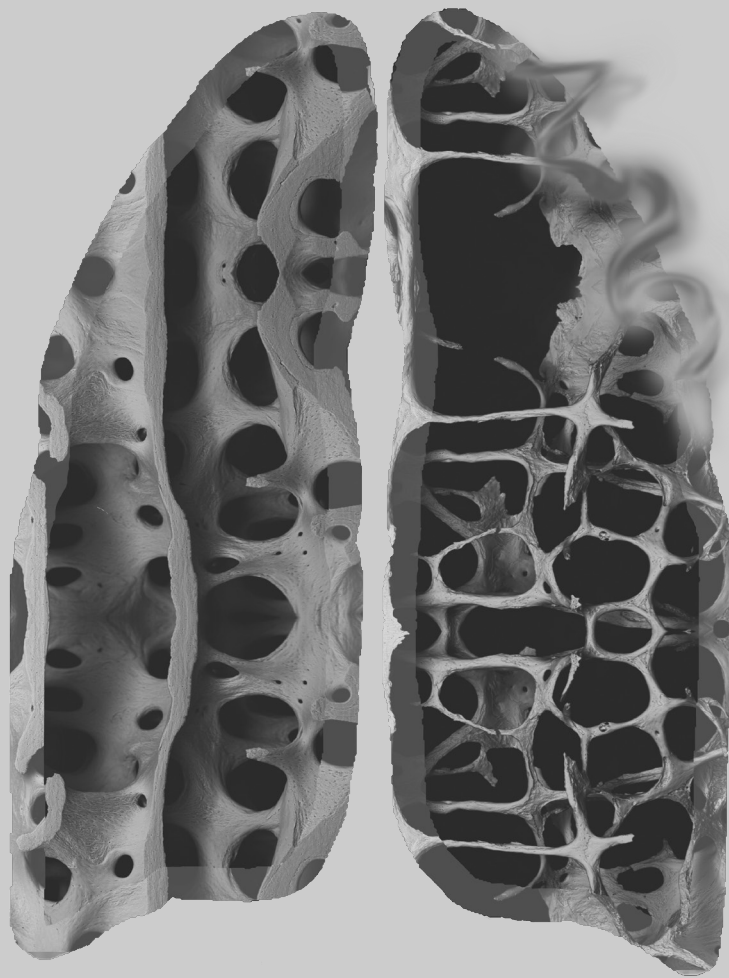
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Chapter 1

General introduction and outline of this thesis

GENERAL INTRODUCTION

Definition of COPD

Chronic obstructive pulmonary disease (COPD) is defined as “A common preventable and treatable disease which is characterised by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients.”^{1,2}

1

COPD should be considered in any patient who has dyspnoea, chronic cough or sputum production and a history of exposure to COPD risk factors.³ Diagnosis of COPD is confirmed when the ratio between post-bronchodilator forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC) is below 0.70.^{1,2}

Prevalence of COPD

Data on the prevalence of COPD have shown remarkable variation due to differences in survey methods, diagnostic criteria and analytic approaches. The World Health Organisation showed that moderate to severe COPD was found in 65 million people worldwide.⁴ A systematic review and meta-analysis demonstrated that the prevalence of physiologically defined COPD was approximately 9 to 10% in adults aged 40 or older.⁵

COPD is more common in smokers and ex-smokers than in non-smokers and in subjects aged 40 or older than in subjects under age 40.⁵ In the past, COPD was more common in men than women,⁵ but the disease now affects men and women almost equally because of increased tobacco use among women in high-income countries and higher risk of exposure to indoor air pollution in low-income countries.⁴

Burden of COPD

COPD is an important cause of morbidity and mortality worldwide and results in an economic and social burden that is both substantial and increasing. More than 3 million people died of COPD in 2005.⁴ COPD was the fifth leading cause of death in the world in 2002, and is projected to be the third leading cause of death by 2030.⁴ The total direct costs of respiratory diseases are estimated to be about 6% of the total health care budget in the European Union, with COPD accounting for 56% (38.6 billion Euros) of the total costs of respiratory diseases.¹ The social burden of a disease can be estimated in Disability-Adjusted Life Years (DALYs). This is the sum of years lost due to premature mortality and years of life lived with disability, adjusted for the severity of disability. COPD was the twelfth leading cause of DALYs lost in the world in 1990, and is projected to be the seventh leading cause of DALYs lost worldwide by 2030.⁶

Global Strategy for the Diagnosis, Management and Prevention of COPD

In order to increase the awareness of COPD and to help the millions of people who suffer from it, a committed group of scientists formed the Global Strategy for the Diagnosis,

Management and Prevention of COPD (GOLD) in 1998. A consensus report was released in 2001 and revised in 2006, 2011 and 2013.¹

In the latest report, some major revisions were made.¹ At the time of the first report, it was believed that the majority of COPD patients followed a path of disease progression in which the severity of the disease tracked the severity of airflow limitation. However, the severity of airflow limitation has been shown to be an unreliable marker of the severity of breathlessness, exercise limitation and health status impairment of the individual patient. Therefore, the staging system for classifying COPD severity has been replaced by a grading system, and additionally, a new assessment approach has been introduced to better reflect the complexity of COPD (Figure 1). This assessment approach uses a combination of spirometry, symptomatic assessment and exacerbation rate to classify patients to either category A, B, C or D.

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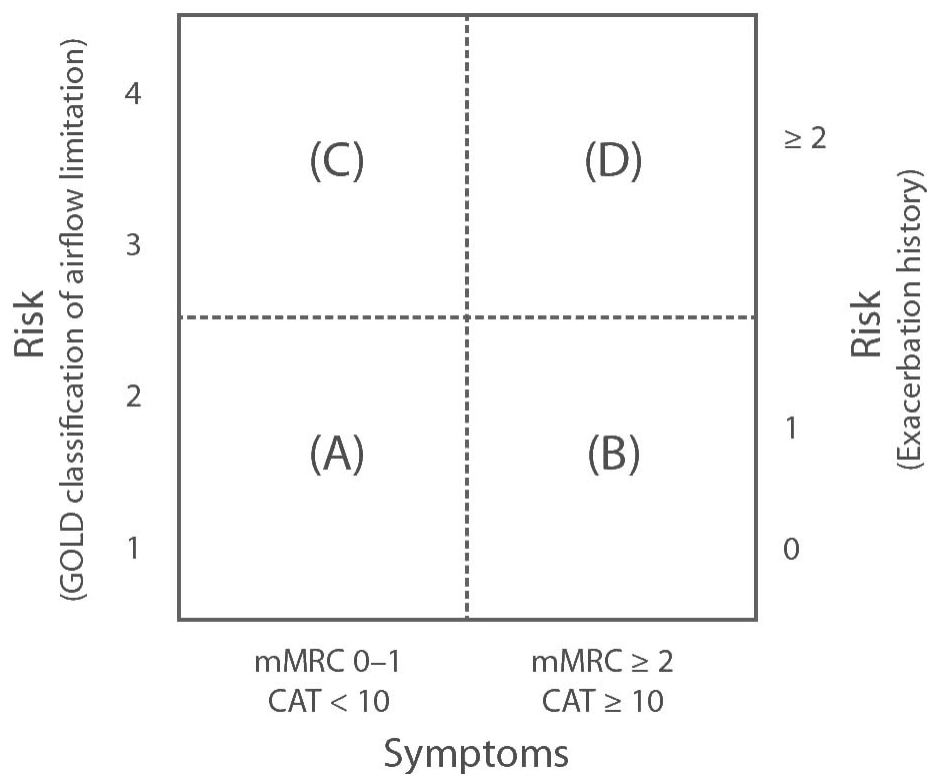


Figure 1. The combined COPD assessment approach

mMRC=modified Medical Research Council Dyspnoea Scale, CAT=COPD assessment test
Source: Global Initiative for Chronic Obstructive Lung Disease: Global strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease^{1,2}

Multi-component involvement in COPD

In addition to persistent airflow limitation, COPD is characterised by several pulmonary (e.g. emphysema, lung cancer) and extrapulmonary comorbidities (Table 1). COPD-related comorbidities are highly variable between patients and only weakly related to the severity of airflow limitation.⁷ They may influence the course of the disease.⁸⁻¹⁰ Comorbidities have been shown to increase the number of hospitalisations,¹¹ influence outcomes of exacerbations¹² and contribute to the economic burden of COPD.¹³ In addition, COPD patients are more likely to die from a comorbidity than from COPD itself.^{14,15} Therefore, COPD is nowadays being considered as a complex heterogeneous disease with clinically significant pulmonary and extrapulmonary comorbidities.¹⁶

Table 1. Extrapulmonary comorbidities of COPD

Comorbidity	Prevalence in COPD (%)
Osteoporosis/osteopenia	50-70
Hypertension	40-60
Gastro-oesophageal reflux disease	30-60
Skeletal muscle dysfunction	32
Depression	25
Ischemic heart disease	10-23
Previous myocardial infarction	4-23
Anaemia	17
Diabetes	12-13
Previous stroke	10-14
Arrhythmia	6-14
Chronic renal failure	6-11
Congestive heart failure	5-7
Obstructive sleep apnoea	1-4

Source: Extrapulmonary comorbidities in chronic obstructive pulmonary disease: state of the art¹⁷

Noncommunicable diseases and phenotyping

COPD is considered to be one of the major noncommunicable diseases. Other major noncommunicable diseases are cardiovascular diseases (e.g. heart attacks and stroke), cancers and diabetes. Noncommunicable diseases are the leading causes of death globally, killing more people each year than all other causes combined. Of the 57 million deaths that occurred globally in 2008, 36 million were due to major noncommunicable diseases.¹⁸

Noncommunicable diseases are associated with complex gene-environment interactions. Figure 2 shows the interactions between genes, lifestyle, socio-economic determinants, age and gender. The products of these interactions might lead to the biological expression of noncommunicable diseases, and hence, to their clinical expression and complex phenotypes.¹⁹

A phenotype traditionally reflects the observable structural and functional characteristics of an organism determined by its genotype and modulated by its environment, i.e. the interactions between “nature” and “nurture”.²⁰ Since this definition of a phenotype is not necessarily clinically relevant, the term “clinical phenotype” has been introduced.²¹ A “clinical phenotype” is defined as “A single or combination of disease attributes that describes differences between individuals as they relate to clinically meaningful outcomes (e.g. symptoms, exacerbations, response to therapy, rate of disease progression or death).”²¹

Since individuals with a unique COPD phenotype exhibit similar clinical outcomes, they might share a similar underlying mechanism and therapeutic response profile. Previous studies have shown that a specific therapy can be more effective in individuals sharing a specific phenotype.²² For instance, the National Emphysema Treatment Trial showed that lung volume reduction surgery improved prognosis in a subgroup of patients with upper lobe-predominant emphysema and low exercise capacity after rehabilitation.²³ Thus, identification of COPD phenotypes might be helpful to gain insight into pathophysiologic mechanisms and improve management of COPD.

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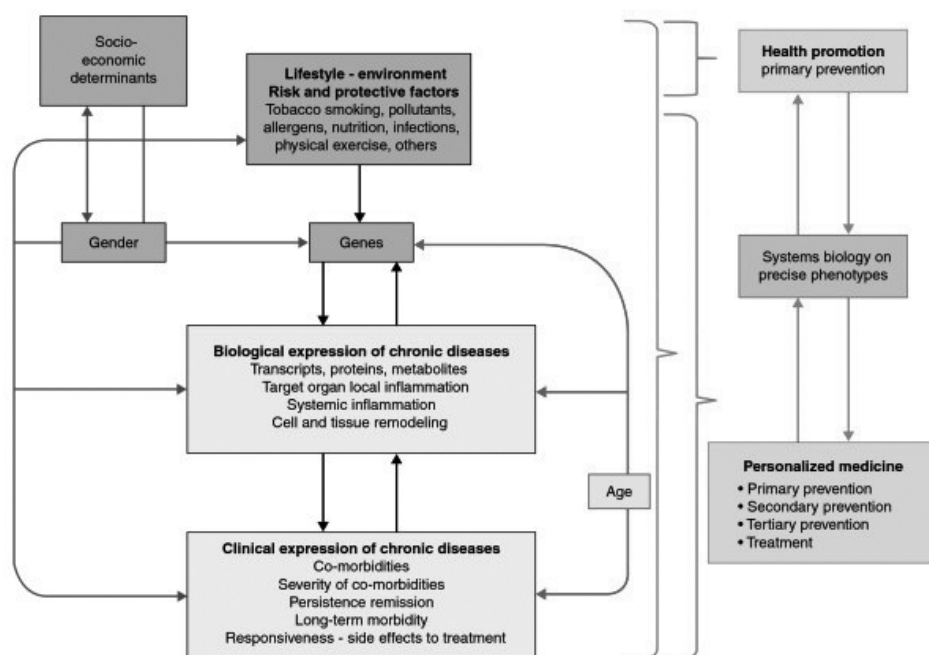


Figure 2. Noncommunicable diseases are associated with complex gene-environment interactions modulated by socio-economic determinants, psychological factors, age and gender

Source: Systems medicine and integrated care to combat chronic noncommunicable diseases¹⁹
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Current understanding of the pathogenesis of multi-component involvement

Previous research has identified several factors linking COPD with comorbidities, including shared risk factors, physical inactivity, side effects of treatments given for COPD and systemic inflammation (Table 2). Tobacco smoking and older age have been shown to be important risk factors for both COPD and multimorbidity.²⁴⁻²⁶ In addition, COPD patients are less physically active than smoking controls,²⁷⁻²⁹ and physical inactivity has been related with coronary heart disease, type 2 diabetes, breast cancer and colon cancer.³⁰ Moreover, corticosteroids that are widely used for the prevention and treatment of COPD exacerbations may induce pneumonia,³¹ osteoporosis³²⁻³⁷ and myopathy.³⁸ Furthermore, parameters of systemic inflammation have been shown to be increased in COPD patients and to be related with lower health related quality of life, more frequent COPD exacerbations, worse exercise tolerance, obesity and cardiovascular disease.^{39,40} Although several factors have been related with COPD and its comorbidities, their underlying pathophysiologic mechanisms are still not fully understood.

Osteoporosis in COPD

This thesis is focussed on a well-recognised comorbidity of COPD, osteoporosis. Osteoporosis is characterised by low bone mass or microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and, consequently, an increased risk of fracture.⁴¹ The gold standard for diagnosing osteoporosis is dual energy X-ray absorptiometry (DXA). The World Health Organisation⁴¹ and the International Society for Clinical Densitometry⁴² recommend a diagnosis of osteoporosis based on the lowest T-score of the hip or the lumbar spine assessed on DXA (Table 3). The T-score is defined as the number of standard deviations by which the bone mineral density differs from the average bone mineral density of a young adult at peak bone density. In this thesis, we will give a clear overview of the current literature on the pathophysiology, prevalence, risk factors and management of osteoporosis in COPD patients (chapter 2).

In the general population, vitamin D deficiency is a well-established risk factor of osteoporosis.⁴³ In addition to its role in bone health, vitamin D deficiency has been related with several other diseases, including infectious and autoimmune diseases, diabetes mellitus, cardiovascular disease, cancer, muscle weakness, poor exercise capacity and respiratory diseases.^{44,45} In this thesis, we will study associations between vitamin D, bone mineral density, muscle strength and functional exercise capacity in patients with moderate to very severe COPD (chapter 3).

Although DXA has a low radiation dose and is easy to use, previous studies have reported underdiagnosis of osteoporosis.⁴⁶ In order to diagnose osteoporosis in an early stage, current research is focussed on screening for osteoporosis using Computed Tomography (CT) scans that were performed for other purposes. Abdominal and coronary CT have already been shown to be useful for assessing bone mineral density and osteoporosis screening.⁴⁷⁻⁴⁹ Since chest CT scans are frequently made in COPD patients, we will study whether chest CT can provide useful information on bone health in COPD patients. In this thesis, we will describe an

algorithm for assessing bone attenuation of the thoracic vertebrae on chest CT and validate this technique against the gold standard, DXA (chapter 4).

Table 2. Potential mechanisms of multi-component involvement in COPD

Inactivity/ deconditioning
Direct consequence of exertional dyspnoea
Genetic factors
Behavioural factors
Systemic inflammation
Spillover of inflammation from the lung to the systemic circulation
Presence of inflammation in other organs in systemic inflammatory disease
Blood gas disturbances
Hypoxemia
Hypercapnia
pH changes
Electrolyt disturbances
Fluid imbalance
Malnutrition
Risk factors for COPD
Smoking
Genetic pre-disposition
Genetic pre-dispositions for smoking, addiction to food
Side-effects of treatments given for COPD
Inhaled corticosteroids
Systemic steroids
Bronchodilators
Endocrine disturbances
Low testosterone levels
Growth hormone-resistance
Low insulin-like growth factor-I levels
Insulin resistance
Suppression of erythropoiesis
Unknown factors

Source: COPD as a lung disease with systemic consequences – clinical impact, mechanisms, and potential for early intervention⁸

Chest CT might be helpful to better characterise COPD patients and separate various COPD phenotypes.⁵⁰ Previous studies have shown that chest CT is useful for lung cancer screening, quantifying emphysema and assessing vascular calcification. The National Lung Screening Trial showed that lung cancer screening using chest CT reduced lung cancer-specific mortality by more than 20% and all-cause mortality by 7%.⁵¹ In addition, more severe emphysema has been related with increased all-cause mortality in COPD patients^{52,53} and coronary artery calcification has been shown to be a predictor of cardiovascular events and mortality in smokers.⁵⁴⁻⁵⁷ In this thesis, we will assess extent of emphysema, markers of cardiovascular disease (coronary artery calcium and thoracic aortic calcium) and bone attenuation of the thoracic vertebrae on routine chest CT. Subsequently, we will study associations between CT-measured bone attenuation of the thoracic vertebrae and clinical features of COPD in two large cohorts (chapters 5 and 6).

In addition to bone mineral density, bone strength is influenced by material and structural properties of bone.⁵⁸ One of the most promising developments over the past 10 years has been the introduction of High Resolution peripheral Quantitative Computed Tomography (HR-pQCT).⁵⁹ HR-pQCT can be used to assess structural parameters of trabecular and cortical bone, such as trabecular thickness, trabecular number and cortical thickness. In addition, HR-pQCT images can be used to assess mechanical parameters of bone, such as bone stiffness and failure load, based on micro-finite element models.⁵⁹⁻⁶¹ Structural and mechanical parameters of bone are related with fragility fractures^{59,62} and might even be superior to bone mineral density in discriminating men with and without vertebral fractures.⁶³ In this thesis, we will study structural and mechanical parameters of bone using HR-pQCT and micro-finite element analysis (μ FEA) in men with and without COPD (chapter 7).

Table 3. Diagnosis of osteoporosis

	T-score
Normal bone mass	≥ -1.0
Osteopenia	-1.0 to -2.5
Osteoporosis	≤ -2.5

OUTLINE OF THIS THESIS

Main objectives of this thesis were 1) to give an overview of the current literature on osteoporosis in COPD; 2) to develop a new algorithm for measuring bone density on routine chest CT; 3) to study associations between CT-measured bone attenuation and clinical features of COPD; and 4) to study structural and mechanical parameters of bone in subjects with and without COPD.

Chapter 2 gives an overview of the current literature on the pathophysiology, prevalence, risk factors and management of osteoporosis in COPD patients.

Vitamin D deficiency is a well-established risk factor of osteoporosis in healthy elderly, and additionally, vitamin D deficiency might play a role in respiratory diseases and skeletal muscle function. **Chapter 3** describes the prevalence of vitamin D deficiency and its associations with bone mineral density, quadriceps muscle strength and functional exercise capacity in patients with moderate to very severe COPD.

Chapter 4 describes an algorithm for measuring bone attenuation of the thoracic vertebrae on routine chest CT and its validation against DXA, which is the gold standard for diagnosing osteoporosis. Subsequently, this algorithm is applied to two large cohort studies. **Chapter 5** describes comparisons in CT-measured bone attenuation between COPD subjects and smoker and non-smoker controls, and associations between CT-measured bone attenuation and clinical features of COPD in the ECLIPSE cohort. **Chapter 6** describes associations between CT-measured bone attenuation, arterial calcification and stiffness, emphysema and all-cause mortality in a Scottish cohort of COPD patients.

Although studies on structural and mechanical parameters of bone have shown interesting findings, studies on these bone parameters in COPD patients are limited. **Chapter 7** describes comparisons in structural and mechanical parameters of bone between men with and without COPD and associations between parameters of bone and clinical features of COPD.

Finally, **chapter 8** discusses the previous chapters and future perspectives and **chapter 9** summarises the main findings of this thesis.

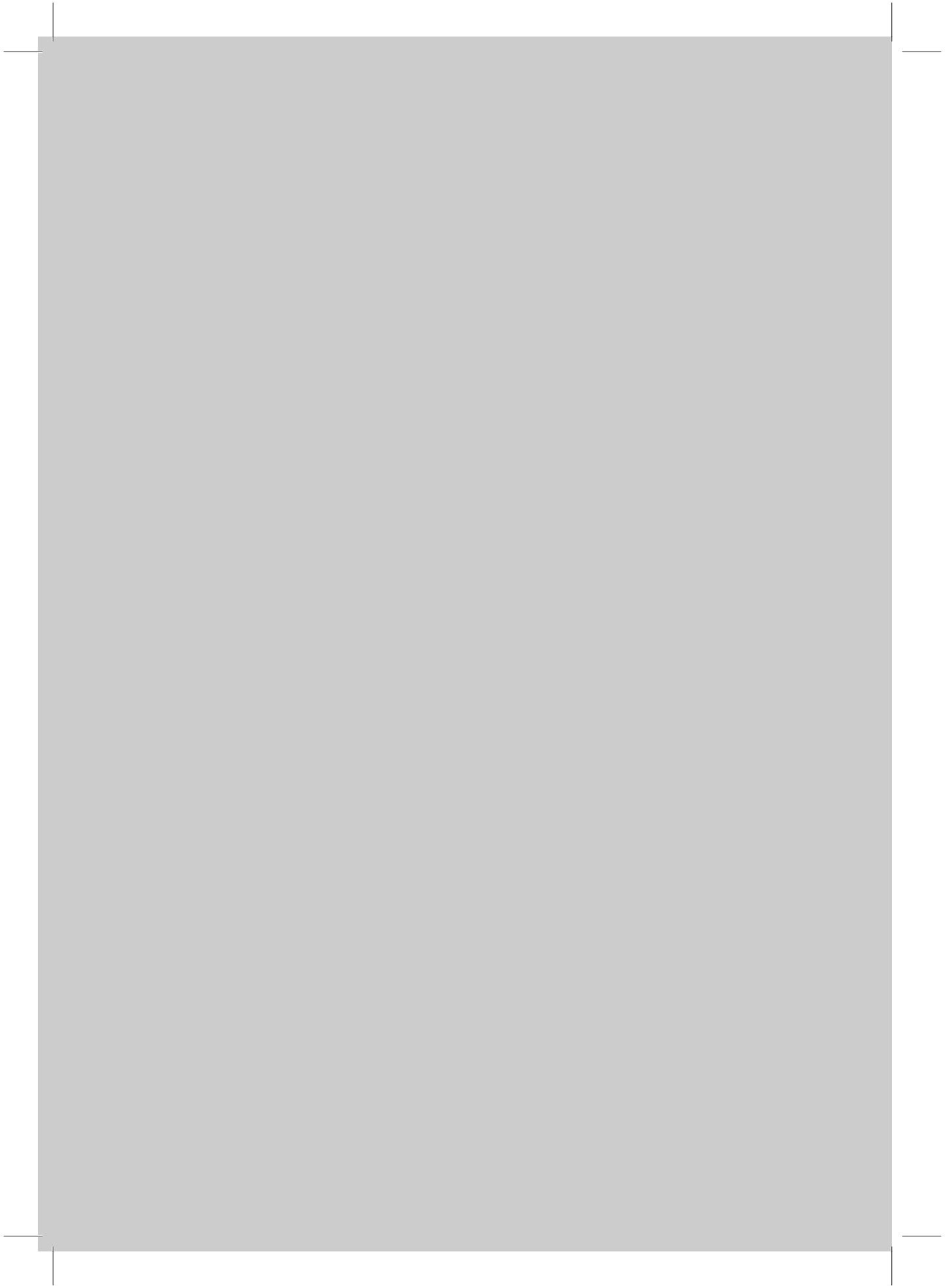
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Chapter 2

Osteoporosis in chronic obstructive pulmonary disease

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European Respiratory Monograph 2013; number 59: COPD and comorbidity

SUMMARY

Chronic obstructive pulmonary disease (COPD) is, in addition to progressive airflow obstruction, characterised by extrapulmonary manifestations that contribute to the disease severity in individual patients. Osteoporosis is recognised as one such extrapulmonary manifestation, since the prevalence of osteoporosis is higher in COPD patients than in control subjects matched for age and sex. Osteoporosis is a skeletal disease characterised by low bone mineral density or micro-architectural deterioration, resulting in increased risk of fracture. The high prevalence of osteoporosis in COPD is likely to be due to common risk factors such as advanced age and smoking, and to COPD-specific risk factors such as systemic inflammation and the use of corticosteroids. Interventions against common risk factors, like smoking cessation, exercise and healthy diet, might reduce the risk of fracture in patients with osteoporosis. In addition to these lifestyle guidelines, pharmacological treatment with calcium and vitamin D supplementation and antiresorptive treatment (e.g. bisphosphonates) have been indicated to prevent fractures in patients with osteoporosis.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) originates from an abnormal inflammatory response of the lung to noxious particles and gasses. It is characterised by airflow limitation that is not fully reversible and by significant extrapulmonary manifestations that contribute to the disease severity in individual patients.¹ COPD is a major health problem with a significant financial and medical impact, and its prevalence is estimated to be about 10% in adults aged 40 and older.^{2,3}

Nowadays, COPD is considered a complex and heterogeneous disease.⁴ This was illustrated, for instance, by the baseline data of the study Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE), which showed that the clinical manifestations of COPD were highly variable between patients and only weakly related to the severity of airflow limitation.⁵ Both the pulmonary and extrapulmonary manifestations of COPD contribute to morbidity and mortality in COPD. The extrapulmonary manifestations might even be more important than the pulmonary manifestations. Indeed, cardiovascular diseases were a more frequent cause of hospitalisation or death than COPD itself.⁶ In addition, the BODE index (an index compiled of body mass index, airflow obstruction, dyspnoea and exercise capacity) was a better predictor of risk of death from any cause or from respiratory causes than the severity of airflow limitation alone.⁷ Recently, the COPD comorbidity (COTE) index, which is based on 12 comorbidities, appeared to be correlated with risk of death from any cause, independent of the BODE index.⁸

Since the prevalence of osteoporosis is higher in COPD patients than in control subjects matched for age and sex,^{5,9} osteoporosis is recognised as an extrapulmonary manifestation of COPD that might contribute to morbidity and mortality in COPD.¹⁰ In this chapter, we will give an overview of the prevalence, risk factors and treatment of osteoporosis in patients with COPD.

OSTEOPOROSIS

Osteoporosis is a systemic skeletal disease that is characterised by low bone mineral density or micro-architectural deterioration resulting in bone fragility and hence increased risk of fracture.¹¹ Osteoporosis-related fractures may cause significant morbidity and mortality, particularly in patients with COPD, in whom vertebral compression fractures may reduce already compromised pulmonary function.^{10,12} Moreover, COPD results in a higher operation risk for hip surgery after osteoporosis related fractures.¹³

At present, the gold standard to diagnose osteoporosis is dual energy X-ray absorptiometry (DXA). The World Health Organisation (WHO)¹¹ and the International Society for Clinical Densitometry¹⁴ recommend a diagnosis of osteoporosis based on the lowest T-score of the hip or the lumbar spine measured on DXA (Table 1). The T-score is defined as the number of standard deviations by which the bone mineral density differs from the average bone mineral density of a young adult at peak bone density.

Table 1. Diagnosis of osteoporosis

	T-score
Normal bone mass	≥ -1.0
Osteopenia	-1.0 to -2.5
Osteoporosis	≤ -2.5

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In addition to DXA scanning, vertebral fracture assessment on X-rays of the spine has been recommended in patients with moderate to very severe COPD,¹⁴ since vertebral fractures are highly prevalent in COPD¹⁵ and related to a high annual number of incidental vertebral fractures.¹⁶ The clinical technique of choice for diagnosing vertebral fracture is the Genant visual semi-quantitative method.¹⁷ With this method, vertebral deformities are classified into wedge, biconcave or crush and into grade 1 (20 to 25% reduction in height and 10 to 20% reduction of the projected vertebral area), grade 2 (25 to 40% reduction in height and 20 to 40% reduction of the projected vertebral area) and grade 3 (more than 40% reduction in height and area).

PATHOPHYSIOLOGY OF OSTEOPOROSIS

Bone is generally classified into two types: cortical bone, which is dense and strong and primarily present in the shafts of long bones, and trabecular bone, which is weak and porous and present at the ends of long bones or at the interior of vertebrae and flat bones. Bone tissue is continuously renewed throughout life. It is estimated that about 25% of trabecular bone and about 3% of cortical bone are replaced in adults every year.

Osteoporosis can occur because of failure to achieve peak bone mass, or it can be due to excessive bone resorption and decreased bone formation during bone remodelling. Bone remodelling is a complex interplay between osteoblasts, osteoclasts and osteocytes. These cells remove an area of bone and then replace the lost bone with new matrix which subsequently mineralises. Excessive bone resorption due to an imbalance in the amount of bone removed relative to the amount of bone replaced will lead to a decline in the total amount of bone and will increase the risk of fracture.

Bone remodelling is controlled by several mechanisms such as the osteoprotegerin (OPG)/receptor activator of nuclear factor κ B (RANK)/ RANK ligand (RANKL) system and the Wingless tail (Wnt)/ β catenin signalling pathway (Figure 1). RANKL is expressed on the surface of osteoblasts, and its expression increases in response to a variety of pro-resorptive signals, such as parathyroid hormone (PTH) and inflammatory cytokines. RANKL binds to the RANK receptor, which is expressed on osteoclasts and their precursors, thereby stimulating the differentiation and activation of osteoclasts and hence promoting bone resorption. OPG is a decoy receptor for RANKL that is secreted by osteoblasts and other stromal-derived cells and acts to reduce bone resorption. Imbalance between RANKL and OPG results in excessive

activity of osteoclasts and is considered a major cause of osteoporosis. The Wnt/ β -catenin signalling pathway is less well understood, but it is known that it has an important role in bone formation by activating osteoblasts. Wnt inhibitors such as inflammatory cytokines negatively regulate this pathway resulting in bone loss.^{10,18}

PREVALENCE OF OSTEOPOROSIS IN COPD

The prevalence of osteoporosis is high in patients with COPD. In the study Towards a Revolution in COPD Health (TORCH), which included 658 COPD patients, 23% had osteoporosis and 43% had osteopenia at the hip or the lumbar spine on DXA according to the WHO guidelines.¹⁹ This is in line with another study on 255 COPD patients admitted for pulmonary rehabilitation, 24% of whom had osteoporosis and 46% had osteopenia.²⁰ When taking the vertebral fractures into account, the prevalence of osteoporosis even increased to 51%.²⁰

Smaller studies have demonstrated that the prevalence of osteoporosis is higher in patients with COPD than in healthy control subjects. In a group of 81 COPD patients and 38 sex matched controls, 30% of the COPD patients and 13% of the controls had osteoporosis.²¹

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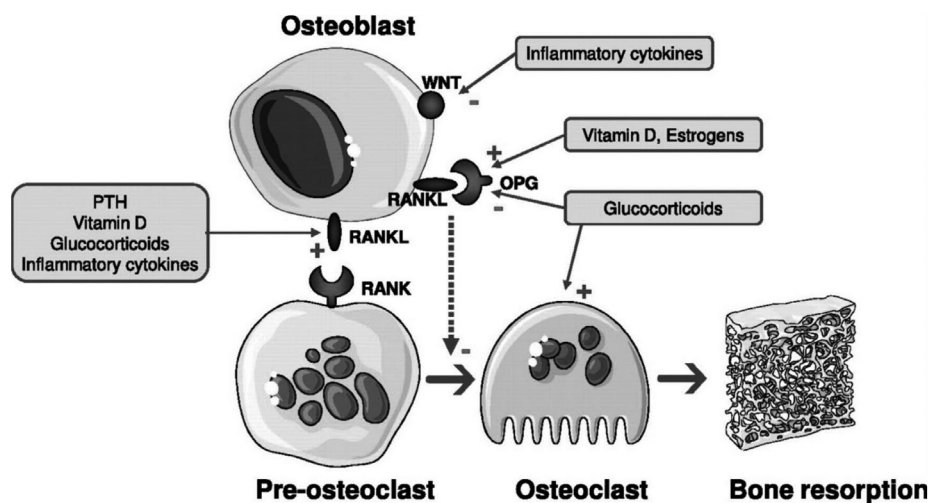


Figure 1. Key mechanisms in the pathogenesis of osteoporosis in COPD

Figure legend. Key mechanisms in the pathogenesis of osteoporosis in COPD. Osteoblasts direct osteoclast precursors into mature activated osteoclasts through RANK/RANKL, an interaction that is blocked by OPG.

OPG = osteoprotegerin; PTH = parathyroid hormone; RANK = receptor activator of nuclear factor- κ B; RANKL = receptor activator of nuclear factor- κ B ligand; WNT = Wnt signaling pathway. Source: COPD, bone metabolism and osteoporosis¹⁰

However, in this study the controls were younger than the COPD patients. Nevertheless, in a more recent study the prevalence of osteoporosis was 24% in COPD patients and 5% in controls matched for age and sex.²² Although large case-control studies are not yet available, the available data suggest a higher prevalence of osteoporosis among patients with COPD than in subjects without coexisting COPD.

RISK FACTORS OF OSTEOPOROSIS IN COPD

In healthy men and women, the main risk factors for osteoporosis are advanced age, smoking, low body weight, physical inactivity, prevalent fractures after the age of 50 and postmenopausal status.^{23,24} A collection of these risk factors is summarised in the fracture risk assessment (FRAX) tool, which predicts the 10 year probability of fracture.²⁵ Since some of these risk factors like advanced age, smoking and low body weight coincide in patients with COPD, it is not surprising that osteoporosis and COPD are strongly related. However, there is evidence that various COPD-specific factors such as systemic inflammation, vitamin D deficiency, use of corticosteroids and lung function impairment themselves might contribute to the increased risk of osteoporosis in patients with COPD. In the following paragraphs, we will discuss the most important risk factors of osteoporosis in patients with COPD.

Airflow obstruction and emphysema

Osteoporosis has been related to severity of airflow obstruction. The Third National Health and Nutrition Examination Survey, which included 9502 participants, showed that the prevalence of osteopenia and osteoporosis increased with more severe airflow obstruction.²⁶ In line, in 4830 women recruited from general practice registers, forced expiratory volume in one second (FEV₁) was positively correlated with bone mineral density after adjustment for confounders, including e.g. corticosteroid use.²⁷ More recently, a cross-sectional study with 95 COPD patients demonstrated that the patients with osteoporosis had lower FEV₁ than the patients with normal bone mass.²⁸ In line, a review stated that osteoporosis was associated with more severe airflow obstruction in patients with COPD.⁹ In contrast, some studies on patients with COPD did not find a relationship between bone mineral density and severity of airflow obstruction after correction for confounders.^{29,30}

In addition to its association with severity of airflow obstruction, bone density has been related to the extent of emphysema.³¹ Already in 1999, a study on about 100 patients with severe COPD who had been admitted for pulmonary rehabilitation showed that total body bone mineral density was lower in the patients with emphysema, based on visual scores on high resolution computed tomography (HRCT) scans, than in those without emphysema.³² Bon and colleagues³³ recently confirmed these data in a tobacco-exposed cohort of which only a subset of subjects had obstructive lung disease. They showed that radiographic emphysema was an independent predictor of low bone mineral density. However, they did not correct for body mass index, even though body mass index is related to both emphysema and bone mineral density. Still, in another study on 65 male patients with COPD radiographic emphysema was correlated with CT-measured bone mineral density of the thoracic vertebrae even after adjustment for body mass index.³⁴

Since bone mineral density was shown to be correlated independently with both the severity of airflow obstruction and the extent of emphysema, recent research has been focused on common links between the skeletal and pulmonary systems.³¹ Both direct and indirect pathways have been suggested.

Regarding the indirect pathways, COPD is associated with increased plasma markers of systemic inflammation that might stimulate osteoclastogenesis and generate RANKL, resulting in decreased bone mass. In a clinical study with 80 subjects, plasma markers of systemic inflammation, interleukin-6 (IL-6) and tumour necrosis factor- α (TNF- α) were higher in the COPD patients than in the control subjects and higher in the COPD patients with low bone density than in the COPD patients with normal bone density.³⁵ In addition, the RANKL concentration and the RANKL/OPG ratio were higher in the COPD patients with low bone density than in the COPD patients with normal bone density. Therefore, it seems likely that systemic inflammation in COPD results in a disturbance of the RANK/RANKL/OPG pathway and, hence, in osteoporosis. A review stated indeed that systemic inflammation might result in disturbance of the RANK/RANKL/OPG pathway in patients with inflammatory diseases.¹⁸

Regarding the direct pathways, the Wnt/ β -catenin signalling is involved in bone remodeling and repair of micro fractures, but it has also been associated with lung epithelial injury and repair processes. In a small study with 12 COPD and 12 transplant donor lung samples, Wnt/ β -catenin activation by lithium chloride attenuated experimental emphysema as assessed by decreased airspace enlargement, improved lung function, reduced collagen content and elevated expression of alveolar epithelial cell markers.³⁶ Therefore, it might be the case that impairment of Wnt/ β -catenin signalling results in both osteoporosis and emphysema. However, only indirect and experimental evidence supporting this interaction is available so far.

Aging

Advanced age is a well-established risk factor for osteoporosis^{11,25} and has been related to the presence of COPD in a large population-based cohort study.³⁷ COPD has even been suggested to be a syndrome of abnormal lung aging.³⁸ Since patients with COPD show evidence of increased oxidative stress³⁹ and shorter telomeres compared with controls matched for age and sex,⁴⁰ there seems to be evidence that COPD is also associated with systemic abnormal aging.⁴¹

The underlying patho-physiologic mechanism of the relationship between advanced age and bone loss has been studied widely.⁴² In a healthy young skeleton the rate of bone formation and matrix mineralisation equals the rate of bone resorption and matrix degradation. However, during the process of aging significant amounts of bone are lost due to enhanced bone resorption coupled with decreased bone formation. In addition to bone loss, advanced age is associated with increased fall risk due to muscle weakness and balance disorders resulting in increased risk of fracture.^{43,44}

Body composition*Body mass/ fat free mass*

Low body mass and low fat free mass are well-known risk factors for osteoporosis in the general population.^{11,25} Moreover, low body mass and low fat free mass are both commonly present and have been investigated extensively in patients with COPD as they are associated with decreased exercise tolerance,⁴⁵ disease-related quality of life⁴⁶ and increased mortality risk.⁴⁷ In addition, accumulating evidence shows a relationship between low body and muscle mass and osteoporosis in patients with COPD even after adjustment for confounders such as age and the use of corticosteroids.^{9,21,29,30,48}

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Low body mass, low fat free mass and the poor exercise capacity related to it⁴⁵ might induce bone loss due to decreased mechanical loading. Indeed, astronauts lose bone mass in the proximal femur during space flights,⁴⁹ and long term bed rest leads to loss of bone mass.⁵⁰ Although 'disuse' osteoporosis has been investigated widely,⁵¹ its underlying mechanism has not been fully understood yet. In addition to decreased mechanical loading, poor exercise capacity might cause sarcopenia and lower-limb muscle weakness which has been related to increased fall risk and hence increased risk of fracture. However, more research concerning the underlying patho-physiological mechanism of the relationship between low body mass and fat free mass and osteoporosis is warranted in patients with COPD.

Fat mass

Overweight and obesity are, in addition to underweight, common in patients with COPD. Indeed, 28 to 64% of male COPD patients and 33 to 50% of female COPD patients were overweight (body mass index > 25 kg/m²).⁴⁷ Notably, an overweight or obese body mass index is protective of osteoporosis.⁵² This might be due to an interaction between fat and bone tissue such as the effects of fat mass on the secretion of bone active hormones from the pancreatic beta cells (e.g. insulin and amylin) and the secretion of bone active hormones from adipocytes (e.g. leptin).⁵²

Several studies have investigated the effects of leptin, an adipokine which is related to the amount of body fat.^{52,53} Leptin acts both via the central nervous system and via the circulation, resulting in different effects on bone metabolism (Figure 2). Circulating leptin increases the proliferation and differentiation of osteoblasts and promotes bone nodule formation. It also regulates osteoclast development, at least partly, through the RANK/RANKL/OPG pathway, which results in net bone formation. Via the central nervous system, leptin has the opposite effect by influencing satiety and insulin secretion. It is believed that the local effects of leptin from adipose tissue are dominant over the central effects, resulting in a stronger skeleton, which is needed to support a greater soft tissue mass.⁵²

In patients with COPD, an overweight or obese body mass index was shown to be protective against osteoporosis.³⁰ More recently, adipose tissue leptin and OPG expressions correlated positively with bone density variables and serum β -crosslaps concentrations in 19 COPD patients with osteoporosis and 21 COPD patients with normal bone mass.⁵⁴ These findings might suggest that leptin and OPG act as mediators between fat mass and bone density in

patients with COPD. However, more research on the interaction between fat and bone is warranted in patients with COPD.

Corticosteroids

Oral and inhaled corticosteroids are widely used in patients with COPD despite their adverse effects, such as oropharyngeal candidiasis, hoarseness and pneumonia.⁵⁵ In addition, the use of oral corticosteroids has been associated with decreased bone mass and increased risk of fracture. Indeed, the total cumulative dose of oral corticosteroids was inversely correlated with bone mineral density,⁵⁶ and prior or current exposure to oral corticosteroids was associated with increased risk of fracture.⁵⁷ With respect to COPD patients, patients receiving oral corticosteroids were more likely to have one or more vertebral fractures.^{58,59}

The effects of inhaled corticosteroids on bone health are less clear. A randomised controlled trial in 658 patients with moderate to severe COPD demonstrated that inhaled corticosteroids had no effect on bone mineral density at the hip and lumbar spine over 3 years.¹⁹ However, a case-control study including 1708 cases with non-vertebral fractures and 6817 matched controls showed that the use of high-dose corticosteroids (≥ 700 microgram per day) was associated with increased risk of fracture compared with patients who did not use inhaled corticosteroids.⁶⁰ More recently, a systematic review concluded that long-term use of inhaled fluticasone or budesonide was associated with a dose-dependent increased risk of fracture.⁶¹

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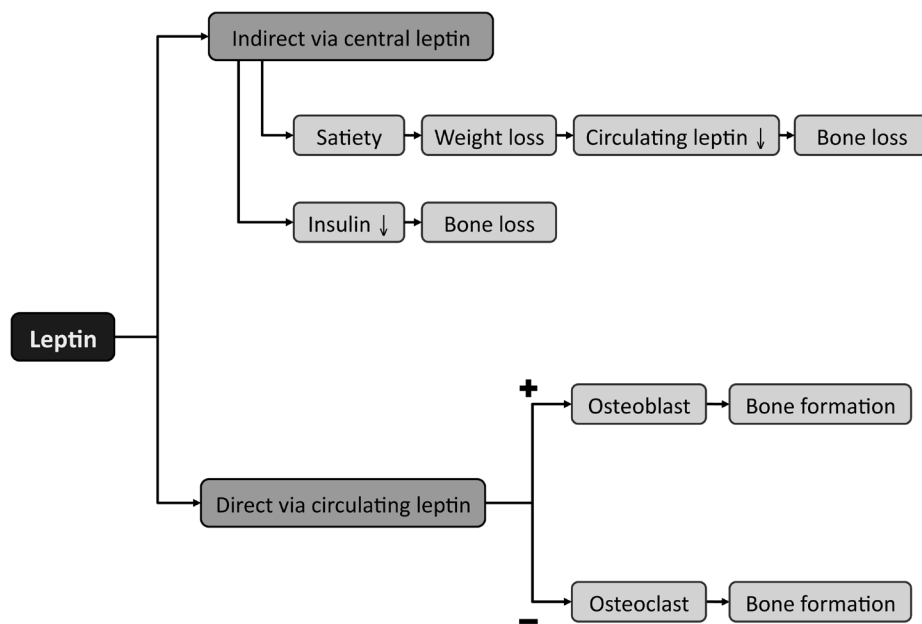


Figure 2. The effects of leptin on bone metabolism

Although accumulating evidence shows that the use of inhaled corticosteroids is correlated with increased risk of fracture, there is need for more prospective studies that correct for confounders such as COPD severity.

Corticosteroids cause bone loss due to disruption of bone remodelling. Several mechanisms have been associated with corticosteroid-induced osteoporosis including impaired calcium intestinal absorption, decreased formation of osteoblasts, increased osteocytes apoptosis and altered sex hormone status in both men and women (Table 2).^{18,62} In addition, corticosteroids might also cause muscle dysfunction resulting in increased risk of falls.

Since oral and inhaled corticosteroids have been correlated with increased risk of fracture, clinicians should carefully consider the risk of fracture associated with the use of oral and inhaled corticosteroids for treating and preventing exacerbations.

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Vitamin D deficiency

Vitamin D deficiency is related to osteoporosis and is highly prevalent in patients with COPD. The prevalence of vitamin D deficiency, defined as plasma 25-hydroxyvitamin D concentrations below 50 nmol/L, was 58% in a cross-sectional study with 151 COPD patients entering pulmonary rehabilitation during summer.⁶³ The prevalence of vitamin D deficiency seems to be higher in patients with COPD than in subjects without coexisting COPD, and it seems to be related to the severity of COPD. In the Bergen COPD cohort study, the

Table 2. Metabolic effects of corticosteroids leading to bone loss

Effects on calcium metabolism

Decrease intestinal absorption of calcium and phosphate

Increase urinary calcium excretion

Factors listed above promote the development of secondary hyperparathyroidism, which can increase bone resorption

Effects on sex hormones

Direct and indirect effects on adrenal androgen and gonadal hormone release leading to the loss of anabolic effects of these hormones on bone formation and resorption

Direct bone effects

Inhibition of osteoclast proliferation

Inhibition of osteoclast attachment to bone matrix

Inhibition of type I collagen and other proteins produced by osteoblasts

Other effects

Steroid myopathy may slow or prevent exercise-induced benefits in bone formation as well as reduce normal physical forces of muscle tension on bone

Source: Chronic glucocorticoid therapy-induced osteoporosis in patients with obstructive lung disease⁹⁵

prevalence of vitamin D deficiency was higher in the COPD patients than in the control subjects independent of season, age, smoking, comorbidities and body mass index.⁶⁴ In addition, the prevalence of vitamin D deficiency was 39% in GOLD stage I, 47% in GOLD stage II, 60% in GOLD stage III, and 77% in GOLD stage IV COPD patients.⁶⁵ There are several potential explanations for the increased risk of vitamin D deficiency in patients with COPD including poor diet, less exposure to sunlight due to poor physical activity, accelerated skin aging due to smoking, renal dysfunction and treatment with corticosteroids.

The uptake of vitamin D and its role in bone homeostasis is well established. Humans get vitamin D by exposure to sunlight, from their diet (e.g. fat fish, butter, eggs) and from dietary supplements. In the liver, vitamin D₃ is metabolised to 25-hydroxyvitamin D, which is the major circulating metabolite of vitamin D. 25-hydroxyvitamin D is metabolised further to its active form, 1,25-dihydroxyvitamin D, in the kidneys by the enzyme 1- α -hydroxylase. The renal production of 1,25-dihydroxyvitamin D is tightly regulated by plasma PTH levels and serum calcium and phosphorus levels. The efficiency of intestinal calcium and phosphorus absorption is increased through the interaction of 1,25-dihydroxyvitamin D with the vitamin D receptor. In case of vitamin D deficiency, decreased calcium absorption causes a compensatory increase in PTH. PTH enhances the tubular reabsorption of calcium and stimulates the kidneys to produce 1,25-dihydroxyvitamin D. PTH also activates osteoblasts, which stimulate the transformation of preosteoclasts into mature osteoclasts. Osteoclasts dissolve the mineralised collagen matrix in bone, causing osteopenia and osteoporosis.⁶⁶ In addition, low 25-hydroxyvitamin D concentrations might also cause muscle dysfunction and hence increase the risk of falls, resulting in increased risk of fracture.⁶⁷

Although the role of vitamin D in bone health is well established in non-COPD populations, research in patients with COPD is limited. In underweight patients with end-stage pulmonary diseases waiting for lung transplantation, vitamin D deficiency was associated with reduced femur neck T-scores,⁶⁸ and in COPD patients admitted for pulmonary rehabilitation vitamin D concentration was positively correlated with the lowest T-score of the hip and lumbar spine.⁶³

Physical inactivity

COPD patients are less physically active compared with control subjects.⁶⁹ In addition, reduced physical activity is associated with bone loss and osteoporosis-related fractures,^{70,71} whereas, on the other hand, exercise interventions may increase bone mineral density⁷² and reduce the risk of falls and fractures.⁷³ In COPD patients, research on a relationship between physical activity and bone health is limited. Silva and colleagues²⁸ showed that the International Physical Activity Questionnaire total activity score was related to the T-score of the femoral neck in 95 COPD patients, and Nishimura and colleagues⁷⁴ demonstrated that the twelve minute walk test was related to changes in bone mineral content in 22 COPD patients.

Smoking and alcohol use

Smoking is a risk factor for both osteoporosis and COPD.^{11,37} Smoking has been found to induce parenchymal destruction by inflammation. This parenchymal destruction occurs in an early

stage of COPD and increases with more pack-years of smoking. In addition to parenchymal destruction, smoking has been associated with osteoporosis. Indeed, smokers had a 2-4 fold increased odds ratio for osteoporotic fractures compared with non-smokers. The effect of smoking on bone loss has been suggested to be dose-dependent and related to several mechanisms.⁷⁵ Firstly, smoking may increase bone loss through its effect on body weight. Smokers weigh less than non-smokers and smoking cessation has been associated with increased weight within three months after cessation. Secondly, smoking might influence bone health through an earlier menopause, because on average, smoking women begin natural menopause 1 to 2 years earlier than non-smokers, and age at menopause is a strong predictor of osteoporosis. Thirdly, cigarette smoke negatively affects hormones and enzymes engaged in the regulation of bone metabolism such as PTH and alkaline phosphatase.

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COPD has been associated with high alcohol consumption in Japan,⁷⁶ but not yet in the Caucasian population. Since alcohol consumption is recognised as a risk factor for osteoporosis,^{77,78} it might be that increased alcohol consumption contributes to osteoporosis in patients with COPD. The mechanisms of the action of ethanol on bone are not completely understood, but these are suggested to be both indirect and direct. Indirectly, high alcohol consumption might interact with bone tissue via poor nutritional intake and caloric restriction, which results in a reduced body and fat mass. In addition, alcohol consumption might also interact directly with bone remodeling by changes on the number and activity of osteoblasts and osteoclasts, increased osteocytes apoptosis, increased oxidative stress and increased fat accumulation in the bone marrow.⁷⁸

Taken together, both COPD and osteoporosis will particularly occur later in life and are dependent on common shared risk factors such as nutritional and lifestyle factors. However, more research is warranted to discover whether COPD in itself is an independent risk factor due to shared underlying mechanisms such as systemic inflammation and the use of corticosteroids.

NON-PHARMACOLOGICAL AND PHARMACOLOGICAL TREATMENT

Since several lifestyle factors such as smoking, alcohol use and physical inactivity have been associated with fractures due to osteoporosis, intervention against these factors might improve bone density and reduce risk of fracture. A systematic review stated that exercise had a positive effect on bone mass in postmenopausal women,⁷² and smoking cessation was associated with improvement in bone density.⁷⁹ Although multidisciplinary rehabilitation in patients with COPD has shown to have positive short-term and long-term functional effects, research on the effects of multidisciplinary rehabilitation on bone density and fracture risk is still lacking.

Calcium and vitamin D supplementation

Nowadays, calcium and vitamin D supplementation are recommended in the treatment of osteoporosis since they have positive effects on bone health and muscle function, resulting in reduced risk of fracture. A meta-analysis stated that calcium supplementation alone or

in combination with vitamin D was effective in the preventive treatment of osteoporosis-related fracture.⁸⁰ In addition, another meta-analysis stated that vitamin D supplementation with doses of 700 to 800 IU per day reduced the relative risk of hip fracture by 26% and of any non-vertebral fracture by 23% compared with calcium supplementation or placebo in individuals 60 years or older.⁸¹ In contrast, a Cochrane review stated that vitamin D without calcium supplementation appeared unlikely to be effective in preventing hip fracture, vertebral fracture or any new fracture.⁸² These data suggest that both calcium and vitamin D are important in the prevention of osteoporosis-related fracture. In addition to its effect on fracture risk, vitamin D supplementation had beneficial effects on fall prevention among ambulatory or institutionalised older individuals with stable health.⁸³ Vitamin D supplementation with doses of 700 to 1000 IU per day reduced falls by 19 to 26%, whereas vitamin D doses below 700 IU did not prevent falls.⁸⁴

Based on evidence from randomised controlled trials and meta-analyses, it has been suggested that adequate vitamin D supplementation with doses of at least 700 IU per day is required for improving physical function and prevention of falls and fractures in the elderly.⁸⁵ Additional calcium supplementation may be considered when dietary calcium intake is below 700 mg per day, using a supplementation dose that leads to a maximum total daily calcium intake of 1000 to 1200 mg.⁸⁵ However, dietary advice to attain an adequate calcium intake is preferred to calcium supplementation, since calcium supplementation has been associated with increased risk of myocardial infarction.⁸⁶

Antiresorptive therapy

The role of bisphosphonates in the prevention and treatment of osteoporosis is well established. Bisphosphonates are chemically stable derivatives of inorganic pyrophosphate and inhibit calcification by binding to hydroxyapatite crystals. In addition, bisphosphonates inhibit hydroxyapatite breakdown, thereby effectively suppressing bone resorption. It has been suggested that bisphosphonates also function to limit both osteoblast and osteocytes apoptosis. In postmenopausal women with osteoporosis, alendronate was associated with significant and clinically important reductions in the incidence of hip fracture.⁸⁷ In patients treated with corticosteroids, bisphosphonates were shown to increase bone mineral density and prevent the development of new fractures.⁸⁸ In patients with airway disorders (asthma or chronic obstructive airway disease) daily intake of alendronate for 12 months was shown to significantly improve bone mineral density at the lumbar spine.⁸⁹

In addition to bisphosphonates, teriparatide and denosumab have been shown to be effective in reducing the risk of fragility fractures.⁹⁰ In patients with corticosteroid-induced osteoporosis, patients treated with teriparatide had an even greater increase in lumbar spine bone mineral density and less incidental vertebral fractures than patients treated daily with alendronate.⁹¹ Denosumab, a human monoclonal antibody to RANKL, is a relatively new drug that prevents the interaction of RANKL to RANK, thereby blocking the formation, function and survival of osteoclasts and resulting in decreased bone resorption. In postmenopausal

women with osteoporosis, denosumab was associated with a significant reduction in the risk of vertebral as well as hip and other non-vertebral fractures.⁹²

COPD-SPECIFIC RECOMMENDATIONS

Currently, osteoporosis is generally recognised as one of the systemic manifestations of COPD which contribute to worsening of the disease progression. Patients at risk of developing osteopenia or osteoporosis particularly include patients with advanced age, low body mass, frequent use of oral corticosteroids and vitamin D deficiency. These patients, but preferably all patients, should be screened for osteoporosis by DXA scan and vertebral fracture assessment, and, if necessary, treatment should be initiated. As no COPD-specific treatment has been developed yet, standard treatment for osteopenia and osteoporosis should be prescribed. However, COPD patients who use corticosteroids should be treated according to the guidelines for management of corticosteroid-induced osteoporosis.⁹³ The American College of Rheumatology recommends a daily calcium intake of 1200 to 1500 mg per day and vitamin D supplementation to achieve 'therapeutic' vitamin D concentrations or vitamin D dosages of 800 to 1000 units per day, in all patients who use corticosteroids.⁹⁴ In addition, they recommend bisphosphonates in patients at low-risk of fractures who use ≥ 7.5 mg prednisone equivalents per day, and in patients at medium or high-risk of fractures who use any dose of corticosteroids.

CONCLUSION

Since osteoporosis is highly prevalent in patients with COPD and might contribute to the morbidity and mortality, chest physicians should screen all COPD patients at risk for osteoporosis. Diagnosis of osteoporosis should be based on bone mineral density assessed on DXA and vertebral fracture assessment on X-rays of the spine. Main risk factors of osteoporosis in COPD include advanced age, low body and muscle mass, smoking and alcohol use and vitamin D deficiency. In addition to these main risk factors, COPD-specific factors such as the use of corticosteroids and systemic inflammation might contribute to the development of osteoporosis in patients with COPD. Treatment of osteoporosis is primarily focused on reducing the risk of fracture and include intervention of risk factors by nutritional and lifestyle guidelines, calcium and vitamin D supplementation and antiresorptive therapy (e.g. bisphosphonates). In order to prevent and optimise treatment of osteoporosis in COPD, more research on its underlying pathophysiologic mechanisms is warranted.

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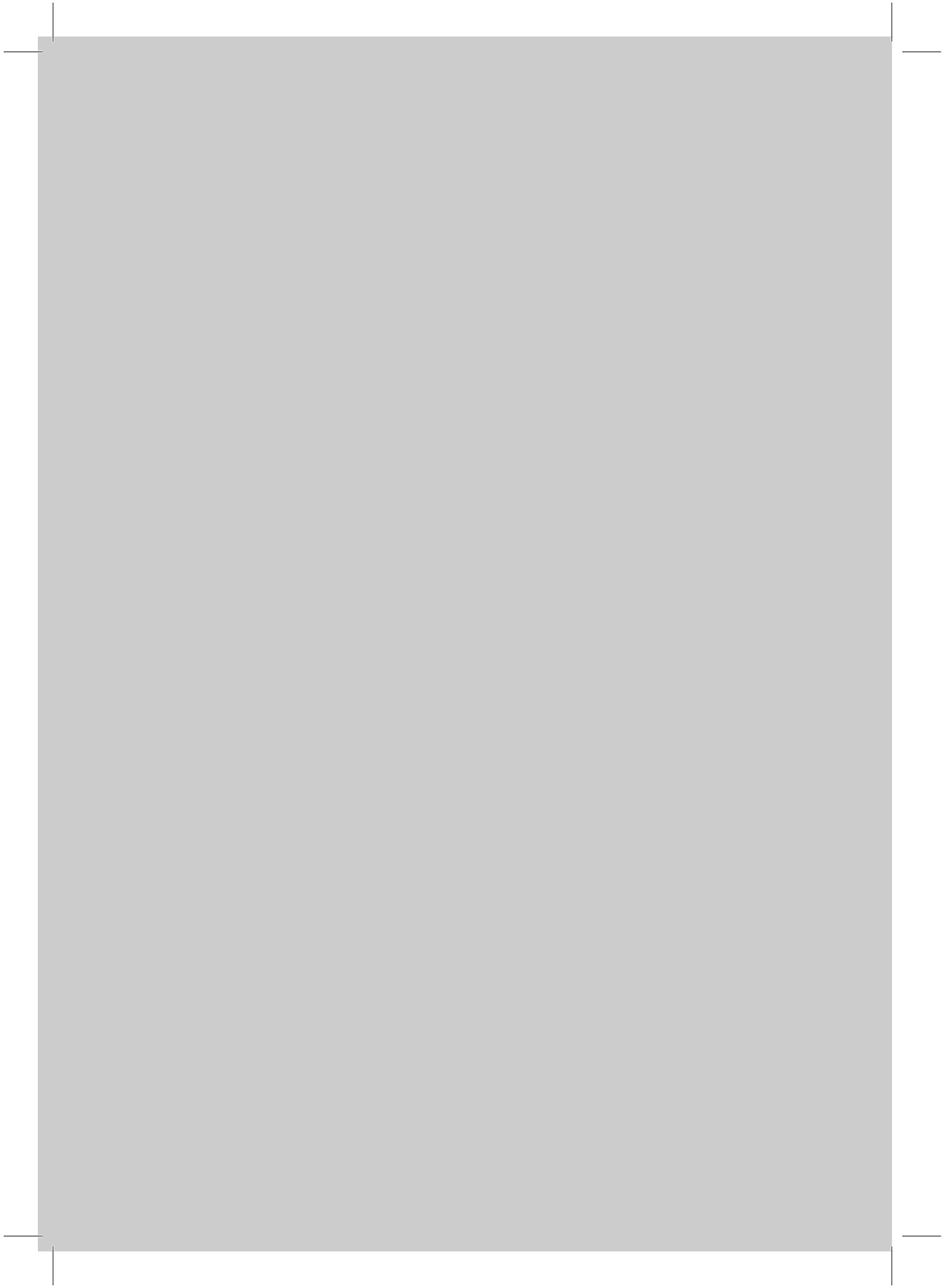
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Chapter 3

Vitamin D status is associated with bone mineral density and functional exercise capacity in patients with chronic obstructive pulmonary disease

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ABSTRACT

Background

Chronic obstructive pulmonary disease (COPD) is associated with several extrapulmonary effects that contribute to the severity of the disease. Vitamin D is suggested to play a role in COPD and its related extrapulmonary effects.

Aims

To determine the prevalence of vitamin D deficiency and its relation with bone density, muscle strength and exercise capacity in patients with COPD.

Methods

Our cross-sectional study included patients with moderate to very severe COPD. We collected data on lung function, body composition, bone density, quadriceps muscle strength, 6-minute walking distance and plasma 25-hydroxyvitamin D (25(OH)D) concentration. Vitamin D deficiency was defined as plasma 25(OH)D concentration below 50 nmol/L.

Results

In total, 151 COPD patients were included. Eighty-seven patients (58%) had vitamin D deficiency. Plasma 25(OH)D concentration was positively associated with bone density ($p=0.005$) and 6-minute walking distance ($p<0.001$) after adjustment for potential confounders. Plasma 25(OH)D concentration was not associated with quadriceps muscle strength.

Conclusions

The majority of COPD patients had vitamin D deficiency. Plasma 25(OH)D concentration was positively associated with bone density and exercise capacity. Intervention studies are necessary to determine whether vitamin D supplementation is of benefit in the prevention or treatment of osteoporosis and poor exercise capacity in patients with COPD.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is primarily characterised by the presence of airflow limitation that is not fully reversible.¹ However, COPD is also characterised by extrapulmonary effects that may contribute to the severity of the disease.² Osteoporosis, impaired skeletal muscle strength and poor exercise capacity can be considered as extrapulmonary effects of COPD, as these are more frequently observed in patients with COPD than in age-matched controls.³⁻⁵

Osteoporosis is characterised by low bone mineral density or micro-architectural changes resulting in impaired bone strength and hence increased fracture risk.⁶ Bone strength is influenced by the rate of bone remodelling and the balance between bone formation and resorption. Several factors, like systemic inflammation, use of oral and inhaled corticosteroids and vitamin D deficiency, have been suggested to interact with pathways of bone remodelling in patients with COPD.⁷

In healthy individuals the role of vitamin D in bone health is well established.⁸ Vitamin D is important in maintaining calcium homeostasis and subsequently mineralisation of bone. Indeed, in a randomised controlled trial with subjects aged 65-85 years oral vitamin D supplementation reduced the number of fractures.⁹

Another COPD-related systemic effect is skeletal muscle dysfunction.⁴ Skeletal muscle dysfunction is an independent predictor of mortality in patients with COPD.¹⁰ It is characterised by two related phenomena: net loss of muscle mass and malfunctioning of the muscle.¹¹ Indeed, in patients with COPD reduced skeletal muscle mass has been related with impaired skeletal muscle strength. However, many more patho-physiological findings, such as physical inactivity, use of corticosteroids, abnormal protein turnover, systemic inflammation, vitamin D deficiency and angiotensin converting enzyme and vitamin D receptor genotypes, have been related with skeletal muscle dysfunction.

Vitamin D is suggested to affect muscle strength and function by several processes, including calcium homeostasis, cell proliferation, cell differentiation, fibre size, prevention of fatty degeneration, protection against insulin resistance and arachidonic acid mobilisation.¹² Indeed, vitamin D receptors were identified in human skeletal muscle tissue¹³ and a meta-analysis demonstrated that vitamin D supplementation reduced the risk of falling among older individuals.¹⁴

Nowadays, it is suggested that vitamin D plays an important role in COPD and its related systemic effects.¹⁵ Recent data showed that the prevalence of vitamin D deficiency was higher in patients with COPD than in smoking controls.¹⁶ Additionally, in patients with advanced pulmonary diseases waiting for lung transplantation vitamin D deficiency was associated with reduced femur neck T-scores and a lower 6-minute walking distance.^{17,18} Moreover, in patients with COPD FokI and BsmI polymorphisms of the vitamin D receptor gene were associated with quadriceps muscle strength.¹⁹

Based on these findings we hypothesised that vitamin D might play a role in COPD-related osteoporosis and skeletal muscle dysfunction. The aims of our cross-sectional study were to examine the prevalence of vitamin D deficiency and its relation with bone mineral density, quadriceps muscle strength and functional exercise capacity in patients with COPD.

SUBJECTS AND METHODS

Subjects

Data were extracted from the records of 168 clinically stable patients with COPD who were evaluated at CIRO⁺, centre of expertise for chronic organ failure, in Horn (the Netherlands) between June and September 2009. The inclusion criteria were: Caucasian race, aged 40 years or older and moderate to very severe COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.¹ In total, 151 patients fulfilled the inclusion criteria. Seventeen patients were excluded due to the following reasons: 1 patient was 37 years old; 4 patients had an FEV₁/FVC ratio above 0.70; 7 patients had mild COPD and in 5 patients no blood samples were collected. Because of the use of de-identified and pre-existing data, our retrospective study is institutional review board exempt.

Measurements

Before entering pulmonary rehabilitation, all patients were screened for disease related physiological problems. Medical Research Council (MRC) dyspnoea scale was used to assess dyspnoea perception. Daily vitamin D intake was assessed using a validated cross-check dietary history method and calculated using the Dutch Food Composition Database.

Pulmonary function measurements were performed with standardised equipment (Masterlab[®], Jaeger, Germany) according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines. Forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC) were measured. The diffusing capacity of the lung (D_LCO) was determined by the single breath carbon monoxide gas transfer method and expressed as percentage predicted of reference values.

Total body weight and height were measured to calculate body mass index (BMI). Fat free mass (FFM) was measured by using dual-energy X-ray absorptiometry (Lunar Prodigy system, GE Healthcare, Madison, USA). Furthermore, FFM index (FFMI) was calculated as FFM divided by height².

Bone mineral density was measured at the hip and the lumbar spine (L1-L4) by using dual-energy X-ray absorptiometry. Diagnosis of osteoporosis was based on the lowest T-score of these locations and defined according to the World Health Organisation (osteoporosis: T-score ≤ -2.5 ; osteopenia: T-score between -1.0 and -2.5; and normal bone tissue: T-score ≥ -1.0).⁶

Isometric quadriceps maximum voluntary contraction strength (QMVC) was measured using a Biodex dynamometer (Biodex Medical Corporation, Shirley, NY). The best of three efforts

was used. The 6-minute walking distance (6MWD), including a practice walk, was determined to assess functional exercise capacity.

Plasma 25-hydroxyvitamin D (25(OH)D) concentration was assayed by radioimmunoassay (Immunodiagnostic Systems, Boldon, UK) at the department of Clinical Chemistry of Maastricht University Medical Centre[†], the Netherlands. The serum was extracted with acetonitrile in alkaline conditions to precipitate serum proteins. Next, the radioimmunoassay was performed using sheep anti-25(OH)D and ¹²⁵I 25(OH)D. Precipitation of the formed antigen-antibody complex was obtained by adding anti-sheep IgG coupled to cellulose.

Data on the optimal plasma 25(OH)D concentration for bone and muscle health are conflicting. A Dutch population-based study determined the threshold plasma 25(OH)D concentration with regard to parathyroid hormone, bone turnover markers, bone mineral density and physical performance in a subpopulation of the Longitudinal Aging Study Amsterdam.²⁰ They showed a threshold of about 40 nmol/L for osteocalcin and deoxypyridinoline/creatinine, 50 nmol/L for bone mineral density and 60 nmol/L for physical performance. In our study plasma 25(OH)D concentrations below 50 nmol/L (20 ng/mL) were classified as deficient.^{16,21,22}

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Statistical analysis

All statistical analyses were performed using Statistical Package for Social Sciences version 17.0 (SPSS Inc., Chicago, IL, USA). Two-sided p-values <0.05 were considered statistically significant. All data were first assessed for normal distribution.

Discrete variables were compared by the chi-square test and presented as percentages. Moreover, continuous variables were presented as mean $\pm$ standard deviation (SD) and were compared by the standardised Student t-test.

Determinants of bone mineral density, quadriceps muscle strength and functional exercise capacity were assessed by standard multiple regression analyses (enter procedure). Covariates were based on the literature. Covariates used to assess determinants of the lowest T-score were gender, age, BMI, FEV₁, 25(OH)D, 6MWD and corticosteroid use.^{3,6,7,23} Additionally, covariates used to assess determinants of quadriceps muscle strength and functional exercise capacity were gender, age, height, FFMI, FEV₁, 25(OH)D, MRC and 6MWD or QMVC.^{4,24} These covariates were included into the final multivariate regression analyses when significant at p<0.10 in the univariate regression analyses. Multicollinearity was assessed by Pearson Correlation, Tolerance and Variance Inflation Factor (VIF). We found no multicollinearity between variables (Pearson correlation < 0.70, Tolerance > 0.2 and VIF < 10).

RESULTS

Characteristics and vitamin D status

In total, 151 patients with moderate to very severe COPD entering pulmonary rehabilitation met the inclusion criteria. All data were collected before the patients started pulmonary rehabilitation. Thirty-four (22.5%) patients had had rehabilitation previously.

Table 1 shows the patients' characteristics. Vitamin D deficiency was found in 87 patients (58%). No differences were found in gender, age, vitamin D intake, use of oral or inhaled corticosteroids, arterial blood gases, BMI, FFMI, QMVC and bone mineral density between patients with and without vitamin D deficiency. Vitamin D deficient patients had a significantly lower FEV₁ and FVC and performed worse on the 6MWD compared to patients with normal plasma 25(OH)D concentrations.

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The prevalence of vitamin D deficiency was significantly different between the GOLD stages ($p=0.001$). Vitamin D deficiency was found in 43% of GOLD stage II patients, 50% of GOLD stage III patients and 76% of GOLD stage IV patients. Figure 1 shows the plasma 25(OH)D concentrations among the GOLD stages.

Determinants of bone mineral density and skeletal muscle function

Table 2 and Table 3 show the univariate and multivariate analyses for bone mineral density. Gender, 6MWD and the use of corticosteroids were not associated with bone mineral density. In the multivariate analysis, age remained negatively associated with the lowest T-score and BMI and 25(OH)D remained positively associated with the lowest T-score. This model explained 22% of the variability of bone mineral density.

Table 4 and Table 5 show the univariate and multivariate regression analyses for quadriceps muscle strength and functional exercise capacity. In the multivariate analysis for muscle strength, age remained negatively associated with QMVC and height, FFMI and 6MWD remained positively associated with QMVC. This model explained 58% of the variability of muscle strength. In addition, in the multivariate analysis for functional exercise capacity, 25(OH)D and QMVC remained positively associated with 6MWD. This model explained 37% of the variability of functional exercise capacity.

Table 1. Patients' characteristics

	Total group (n=151)	Normal vitamin D (n=64)	Vitamin D deficiency (n=87)	p-value
25(OH)D, nmol/L	49.0±16.1	64.4±10.7	37.7±7.9	<0.001
Men, n (%)	88 (58)	39 (61)	48 (55)	0.479
Age, years	64.8±8.8	64.2±9.1	65.3±8.6	0.479

Table 1 continues on next page

Continuation of table 1

BMI, kg/m ²	25.1±5.4	24.5±3.6	25.6±6.4	0.179
FEV ₁ , % predicted	45.8±16.6	49.2±15.7	43.3±16.8	0.032
FVC, % predicted	94.7±20.6	100.5±20.9	90.5±19.4	0.003
GOLD stage				
II, %	28	38	21	0.001
III, %	36	42	31	
IV, %	36	20	48	
D _L CO, % predicted	53.2±19.7	55.6±22.0	51.4±17.7	0.157
PaO ₂ , kPa	9.6±1.3	9.7±1.4	9.6±1.2	0.415
PaCO ₂ , kPa	5.3±0.6	5.2±0.6	5.4±0.6	0.099
MRC score	3.5±1.1	3.6±1.0	3.5±1.1	0.789
BMD				
Lumbar spine, g/cm ²	1.08±0.20	1.11±0.21	1.06±0.19	0.088
Hip, g/cm ²	0.82±0.14	0.84±0.15	0.80±0.14	0.073
Total, g/cm ²	1.08±0.12	1.10±0.11	1.07±0.12	0.168
Lowest T-score	-1.98±1.12	-1.78±1.12	-2.13±1.11	0.059
Bone classification				
Normal bone, %	21	26	16	0.038
Osteopenia, %	41	44	39	
Osteoporosis, %	38	30	45	
Muscle mass and strength				
FFMI, kg/m ²	17.2±2.3	17.2±2.2	17.2±2.3	0.947
QMVC, kg	28.6±9.8	29.9±9.6	27.4±9.9	0.207
QMVC/FFM	0.59±0.16	0.62±0.15	0.57±0.17	0.159
6MWD, meters	425.7±122.0	477.7±124.2	387.0±105.3	<0.001
Vitamin D intake, µg	5.5±3.1	5.6±3.4	5.5±2.9	0.843
Use of corticosteroids (%)				
Oral	13.9	6.3	19.5	0.059
Inhaled	88.1	87.5	88.5	0.897

Results are presented as mean ± standard deviation unless otherwise indicated. The p-values represent the differences between normal vitamin D and vitamin D deficiency.

25(OH)D = 25-hydroxyvitamin D; BMI = body mass index; FEV₁ = forced expiratory volume in the first second; FVC = forced vital capacity; D_LCO = diffusing capacity for carbon monoxide; PaO₂ = partial pressure of oxygen in arterial blood; PaCO₂ = partial pressure of carbon dioxide in arterial blood; MRC = medical research council dyspnoea scale, BMD = bone mineral density; FFMI = fat free mass index; QMVC = quadriceps maximum voluntary contraction strength; FFM = fat free mass; 6MWD = 6-minute walking distance.

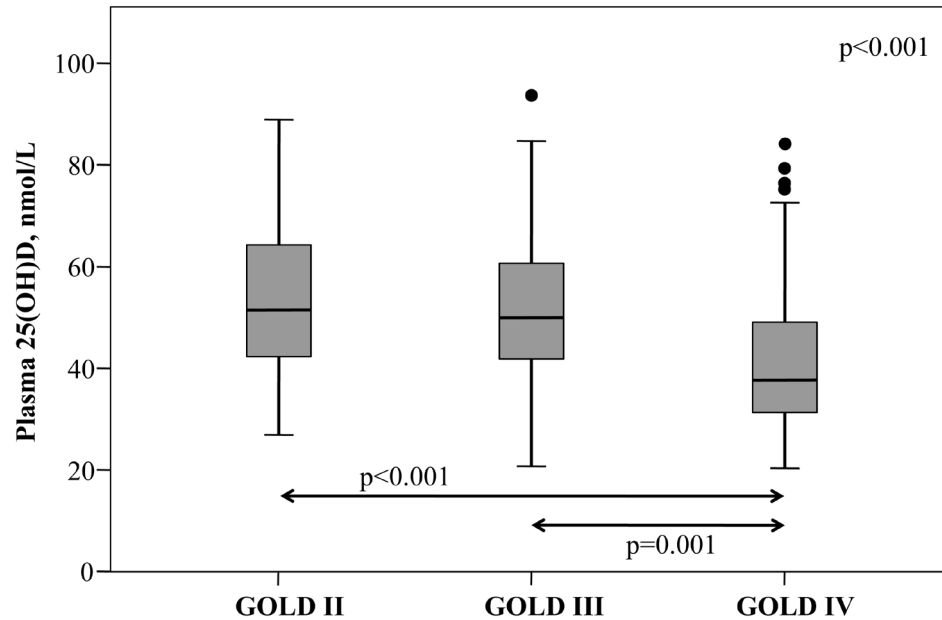


Figure 1. Plasma 25(OH)D concentrations among the GOLD stages

Table 2. Univariate regression analyses for bone mineral density (T-score)

	B	95% CI	p-value
Men	0.188	-0.177 to 0.553	0.311
Age	-0.022	-0.042 to -0.002	0.035
BMI	0.077	0.046 to 0.109	<0.001
FEV ₁	0.011	0.000 to 0.022	0.044
25(OH)D	0.012	0.001 to 0.023	0.034
6MWD	0.001	0.000 to 0.003	0.109
Oral corticosteroids	0.032	0.000 to 0.000	0.697
Inhaled corticosteroids	0.032	0.000 to 0.000	0.696

BMI = body mass index; FEV₁ = forced expiratory volume in 1 second; 25(OH)D = 25-hydroxyvitamin D, 6MWD = 6-minute walking distance.

Table 3. Multivariate regression analyses for bone mineral density (T-score)

	B	95% CI	p-value
Age	-0.024	-0.042 to -0.005	0.011
BMI	0.078	0.047 to 0.109	<0.001
FEV ₁	0.005	-0.005 to 0.015	0.360
25(OH)D	0.015	0.005 to 0.025	0.005

BMI = body mass index; FEV₁ = forced expiratory volume in 1 second; 25(OH)D = 25-hydroxyvitamin D. Adjusted R²: 0.22

Table 4. Univariate regression analyses for quadriceps muscle strength (QMVC) and 6MWD

	QMVC			6MWD		
	B	95% CI	p-value	B	95% CI	p-value
Men	11.529	8.357 to 14.701	<0.001	36.463	-3.023 to 75.949	0.070
Age	-0.215	-0.433 to 0.003	0.053	-4.162	-6.292 to -2.033	<0.001
Height	0.591	0.421 to 0.761	<0.001	3.103	0.939 to 5.267	0.005
FFMI	2.541	1.782 to 3.299	<0.001	3.774	-5.083 to 12.631	0.401
FEV ₁	0.158	0.045 to 0.271	0.007	1.443	0.273 to 2.613	0.016
25(OH)D	0.097	-0.019 to 0.212	0.099	2.778	1.635 to 3.921	<0.001
QMVC	-	-	-	5.783	3.696 to 7.871	<0.001
6MWD	0.041	0.026 to 0.056	<0.001	-	-	-
MRC	0.792	-1.287 to 2.871	0.450	4.550	-16.754 to 25.853	0.673
Oral corticosteroids	-0.099	-0.002 to 0.001	0.329	-0.009	-0.015 to 0.013	0.908
Inhaled corticosteroids	-0.099	-0.002 to 0.001	0.330	-0.009	-0.015 to 0.013	0.909

FFMI = fat free mass index; FEV₁ = forced expiratory volume in 1 second; 25(OH)D = 25-hydroxyvitamin D; QMVC = quadriceps maximum voluntary contraction strength; 6MWD = 6-minute walking distance; MRC = medical research council dyspnoea scale.

Table 5. Multivariate regression analyses for quadriceps muscle strength (QMVC) and 6MWD

	QMVC			6MWD		
	B	95% CI	p-value	B	95% CI	p-value
Men	4.106	-0.569 to 8.781	0.084	27.941	-34.708 to 90.589	0.378
Age	-0.249	-0.412 to -0.087	0.003	-2.033	-4.404 to 0.338	0.092
Height	0.215	0.009 to 0.421	0.041	-1.368	-4.357 to 1.621	0.366
FFMI	1.403	0.573 to 2.234	0.001	-	-	-
FEV ₁	0.020	-0.068 to 0.108	0.654	0.491	-0.702 to 1.685	0.416
25(OH)D	0.004	-0.088 to 0.097	0.927	2.489	1.287 to 3.691	<0.001
QMVC	-	-	-	4.503	1.806 to 7.201	0.001
6MWD	0.023	0.010 to 0.037	0.001	-	-	-

FFMI = fat free mass index; FEV₁ = forced expiratory volume in 1 second; 25(OH)D = 25-hydroxyvitamin D; QMVC = quadriceps maximum voluntary contraction strength; 6MWD = 6-minute walking distance; MRC = medical research council dyspnoea scale.

Adjusted R² for QMVC: 0.58

Adjusted R² for 6MWD: 0.37

DISCUSSION

Our data demonstrated that vitamin D deficiency was present in the majority of patients with COPD entering pulmonary rehabilitation. Additionally, after adjustment for potential confounders plasma 25(OH)D concentration was positively associated with bone mineral density and functional exercise capacity. However, plasma 25(OH)D concentration was not independently associated with quadriceps muscle strength. Based on these findings we suggest there might be a link between vitamin D and COPD-related osteoporosis and poor exercise capacity.

Although all blood samples were collected in summer, vitamin D deficiency was found in the majority of COPD patients (58%). Vitamin D deficiency was found in 43% of GOLD stage II, 50% of GOLD stage III and 76% of GOLD stage IV COPD patients. These data are in line with data collected in Belgium during all seasons by Janssens and colleagues.¹⁶ They found vitamin D deficiency in 47% of GOLD stage II, 60% of GOLD stage III and 77% of GOLD stage IV COPD patients. Moreover, the prevalence of vitamin D deficiency seems to be higher in our COPD cohort compared with the general Dutch population. In the Hoorn Study, a Dutch population-based cohort study, the prevalence of vitamin D deficiency (< 50 nmol/L) was 34% in summer and 51% in winter.²⁵ In the Longitudinal Aging Study Amsterdam the prevalence of vitamin D deficiency (< 50 nmol/L) was 48%.²⁰

Our data showed that COPD patients with vitamin D deficiency had a significantly lower FEV₁ and FVC than COPD patients with normal plasma 25(OH)D concentrations. Additionally, a large study of the general population demonstrated a strong relationship between plasma 25(OH)D concentration and pulmonary function.²⁶ This relationship even remained after adjustment for the degree of leisure time physical activity and vitamin D intake. Moreover, in animal models vitamin D deficiency caused deficits in lung function²⁷ and the rs7041 variant in the vitamin D binding gene was associated with the presence of COPD.¹⁶

Although it is suggested that vitamin D influences lung function, the mechanism is still unknown. However, some mechanisms have been suggested. First, vitamin D deficiency might be related to decreased pulmonary function due to thoracic vertebral fractures. Second, vitamin D deficiency has been suggested to result in altered host defense of the lung with subsequent growth of an abnormal flora that triggers inflammation. Hence, acute exacerbations of COPD are an important cause of hospitalisation and lead to a faster decline in lung function. Third, vitamin D is suggested to have an effect on the extracellular matrix homeostasis within the lung resulting in the development of COPD.²⁸

Furthermore, plasma 25(OH)D concentration was independently associated with bone mineral density. F rli and colleagues¹⁷ demonstrated that vitamin D deficiency was associated with reduced femur neck T-scores in underweight patients with end-stage pulmonary diseases waiting for lung transplantation. However, Franco and colleagues²² did not confirm this association in a small group (n=49) of postmenopausal women and men with COPD.

In healthy subjects it is well established that vitamin D is critical for bone health. A low plasma 25(OH)D concentration is associated with decreased intestinal calcium absorption causing compensatory increased parathyroid hormone concentrations. Additionally, parathyroid hormone, which has been identified as a determinant of osteoporosis in patients with COPD,²⁹ activates osteoblasts which stimulate the transformation of pre-osteoclasts into mature osteoclasts. Mature osteoclasts dissolve the mineralised collagen matrix in bone causing osteopenia and osteoporosis.²¹

Besides low plasma 25(OH)D concentration, more patho-physiological mechanisms have been described to interact with pathways of bone remodelling in patients with COPD. Our data demonstrated that the prevalence of osteoporosis was still high (30%) in patients with normal plasma 25(OH)D concentrations. This finding suggests that more factors besides plasma 25(OH)D concentration correlate with bone mineral density. Indeed, in line with previous data,^{3,23} we showed that older age, lower BMI and lower FEV₁ were associated with reduced bone mineral density. However, many more factors, such as systemic inflammation, genetic background, smoking, physical inactivity, use of oral or inhaled corticosteroids and the presence of emphysema, have been associated with reduced bone mineral density.⁷

Nowadays, it is assumed that vitamin D has a role in skeletal muscle health. Recently, a review stated that vitamin D affects muscle strength and function by several processes, including calcium homeostasis, cell proliferation, cell differentiation, fibre size, prevention of fatty degeneration, protection against insulin resistance and arachidonic acid mobilisation.¹²

In line with previous data in patients with end-stage pulmonary diseases,¹⁸ we showed that plasma 25(OH)D concentration was positively associated with walking distance after adjustment for potential confounders. Moreover, Ringbaek and colleagues³⁰ evaluated the influence of vitamin D on the endurance shuttle walk test in 311 outpatients with COPD who participated in pulmonary rehabilitation. They demonstrated that lower plasma 25(OH)D concentrations were associated with smaller improvements in the endurance shuttle walk test.

Research on the relationship between plasma 25(OH)D concentration and skeletal muscle strength is scarce in patients with COPD. Our data showed no association between plasma 25(OH)D concentration and quadriceps muscle strength. In addition, Førlin and colleagues¹⁸ demonstrated that plasma 25(OH)D concentration was not associated with hand grip strength after adjustment for potential confounders in patients with end-stage pulmonary diseases.

In healthy subjects, cross-sectional data on the relationship between vitamin D and muscle function are conflicting.³¹⁻³⁴ This is partly due to variances in subjects studied and methods used. Recently, a meta-analysis demonstrated that vitamin D supplementation had a positive effect on muscle strength in subjects with plasma 25(OH)D concentrations below 25 nmol/L and no effect in subjects with plasma 25(OH)D concentrations above 25 nmol/L.³⁵ However,

well-designed randomised controlled trials on the effect of vitamin D supplementation on muscle fibre composition, strength and exercise capacity are still lacking.

Some methodological considerations should be mentioned. Primarily, there could be a selection bias due to the inclusion of patients who were referred to pulmonary rehabilitation. However, the included COPD patients represented different stages of disease severity. In addition, a comparable prevalence of vitamin D deficiency was found in COPD patients recruited at a university hospital in Belgium.¹⁶ Secondly, no causal relationship could be established due to the cross-sectional design of the study. Thirdly, we did not include a healthy control group.

The strengths of our study are that all patients were included in summer, well-characterised and diagnosed with COPD according to the GOLD guidelines. By contrast, previous studies on the role of vitamin D in osteoporosis and muscle dysfunction included patients with several different pulmonary diseases.^{17,18}

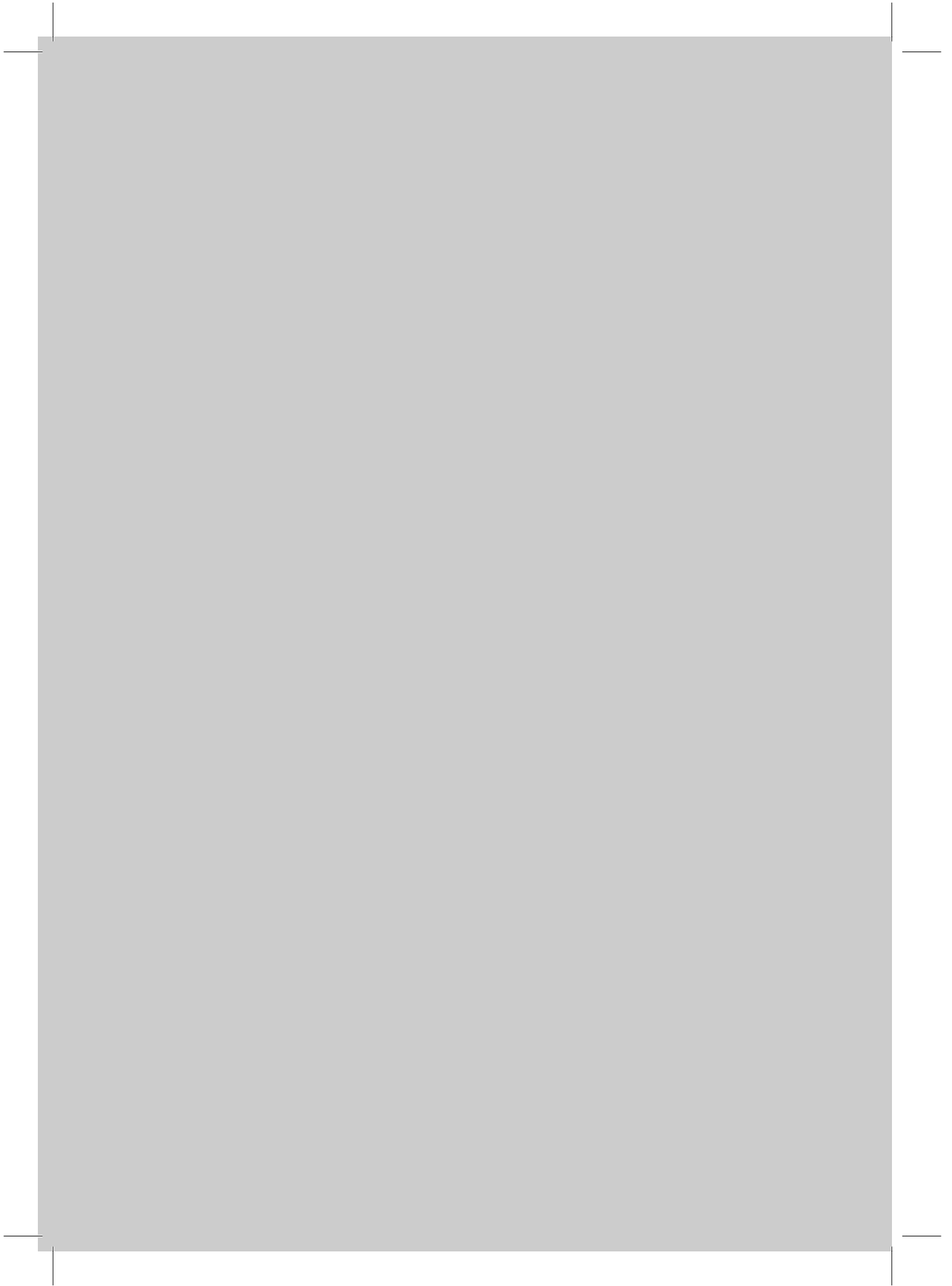
Although randomised controlled trials on vitamin D supplementation in patients with COPD are lacking, we advise chest physicians to be alert for vitamin D deficiency in patients with COPD. It is already known that osteoporosis and muscle dysfunction influence morbidity and mortality in patients with COPD.^{7,10} Our data demonstrated that the prevalence of vitamin D deficiency is high in COPD and that vitamin D status is associated with bone mineral density and functional exercise capacity, suggesting a link between vitamin D and COPD-related osteoporosis and muscle dysfunction. Indeed, in healthy individuals randomised controlled trials have already demonstrated beneficial effects of vitamin D supplementation on bone health and skeletal muscle function. However, further research on the role of vitamin D in bone and muscle health in patients with COPD is warranted.

To conclude, the majority of patients with COPD entering pulmonary rehabilitation had vitamin D deficiency. Additionally, vitamin D status was positively associated with bone mineral density and functional exercise capacity as measured by 6MWD. In future, intervention studies will be necessary to determine whether vitamin D supplementation might be of benefit in the prevention or treatment of osteoporosis and poor exercise capacity in patients with COPD.

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Chapter 4

Bone attenuation on routine chest CT correlates with bone mineral density on DXA in patients with chronic obstructive pulmonary disease

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ABSTRACT

COPD, although primarily a disease of the lungs, is associated with extra pulmonary effects such as muscle weakness and osteoporosis. Fractures due to osteoporosis cause significant morbidity and mortality, particularly in patients with COPD. To prevent osteoporotic fractures, it is important to diagnose osteoporosis in an early stage and to start anti-osteoporotic therapy in at risk patients. Because routine chest Computed Tomography (CT) is increasingly used to assess the extent of emphysema and airways disease in patients with COPD, we investigated whether simple attenuation measurement of the thoracic spine on routine chest CT may provide useful information on bone health in patients with COPD. Fifty-eight patients with moderate to very severe COPD were included in our study. The average attenuation of thoracic vertebrae 4, 7 and 10 on chest CT was correlated with the lowest bone mineral density (BMD) of the hip and lumbar spine (L1 to L4) on dual-energy X-ray absorptiometry (DXA) in patients with COPD. The inter and intra-observer variabilities of the attenuation measurements were low as shown by Bland Altman plots. Pearson's correlation coefficient between the average attenuation of the three thoracic vertebrae and the lowest BMD of the hip and lumbar spine was high ($r=0.827$, $p<0.001$). A ROC analysis of the area under the curve for osteoporosis was 0.969 ($p<0.001$) corresponding to an attenuation threshold of 147 HU. In conclusion, our data demonstrated that bone attenuation measured on routine chest CT correlated strongly with BMD assessed on DXA in patients with COPD. Routine chest CT may provide useful information on bone health in patients with COPD.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD), a condition that primarily affects the lungs, is characterized by airflow limitation that is not fully reversible.¹ In addition to its pulmonary effects, COPD is characterized by extra pulmonary effects such as muscle weakness,² arterial stiffness³ and osteoporosis⁴ that contribute to the severity of the disease.⁵

Osteoporosis is a skeletal disease that is characterized by impaired bone strength due to low bone mineral density (BMD) or micro architectural deterioration.⁶ Patients with osteoporosis are at increased risk of fractures resulting in significant morbidity and mortality, particularly in patients with COPD where vertebral fractures further compromise pulmonary function.^{7,8} The current gold standard to diagnose osteoporosis is dual-energy X-ray absorptiometry (DXA). Indeed, the World Health Organization (WHO)⁶ and International Society for Clinical Densitometry⁹ recommend a diagnosis of osteoporosis based on the lowest T-score of the hip or the lumbar spine on DXA. This method is also recommended in patients with COPD.¹⁰

More recently several other methods to measure BMD have been described. A well-established method is quantitative computed tomography (QCT).¹¹ With standard QCT the lumbar vertebrae are scanned with a mineral reference phantom in the same field. Consequently, the attenuation of the lumbar vertebrae is measured in Hounsfield Units (HU) and transformed into bone mineral equivalents (mg/cm³) using standardized software.¹¹

In addition to standard QCT, routine helical Computed Tomography (CT) has been suggested to be useful for BMD measurement. *In vitro* and *in vivo* data showed that BMD on routine CT correlated strongly with BMD on standard QCT.¹² However, in this study a reference phantom was used in order to standardize measurements and to obtain a mineral reference while with routine CT a phantom is usually absent. More recently Miyabara and colleagues¹³ demonstrated a strong correlation between BMD measurements of the thoracic spine on coronary CT with or without a reference phantom in menopausal women. In addition, Pickhardt and colleagues¹⁴ compared simple attenuation measurement on CT colonography without a reference phantom with BMD measurement on DXA in adults aged 50 years and older. They demonstrated that simple attenuation measurement on CT colonography was effective for osteoporosis screening.

With this in mind we hypothesized that simple attenuation measurement of the thoracic spine on routine chest CT, that are increasingly used to assess the extent of emphysema and airways disease in patients with COPD, may provide useful information on bone health in patients with COPD. Therefore, we measured the average attenuation of thoracic vertebrae 4, 7 and 10 on chest CT and correlated these measurements with the lowest BMD of the hip and lumbar spine (L1 to L4) on DXA in patients with COPD.

MATERIALS AND METHODS

Subjects

Patients with moderate to very severe COPD who were enrolled in a clinical trial at the Catharina Hospital (Eindhoven, the Netherlands) between February 2010 and September 2011 were included in our study. The purpose of the clinical trial was to investigate the pathophysiologic mechanism of osteoporosis in COPD. Since patients with osteopenia were excluded in this clinical trial, no patients with osteopenia were included in our study. All patients underwent both CT and DXA in order to assess the extent of emphysema and to measure BMD.

The inclusion criteria for the clinical trial were: Caucasian race, men or postmenopausal women aged 50 years or older, moderate to very severe COPD diagnosed according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.¹ The exclusion criteria were: malignancy in the last 5 years, hypo- or hyperthyroidism, hypogonadism, inflammatory bowel disease, auto-immune diseases, alcohol abuse, non-vertebral fracture in the last 12 months and pulmonary diseases other than COPD such as pulmonary fibrosis or bronchiectasis. Use of oral corticosteroids or antibiotics 4 weeks before study enrollment and use of anti-osteoporotic medication such as bisphosphonates, calcium or vitamin D supplementation were prohibited.

The study was approved by the medical ethical committee of the Catharina Hospital and registered at www.clinicaltrials.gov (NCT01067248). All patients gave written informed consent.

Measurements

Forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC) were measured using standardized equipment (MasterScreen™ Body, Carefusion, San Diego, California, USA) according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines.¹⁵ Total body weight and height were measured to calculate body mass index (BMI).

BMD of the lumbar spine (L1 to L4) and hip were measured using a Delphi upgraded to a discovery W (S/N70991) DXA scanner (Tromp Medical Engineering BV, Castricum, the Netherlands). Diagnosis of osteoporosis was based on the lowest T-score of these locations and defined according to the WHO criteria (osteoporosis: T-score ≤ -2.5 ; osteopenia: T-score < -1.0 and > -2.5 ; and normal bone tissue: T-score ≥ -1.0).⁶

Chest CT examinations were performed using a single-energy 256 multidetector row scanner (Philips Brilliance intelligent CT, Philips Healthcare, Eindhoven, the Netherlands) with technical parameters of 120 kVp, 350-mm field of view, 2.5 mm slice thickness and ECG gated. The scanner was calibrated daily to ensure accurate CT attenuation numbers. All patients were scanned in supine position during deep inspiration without the use of contrast

media. CT images were stored by an electronic Picture Archiving and Communication System (PACS) and assessed using VOXAR 3D version 16.0 software. Attenuation of thoracic vertebrae 4, 7 and 10 (T4, T7 and T10) were measured using a modification of a method described previously.¹⁶ The most central section of the vertebra was selected by inspecting the sagittal and coronal reformats. In this section, the mean attenuation was determined by placing a circular region of interest (ROI) in the central part of the vertebral body avoiding the basivertebral venous plexus posteriorly and the cortical bone. All ROIs were placed manually by one of the authors (EAR) who was blinded to the patients' personal details, history and BMD. The average attenuation of T4, T7 and T10 was calculated and expressed as Hounsfield Units (HU).

In order to investigate whether the size of the ROI influences the mean attenuation, we used ROIs with different size areas (ROI 1: T4, T7 and T10 50 mm² area; ROI 2: T4, T7 and T10 100 mm² area; ROI 3: T4 100 mm² area and T7 and T10 200 mm² area). In addition, the CT images of a random sample of 20 patients were assessed by two observers (EAR and KF) and assessed by one observer (EAR) twice to calculate the inter and intra-observer variabilities of the attenuation measurements on chest CT.

Statistical analysis

Data were assessed for normal distribution. Discrete variables were presented as percentages and continuous variables were presented as mean $\pm$ standard deviation (SD). Continuous variables were compared by the two-tailed Student *t*-test.

The correlations between attenuation measurements using ROIs of different size areas were assessed by calculating intraclass correlation coefficients. Inter and intra-observer variabilities of the attenuation measurements were determined by using the method as described by Bland and Altman.¹⁷ The limits of agreement were determined by plotting the mean measurement difference ± 2 standard deviations (SD). The correlation between CT-measured bone attenuation and DXA scan BMD was calculated using Pearson's correlation coefficient. A regression equation was calculated using linear regression. The diagnostic ability of CT-measured bone attenuation for osteoporosis was assessed using receiver operating statistic curve (ROC) analysis.

All statistical analyses were performed using the Statistical Package for Social Sciences version 17.0 (SPSS Inc., Chicago, IL, USA). Two-sided *p*-values < 0.05 were considered statistically significant.

RESULTS

Fifty-eight patients with moderate to very severe COPD were included. The mean time interval between chest CT and DXA was 40.6 days. Table 1 shows the patients' demographics and characteristics. Twenty-seven (47%) COPD patients had osteoporosis according to DXA measurements.

The intra class correlation coefficients between the ROIs using different size areas were high (see supplement, e-Figure 1, 2 and 3). The correlation coefficient between ROI 1 and ROI 2 was 0.996 ($p<0.001$) and between ROI 1 and ROI 3 was 0.990 ($p<0.001$) and between ROI 2 and ROI 3 was 0.998 ($p<0.001$). Because of the heterogeneity of bone, we decided to use the ROI with the largest size area for the final analyses.

Table 1. Patients' characteristics

	Normal BMD	Osteoporosis
Number	31	27
Males, n (%)	22 (71)	14 (52)
Age, yrs	65.4±8.2	66.5±7.8
FEV ₁ , % predicted	64.9±11.3	53.7±17.1
FEV ₁ /FVC ratio	55.0±9.3	44.8±10.0
BMI, kg/m ²	29.2±5.5	24.5±4.6
BMD hip, g/cm ²	1.147±0.145	0.800±0.110
BMD L1-L4, g/cm ²	1.187±0.167	0.809±0.155
Lowest BMD, g/cm ²	1.110±0.129	0.747±0.100

Results are presented as mean ± standard deviation unless otherwise indicated.

BMD = bone mineral density; FEV₁ = forced expiratory volume in the first second; FVC = forced vital capacity; BMI = body mass index

Figure 1 shows the inter and intra-observer variabilities. The Bland-Altman 95% limits of agreement between the two observers ranged from -8.87 to 5.41 HU (Figure 1A). In addition, the Bland-Altman 95% limits of agreement between the two observations by one observer ranged from -9.28 to 8.86 HU (Figure 1B).

The mean bone attenuation on chest CT in the patients studied was 152.3 ± 56.5 HU. The mean bone attenuation was nearly 50% lower in COPD patients with osteoporosis compared with COPD patients with normal BMD (see supplement, e-Figure 4, $p<0.001$). The mean attenuation of T4 (175.1 HU) was higher compared with the mean attenuation of T7 (139.3 HU, $p<0.001$) and T10 (141.0 HU, $p<0.001$).

The correlation between CT-measured bone attenuation and the lowest BMD assessed on DXA was high ($r=0.827$, $p<0.001$, Figure 2). The regression equation was: BMD assessed on DXA (in g/cm²) = 0.003 * CT-measured attenuation (in HU) + 0.460. In addition, the correlation coefficient between bone attenuation and BMD of the hip was 0.775 ($p<0.001$) and between bone attenuation and BMD of the lumbar spine was 0.767 ($p<0.001$). Figure 3 shows the ROC curve for predicting osteoporosis with simple attenuation measurement on chest CT. The area under the curve was 0.969 ($p<0.001$). The attenuation threshold with the highest sensitivity and specificity for osteoporosis was 147 HU (sensitivity 93% and specificity 97%).

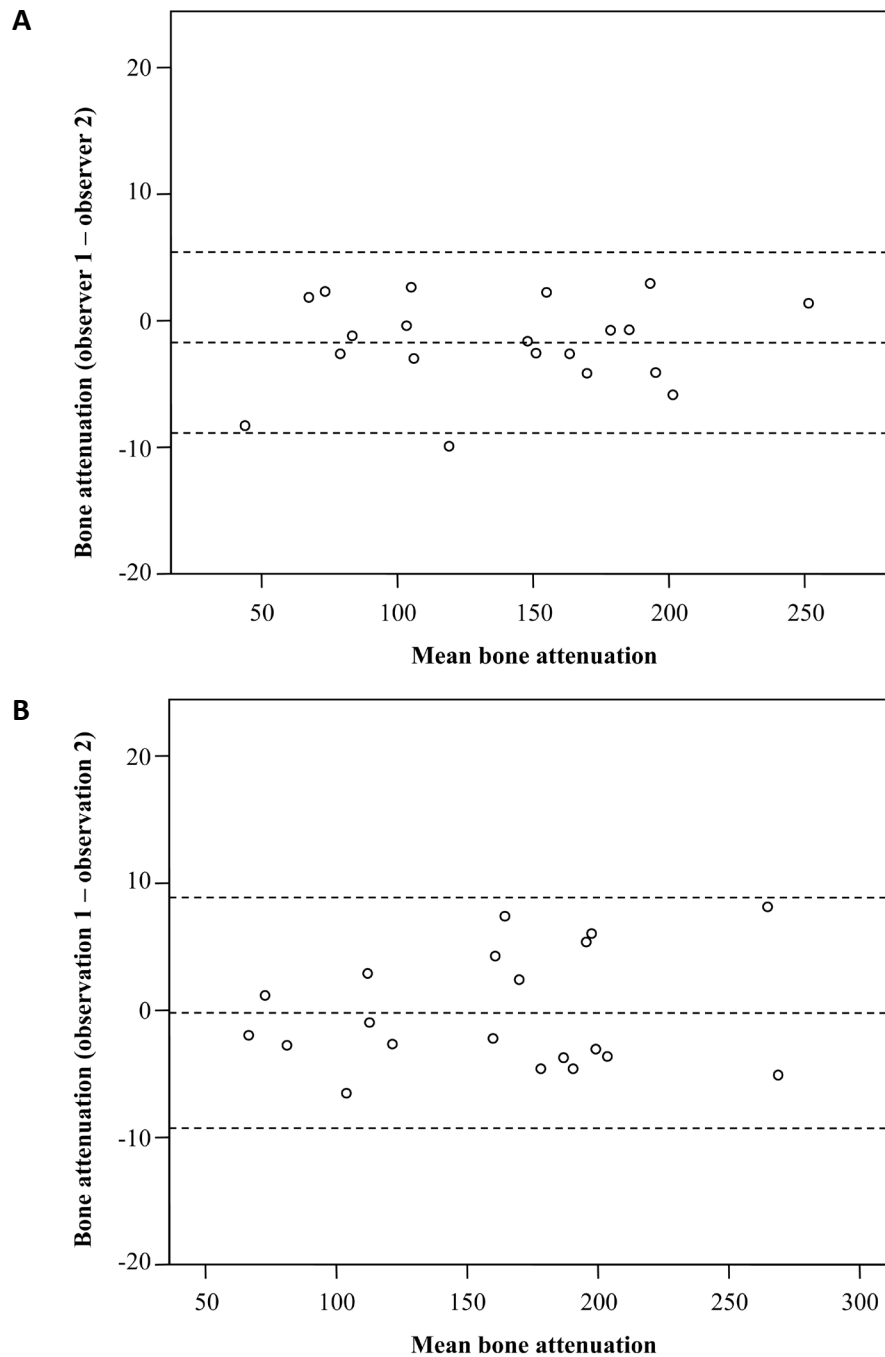


Figure 1. Bland Altman plots for the inter-observer (A) and intra-observer (B) variabilities of the bone attenuation measurements on chest CT

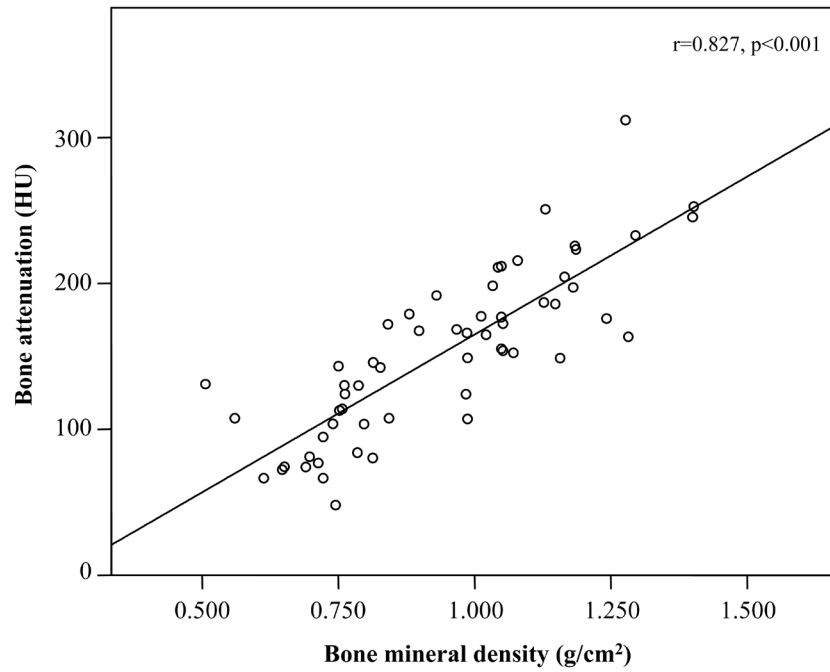


Figure 2. Correlation between CT-measured bone attenuation and DXA scan BMD

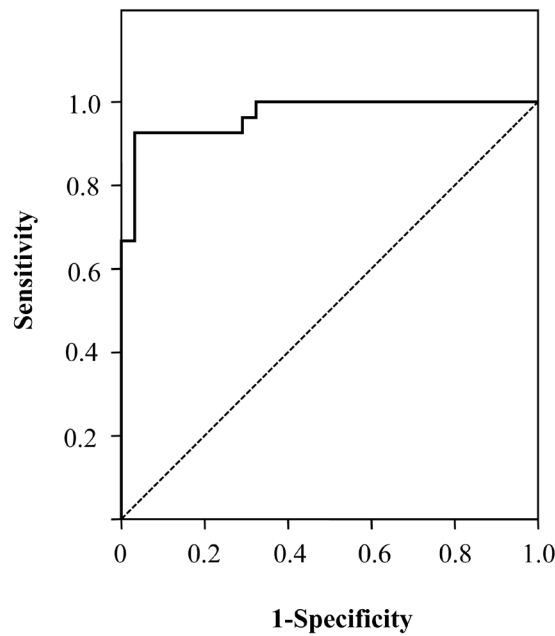


Figure 3. ROC curve for predicting osteoporosis with simple attenuation measurement of the thoracic spine on chest CT

DISCUSSION

This study showed that the average attenuation of thoracic vertebrae 4, 7 and 10 on routine chest CT was strongly correlated with the lowest BMD of the hip and lumbar spine on DXA in patients with COPD. Our data suggest that simple attenuation measurement of the thoracic spine on routine chest CT may provide useful information on bone health in patients with COPD.

Data on the feasibility of simple attenuation measurement on routine CT are scarce. Ohara and colleagues¹⁶ described a method to measure bone density on chest CT. They assessed the average attenuation of thoracic vertebrae 4, 7 and 10 and lumbar vertebra 1 on chest CT. In order to express bone density as milligram per milliliter, they scanned a reference phantom with the same scanning parameters as the subjects. In our study a modification of their method was used. However, we demonstrated in addition to their study that CT-measured bone attenuation was strongly correlated with DXA scan BMD, which is considered the gold standard for diagnosing osteoporosis.

More recently Pickhardt and colleagues¹⁴ compared simple attenuation measurement on CT colonography with BMD measurement on DXA in adults aged 50 years and older. The ROC analysis of the area under the curve for osteoporosis was 0.825. In line with their data, we demonstrated that the area under the curve for osteoporosis was high (0.969). However, Pickhardt and colleagues opted to use an attenuation threshold that would yield 100% sensitivity for osteoporosis (160 HU) resulting in modest specificity (46.4%), whereas our study used a slightly lower threshold (147 HU) giving high sensitivity (93%) and specificity (97%).

Miyabara and colleagues¹³ demonstrated that calibrated and uncalibrated BMD measurements of thoracic vertebrae 8 and 9 on coronary CT scans in 111 menopausal women correlated with BMD measurements of the lumbar spine (L2 to L4) on DXA. However, the correlation in their study ($r=0.60$, $p<0.0001$) was not as strong as in ours. This may have resulted from differences in the methods used since they used the attenuation of the individual vertebrae rather than the average attenuation of the thoracic vertebrae and correlated BMD of the lumbar spine rather than the lowest BMD of the lumbar spine and hip. The poorer correlation in the study by Miyabara and colleagues may also have resulted from differences in the study population since their study population did not include subjects with osteoporosis.

In line with previous data,¹⁶ we showed that attenuation of thoracic vertebra 4 was higher compared with attenuation of thoracic vertebrae 7 and 10. Several studies have shown that BMD is higher in cervical spine compared with lumbar spine¹⁸ and higher in thoracic spine compared with lumbar spine.^{19,20} These data provide a reason why vertebral fractures are more common in the thoracolumbar spine since decreased BMD results in reduced bone strength.^{18,21,22} Wasnich²³ concluded that most osteoporotic vertebral fractures were located in the thoracolumbar spine at thoracic vertebra 8 or between thoracic vertebra 11 and lumbar

vertebra 1. In addition, Graat-Verboom and colleagues⁸ showed that in patients with COPD most vertebral fractures were located at thoracic vertebrae 8 and 12.

Although no reference phantom or external references were used, our data showed a strong correlation between bone attenuation measured on CT and BMD measured on DXA. Mineral reference phantoms are used in order to standardize measurements and obtain a mineral reference.^{11,13,24} Besides reference phantoms, internal references such as muscle and subcutaneous fat can be used as calibration references.²⁵⁻²⁷ However, the use of reference phantoms and internal references has some disadvantages. Reference phantoms may cause beam hardening and scatter effects and internal references have a heterogeneous HU distribution.²⁷

Automated placement of ROIs has been suggested to limit random errors.^{24,28} However, in our study the reproducibility with manually placed ROIs was good. In addition, attenuation measurements using ROIs of different sized areas were strongly correlated and previous data demonstrated that BMD measurements using ROIs of different shaped areas also gave strong correlations.²⁹ These data suggest that ROIs of different size or shape have no significant effect on the CT bone density measurements.

4

Some limitations of our study should be mentioned. Primarily, the number of patients was relatively small and patients with osteopenia were excluded. Since BMD had a normal distribution we do not think inclusion of osteopenia would have changed our results. Secondly, for the purpose of the present study all patients were scanned with the same CT and DXA scanner while in clinical practice several types of CT and DXA scanners are used. Thus while it is likely that similar associations would be shown with other scanners the osteoporosis attenuation threshold value that we have calculated in our study cannot be extrapolated to those scanners. Thirdly, we compared simple bone attenuation measurement on CT that assesses trabecular bone with BMD on DXA that assesses trabecular and cortical bone. It would therefore be of interest to compare simple attenuation measurement with QCT since both methods assess trabecular bone. However, this would result in a higher radiation exposure for the patients. Finally, vertebral fractures were not assessed in our study. Previous research showed that COPD patients with a normal BMD on DXA can have vertebral fractures.^{8,30} Theoretically, CT-measured bone attenuation of the thoracic spine should be superior to DXA scanned BMD of the hip and lumbar spine for prediction of thoracic vertebral fractures. Therefore, it would be interesting to correlate CT-measured bone attenuation of the thoracic spine with thoracic vertebral fractures.

The strengths of our study are the good characterization of the study population and the good reproducibility with simple attenuation measurement. This finding is in line with previous data that showed a good reproducibility with simple attenuation measurement on CT colonography.¹⁴ The reproducibility was even better with simple attenuation measurement than with QCT.¹⁴

Based on our data we suggest that simple attenuation measurement on chest CT is useful to assess bone health in patients with COPD. However, more research is warranted in order to establish a reference range for thoracic spine attenuation and to confirm the attenuation threshold of 147 HU for osteoporosis in larger COPD populations and using different scanners. In addition to more research in COPD patients, it would be interesting to study this method in other patient populations. Furthermore, although CT can provide useful information on bone health, CT will not replace DXA as the gold standard for osteoporosis because of the higher radiation dose and higher costs. We also acknowledge that besides BMD measurements several other factors such as gender, age and body mass index are important for fracture risk prediction.^{4,31,32}

In conclusion, this study shows that simple attenuation measurement on routine chest CT can be used to assess bone health in patients with COPD. In future, more research is warranted to validate simple attenuation measurement on chest CT in order to screen for osteoporosis in patients with COPD.

DISCLOSURES

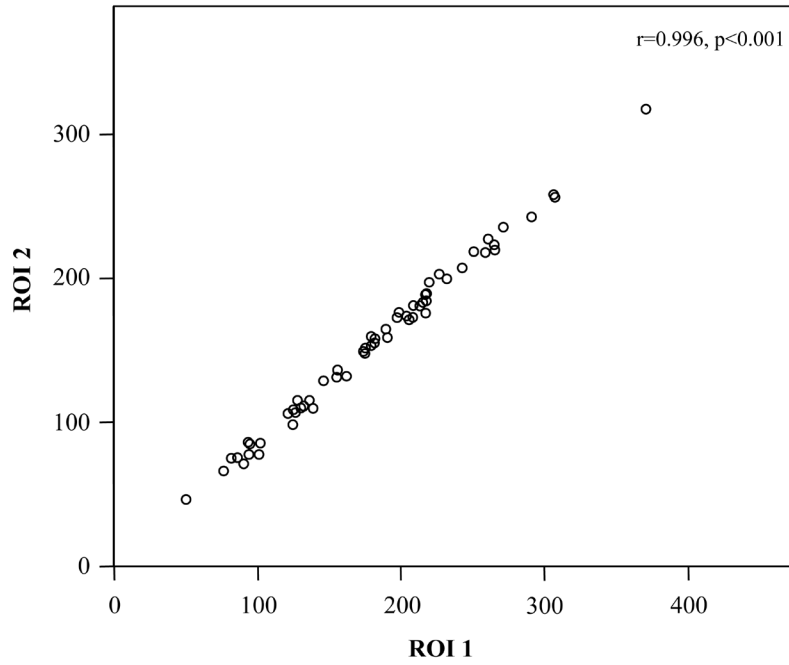
Elisabeth A.P.M. Romme was the recipient of a European Respiratory Society Fellowship (STRTF 381-2011). The work described in this manuscript was performed at the University of Edinburgh as part of this Fellowship.

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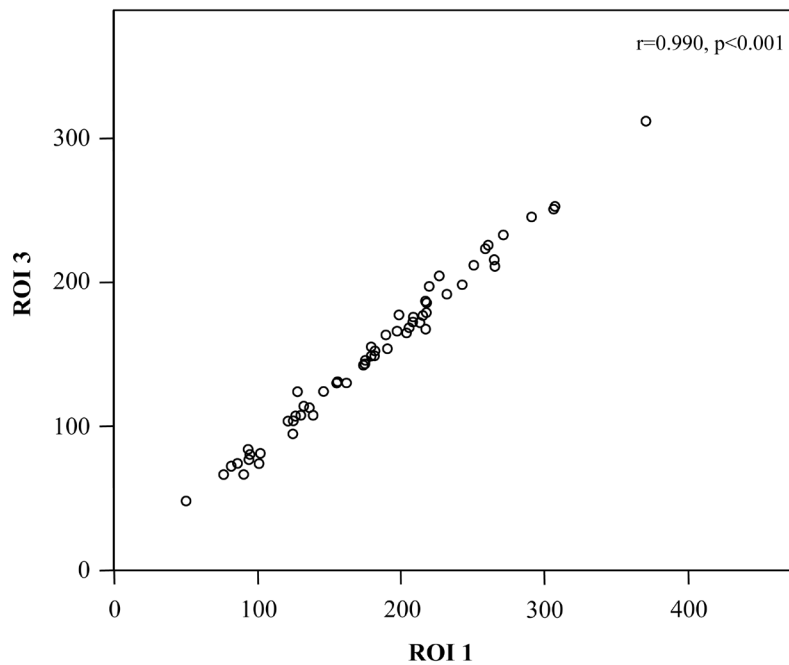
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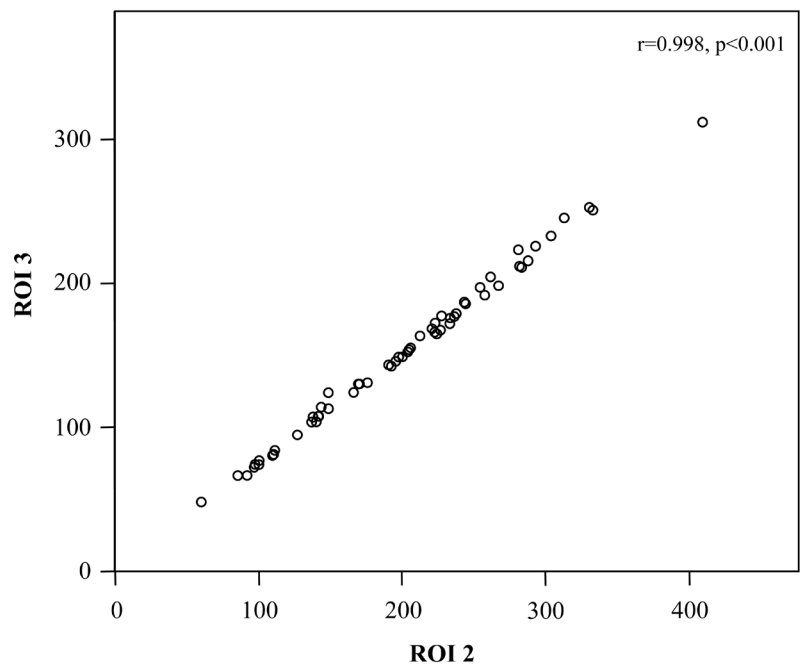
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e-Figure 1. Correlation between attenuation measurements using ROI 1 and ROI 2

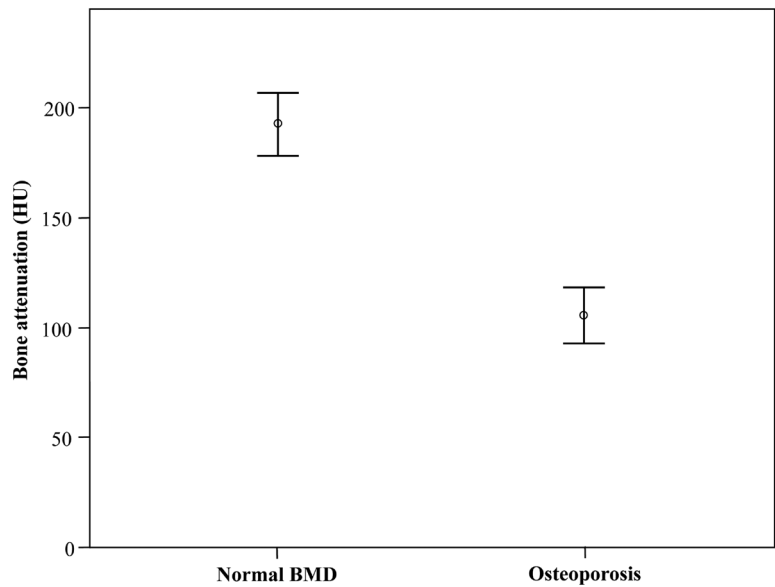


e-Figure 2. Correlation between attenuation measurements using ROI 1 and ROI 3

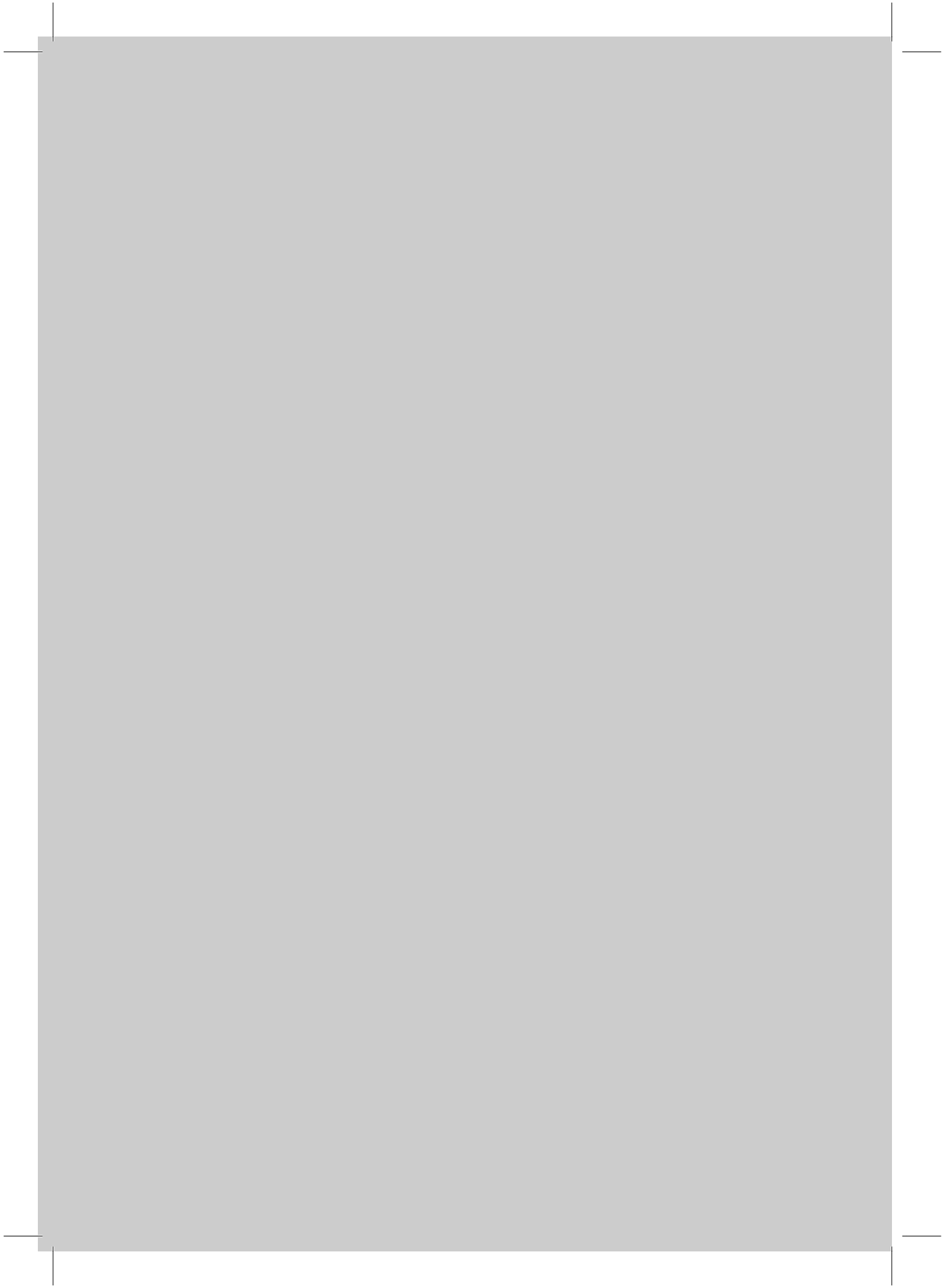


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e-Figure 3. Correlation between attenuation measurements using ROI 2 and ROI 3



e-Figure 4. Mean bone attenuation between COPD patients with normal BMD and osteoporosis





Chapter 5

CT-measured bone attenuation in patients with chronic obstructive pulmonary disease: relation to clinical features and outcomes

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Journal of Bone and Mineral Research 2013; 28: 1369-77

ABSTRACT

Osteoporosis is highly prevalent in COPD patients and has been related to several clinical features. However, most studies have been in relatively small COPD cohorts. Therefore, the objectives of this study were to compare bone attenuation measured on low-dose chest computed tomography (CT) between COPD subjects, smoker and non-smoker controls, and to relate bone attenuation to clinical parameters, inflammatory biomarkers and outcomes in a large, well-characterized COPD cohort. We studied 1634 COPD subjects, 259 smoker controls and 186 non-smoker controls who participated in a large longitudinal study (ECLIPSE). We measured bone attenuation, extent of emphysema and coronary artery calcification (Agatston score) on baseline CT scans, and clinical parameters, inflammatory biomarkers and outcomes. Bone attenuation was lower in COPD subjects compared with smoker and non-smoker controls (164.9 ± 49.5 HU versus 183.8 ± 46.1 HU versus 212.1 ± 54.4 HU, $p < 0.001$). Bone attenuation was not significantly different between COPD subjects and smoker controls after adjustment for age, sex and pack years of smoking. In the COPD subjects, bone attenuation correlated positively with FEV_1 ($r = 0.062$, $p = 0.014$), FEV_1/FVC ratio ($r = 0.102$, $p < 0.001$), body mass index ($r = 0.243$, $p < 0.001$), fat free mass index (FFMI, $r = 0.265$, $p < 0.001$) and C-reactive protein ($r = 0.104$, $p < 0.001$), and correlated negatively with extent of emphysema ($r = -0.090$, $p < 0.001$), Agatston score ($r = -0.177$, $p < 0.001$) and interleukin-8 ($r = -0.054$, $p = 0.035$). In a multiple regression model, older age, lower FFMI and higher Agatston score were associated with lower bone attenuation. Lower bone attenuation was associated with higher exacerbation ($r = -0.057$, $p = 0.022$) and hospitalization ($r = -0.078$, $p = 0.002$) rates, but was not associated with all-cause mortality. In conclusion, CT-measured bone attenuation was lower in COPD subjects compared with non-smoker controls but not compared with smoker controls, after adjustment for age, sex and pack years of smoking. In the COPD subjects, bone attenuation was associated with age, body composition and coronary artery calcification, but was not associated with all-cause mortality.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) has, in addition to its pulmonary effects, several extrapulmonary effects that may contribute to the severity of the disease.¹⁻⁵ Osteoporosis, which is characterized by low bone mineral density and micro-architectural changes,⁶ is recognized as one such extrapulmonary effect. The prevalence of osteoporosis has been suggested to be higher in COPD patients than in control subjects matched for age and sex.⁷ However, as described in a meta-analysis, most of studies on osteoporosis have been performed in relatively small cohorts.⁸

In COPD patients, osteoporosis is associated with older age, lower body mass index (BMI), more severe airflow limitation and the use of oral and inhaled corticosteroids.⁸⁻¹¹ More recently, low bone density has been associated with emphysema,¹²⁻¹⁴ and with cardiovascular disease in patients with chronic kidney disease.¹⁵ Although both osteoporosis and cardiovascular disease are common in COPD patients,^{11,16} research on a relationship between bone health and cardiovascular disease in COPD is sparse.¹⁷

The mechanism linking osteoporosis with COPD is not entirely clear. Osteoporosis has been suggested to be either a comorbidity, due to shared risk factors (e.g. older age and smoking) or a systemic effect of COPD with a cause-and-effect relationship.¹⁸ Several pathophysiological mechanisms linking osteoporosis with COPD have been suggested, including systemic inflammation,¹⁹ disturbance of the osteoprotegerin (OPG)/ receptor activator of NF- κ B (RANK)/ RANK ligand (RANKL) pathway¹⁴ and vitamin D deficiency.²⁰

The Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE; study identification number SCO104960; Clinicaltrials.gov identifier NCT00292552) is a longitudinal study in a large cohort of COPD subjects, smoker and non-smoker controls.²¹ As part of this study, a low-dose chest computed tomography (CT) scan was performed from which measurements of bone density of the thoracic vertebrae can be made,²² in addition to the extent of emphysema and coronary artery calcification. The objectives of this study were 1) To compare CT-measured bone attenuation of the thoracic vertebrae between COPD subjects, smoker and non-smoker controls; and 2) To relate CT-measured bone attenuation to clinical parameters, inflammatory biomarkers and outcomes in a large, well-characterized COPD cohort.

MATERIALS AND METHODS

Our analysis was based on the data collected in the ECLIPSE study. The design and aims of the study have been published previously.²¹ The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All subjects provided written informed consent and the study was approved by the relevant ethics and review boards.

Subjects

COPD subjects who were between the ages of 40 and 75 years were enrolled in the study if they had a history of 10 or more pack years of smoking, a forced expiratory volume in 1 second (FEV₁) of less than 80% of the predicted value after bronchodilator use, and a ratio of FEV₁ to forced vital capacity (FVC) of 0.7 or less after bronchodilator use. In addition, smoker and non-smoker control subjects who were between the ages of 40 and 75 years were enrolled if they had an FEV₁ of more than 85% of the predicted value after bronchodilator use and an FEV₁/FVC ratio of more than 0.7 after bronchodilator use. Smoker controls had a history of 10 or more pack years of smoking, and non-smoker controls had a history of less than 1 pack year of smoking. Subjects were excluded if they had a respiratory disease other than COPD, a significant inflammatory disease (e.g. rheumatoid arthritis and lupus), cancer in the 5 years prior to study entry, evidence of alcohol, drug or solvent abuse, had undergone lung surgery or used oral corticosteroids chronically.

Measurements

At baseline, subjects underwent standard spirometry after the administration of 400 µg of inhaled albuterol/ salbutamol. The subjects' self-reported respiratory symptoms, medications, smoking history, occupational exposure, and coexisting medical conditions were documented at study entry with the use of the American Thoracic Society-Division of Lung disease questionnaire. Nutritional status was assessed by the BMI and fat free mass index (FFMI), the latter was measured using bioelectrical impedance analysis (Bodystat 1500). In COPD subjects, the 6 minute walk was performed according to the American Thoracic Society guideline.²³

Bone attenuation, extent of emphysema and coronary artery calcification were assessed on baseline low-dose CT scans of the chest acquired using multi-detector-row CT scanners (Siemens Healthcare, Erlangen, Germany or GE Healthcare, Milwaukee, WI) with a minimum of 4 rows which have been shown to produce comparable density values when using similar protocols. Imaging was performed in the supine position, at suspended full inspiration, without administration of intravenous contrast. Exposure settings were 120 kVp and 40 mAs, and images were reconstructed using 1.0 mm (Siemens) or 1.25 mm (GE) contiguous slices and a low spatial frequency reconstruction algorithm (GE: Standard; Siemens: b35f). CT scanners were calibrated regularly using industry and institutional standards.

Bone attenuation was measured on CT using the software VOXAR 3D version 16.0 (Toshiba Medical Visualisation Systems, Edinburgh, UK) as described previously, and has been shown to correlate with bone density measurements by DXA scanning.²² Briefly, the mean bone attenuation of thoracic vertebrae 4, 7 and 10 (T4, T7 and T10) were determined by placing circular regions of interest in the central parts of the vertebral bodies. The average bone attenuation of these three vertebrae T4, T7 and T10 was calculated and expressed in Hounsfield Units (HU).

Quantitative assessment of emphysema was performed by attenuation mask analysis (Pulmonary Workstation 2.0, VIDA Diagnostics, Iowa City, IA, USA). The extent of emphysema was expressed as the percent of low attenuation areas (%LAA) with an HU of less than -950.²⁴

Coronary artery calcification was measured as the Agatston score on a dedicated post-processing workstation (Vitrea Fx, version 3.1.0, Vital Images, Minnetonka, USA) using calcium score analysis software (VScore, Vital Images, Minnetonka, USA). The Agatston score was calculated as previously described.²⁵ The calcium score percentile based on age, gender and ethnicity was calculated using previously published distributions from a cohort of healthy, asymptomatic individuals from the Multi-Ethnic Study of Atherosclerosis (MESA).²⁶

Serum and plasma samples for biomarker measurements were collected in the morning, after fasting overnight, at baseline. Blood samples were stored at -80°C until they were analyzed centrally. Circulating white blood cell (WBC) count was measured in a central clinical laboratory. Interleukin-6 (IL-6), interleukin-8 (IL-8) and tumor necrosis factor- α (TNF- α) were measured in serum samples using validated immunoassays on the SearchLight Protein Array Platform (Aushon Biosystems, Inc., Billerica, MA, USA). Fibrinogen (K-ASSAY fibrinogen test, Kamiya Biomedical Co., Seattle, WA, USA) and C-reactive protein (CRP) (Roche Diagnostics, Mannheim, Germany) were measured using immunoturbidometric assays validated for use with EDTA plasma.²⁷ Biomarker values > 95th percentile for healthy non-smokers were considered to be elevated.²⁸ Systemic inflammation was defined as 2 or more elevated biomarker levels (WBC, CRP, IL-6 and fibrinogen) at study entry as previously described.²⁸

Outcomes

All subjects were contacted monthly by telephone to assess the frequency of exacerbations and hospitalizations using a structured interview scheme.²¹ Rate of decline in FEV₁ was determined as previously described.²⁷ Survival status was recorded for all subjects at the 3 year visit date. In the case subjects withdrew from the study early, their survival status was recorded at the next planned visit and again at the 3 year time-point. Date of death or last confirmed alive date were reported.

Statistical analysis

Results are shown as mean (SD or SE), median (interquartile range [IQR]), or frequency (percentage), as appropriate. Comparisons between subject groups were carried out using analysis of variance (ANOVA), Kruskal-Wallis tests, or Cochran-Mantel-Haenszel tests, and the characteristics of each COPD subpopulation were compared with the full ECLIPSE population. Univariate associations between bone attenuation and clinical factors were assessed by Spearman correlation coefficients. Multiple regression models to estimate bone attenuation were constructed based on predictors identified in the literature:^{6,8,11,29} age, sex, pack years of smoking, FEV₁, FEV₁/FVC, FFMI, %LAA, CRP, IL-8, and Agatston score. A Cox proportional hazards model was used to determine the effect of bone attenuation on all-cause mortality. Two-sided p values <0.05 were considered significant with no adjustment for multiple testing. Analyses were conducted with SAS® Version 9.1 (SAS Institute, Cary, NC, USA).

RESULTS

In total, 2164 COPD subjects, 337 smoker controls and 245 non-smoker controls were enrolled in the ECLIPSE study. Six hundred fifty subjects were excluded because their scans were either not available or the scans had not been adequately performed to assess bone attenuation. Seventeen subjects who used oral corticosteroids were also excluded since we did not wish to assess the bone density in these patients with this risk factor for osteoporosis. Thus, our cohort comprised 1634 COPD subjects, 259 smoker controls and 186 non-smoker controls (Table 1). Our study cohort was not significantly different compared to the ECLIPSE cohort as a whole (see supplement, e-Table 1). The Agatston score was measured in a subpopulation of 672 COPD subjects, representative of the total COPD cohort of the ECLIPSE study (see supplement, e-Table 1).

CT-measured bone attenuation was lower in COPD subjects compared with smoker and non-smoker controls (164.9 ± 49.5 HU versus 183.8 ± 46.1 HU versus 212.1 ± 54.4 HU respectively, $p < 0.001$). However, the difference in bone attenuation between COPD subjects and smoker controls was not statistically significant after adjustment for age, sex and pack years of smoking ($p = 0.206$, Figure 1).

In the COPD subjects, CT-measured bone attenuation correlated positively with FEV₁, FEV₁/FVC ratio, BMI, FFMI and CRP, and correlated negatively with %LAA, Agatston score and IL-8 after correction for age, sex and pack years of smoking (Table 2). Figure 2 shows the correlation between bone attenuation and Agatston score. The significantly positive correlation between bone attenuation and CRP disappeared after adjustment for BMI ($r = 0.015$, $p = 0.558$). In a multiple regression model, older age, lower FFMI and higher Agatston score were associated with lower CT-measured bone attenuation (Table 3).

Four hundred forty-eight COPD subjects (27%) had 2 or more elevated biomarker levels and 707 COPD subjects (43%) had no elevated biomarker levels at baseline. CT-measured bone attenuation was not significantly different between the patients with and without systemic inflammation (165.8 ± 49.4 HU versus 163.8 ± 49.1 HU, $p = 0.241$).

CT-measured bone attenuation correlated positively with the rate of decline in FEV₁, and correlated negatively with exacerbation and hospitalization rates after adjustment for age, sex and pack years of smoking (Table 4). One hundred fifty-four (9%) COPD subjects died during 3 years of follow up. The mean bone attenuation in the survivors was 165.9 ± 48.8 HU compared with 156.0 ± 55.5 HU in the non-survivors ($p = 0.223$). Cox proportional hazards modeling showed that bone attenuation was not associated with all-cause mortality in COPD subjects (Table 5).

Table 1. Basic characteristics of COPD subjects, smoker controls, and non-smoker controls

	COPD subjects		Non-smoker controls		P-values		COPD subjects vs Smoker controls		COPD subjects vs Non-smoker controls		Smoker controls vs Non-smoker controls	
	1634	259		186								
Subjects, n	1634	259		186								
Age, yrs	63.3±7.1	55.1±8.8		53.4±8.9		<0.001			<0.001		0.053	
Male, n (%)	1045 (64%)	149 (58%)		68 (37%)		0.047			<0.001		<0.001	
Pack years, n	48.8±27.1	31.2±22.9		0.2±1.2		<0.001			<0.001		<0.001	
FEV ₁ , L	1.35±0.52	3.39±0.76		3.35±0.78		<0.001			<0.001		0.412	
FEV ₁ , % predicted	48.5±15.9	109.7±11.9		116.2±13.6		<0.001			<0.001		<0.001	
FEV ₁ /FVC ratio	44.6±11.5	79.5±5.0		81.4±5.3		<0.001			<0.001		<0.001	
RV/TLC ratio	0.5±0.1	0.3±0.1		0.4±0.1		<0.001			0.001		<0.001	
BMI, kg/m ²	26.5±5.8	26.7±4.3		27.4±5.6		0.258			0.044		0.364	
FFMI, kg/m ²	17.1±2.9	17.1±2.5		17.2±2.7		0.345			0.575		0.964	
6MWD, m	370±122	-		-								
Inhaled steroid use, n (%)	1186 (73%)	0		0		<0.001			<0.001			
%LAA	17.7±12.3	2.3±3.0		4.0±4.2		<0.001			<0.001		<0.001	
Agatston score	129.0 [506.0]	0.0 [77.0]		0.0 [3.0]		<0.001			<0.001		0.003	
Calcium percentile	71.0 [61.0]	0.0 [78.0]		0.0 [43.0]		<0.001			<0.001		0.006	
CRP, mg/L	3.2 [5.7]	1.5 [2.2]		1.3 [1.9]		<0.001			<0.001		0.088	
Fibrinogen, mg/dL	453.0 [125.0]	384.5 [87.0]		372.0 [101.0]		<0.001			<0.001		0.067	
IL-6, pg/mL	1.5 [2.2]	0.6 [1.0]		0.4 [0.6]		<0.001			<0.001		<0.001	
IL-8, pg/mL	6.9 [8.8]	8.3 [12.5]		3.8 [4.6]		<0.001			<0.001		<0.001	
TNF-α, pg/mL	2.4 [10.4]	2.4 [41.0]		2.4 [0.0]		<0.001			0.001		<0.001	
WBC, x10 ⁶ /mL	7.6 [2.6]	7.1 [2.4]		5.7 [2.0]		0.004			<0.001		<0.001	

Results are presented as mean±standard deviation or median [IQR] unless otherwise indicated.

FEV₁=forced expiratory volume in 1 second, FVC=forced vital capacity, RV=residual volume, TLC=total lung capacity, BMI=body mass index, FFMI=fat free mass index, 6MWD=6 minute walking distance, %LAA=percent of low attenuation areas, CRP=C-reactive protein, IL-6=interleukin-6, IL-8=interleukin-8, TNF-α=tumor necrosis factor-α, WBC=white blood cell

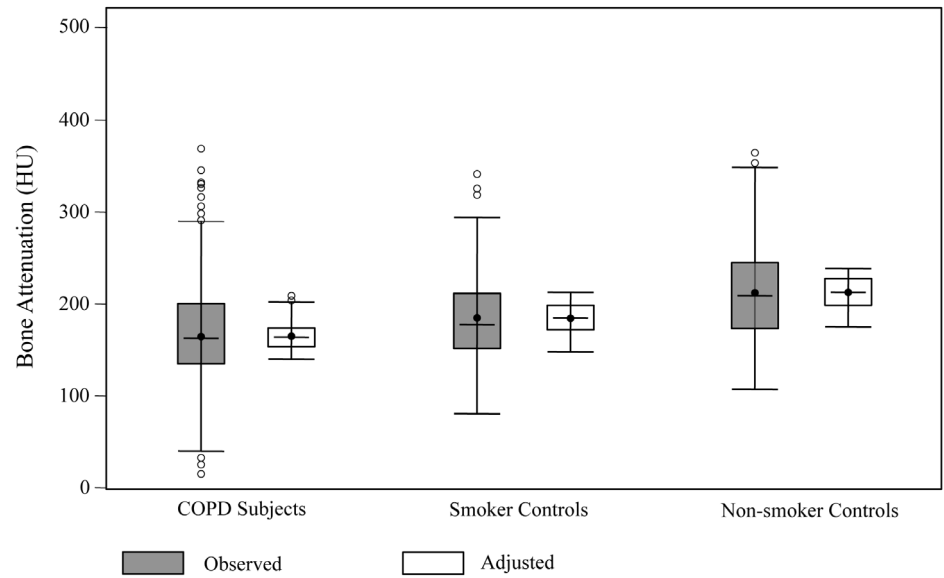


Figure 1. CT-measured bone attenuation in COPD subjects, smoker controls and non-smoker controls

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Observed values: the average bone attenuation of thoracic vertebrae 4, 7 and 10.
Adjusted values: the average bone attenuation of thoracic vertebrae 4, 7 and 10 after adjustment for age, sex and pack years of smoking.

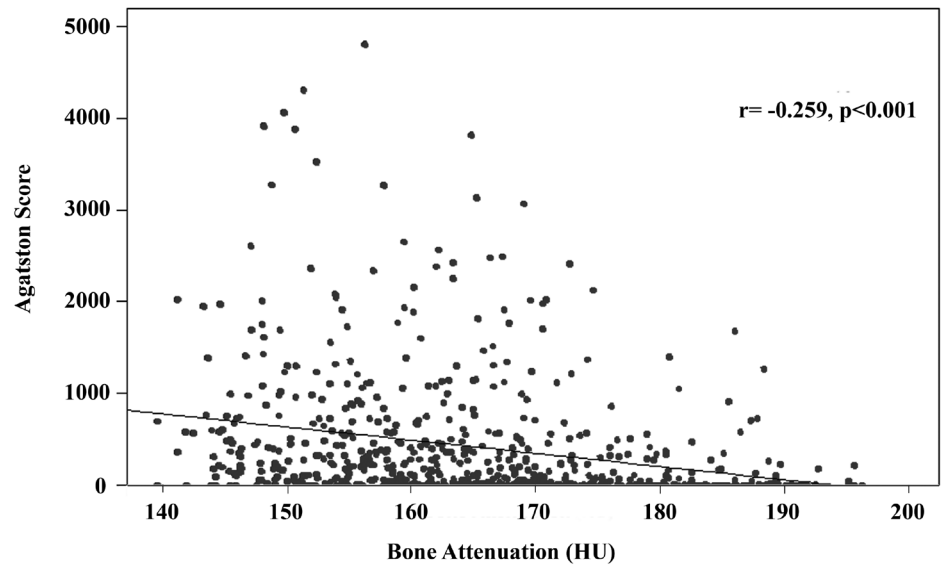


Figure 2. Correlation between CT-measured bone attenuation and Agatston score

Table 2. Correlations between bone attenuation and clinical assessments in COPD subjects after adjustment for age, sex, and pack years of smoking

	Spearman Correlation Coefficient	p-value
FEV ₁ , L	0.062	0.014
FEV ₁ , % predicted	0.077	0.002
FEV ₁ /FVC ratio	0.102	<0.001
RV/TLC ratio	0.010	0.824
BMI, kg/m ²	0.243	<0.001
FFMI, kg/m ²	0.265	<0.001
6MWD, m	0.001	0.957
mMRC score	-0.040	0.112
Inhaled steroid use	-0.004	0.874
%LAA	-0.090	<0.001
Agatston score	-0.177	<0.001
Calcium percentile	-0.172	<0.001
CRP, mg/L	0.104	<0.001
Fibrinogen, mg/dL	0.046	0.070
IL-6, pg/mL	0.036	0.175
IL-8, pg/mL	-0.054	0.035
TNF- α , pg/mL	-0.016	0.525
WBC, $\times 10^6$ /mL	0.033	0.189

FEV₁=forced expiratory volume in 1 second, FVC=forced vital capacity, RV=residual volume, TLC=total lung capacity, BMI=body mass index, FFMI=fat free mass index, 6MWD=6 minute walking distance, mMRC=modified Medical Research Council dyspnoea scale, %LAA=percent of low attenuation areas, CRP=C-reactive protein, IL-6=interleukin-6, IL-8=interleukin-8, TNF- α =tumor necrosis factor- α , WBC=white blood cell

Table 3. Multivariate regression for bone attenuation in COPD subjects

	Total COPD cohort		Agatston cohort	
	Estimate(SE)	p value	Estimate(SE)	p-value
Age	-1.807 (0.181)	<0.001	-1.780 (0.283)	<0.001
Female	4.517 (3.319)	0.174	-5.901 (5.034)	0.242
Pack years	0.019 (0.047)	0.692	-0.043 (0.076)	0.569
FEV ₁	-2.972 (3.554)	0.403	-6.679 (5.469)	0.223
FEV ₁ /FVC	0.244 (0.173)	0.159	0.553 (0.268)	0.039
FFMI	4.506 (0.475)	<0.001	4.528 (0.682)	<0.001
%LAA	-0.043 (0.131)	0.740	0.075 (0.200)	0.706
CRP	0.024 (0.104)	0.819	0.098 (0.145)	0.498
IL-8	-0.075 (0.040)	0.062	-0.089 (0.049)	0.070
Agatston score	-	-	-0.010 (0.003)	<0.001

FEV₁=forced expiratory volume in 1 second, FVC=forced vital capacity, FFMI=fat free mass index, %LAA=percent of low attenuation areas, CRP=C-reactive protein, IL-8=interleukin-8
R-square: 0.141

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Table 4. Correlations between bone attenuation and clinical outcomes in COPD subjects after adjustment for age, sex, and pack years of smoking

	Spearman Correlation Coefficient	p-value
Decline in FEV ₁ , ml/yr	0.064	0.010
Exacerbation rate	-0.057	0.022
Hospitalization rate	-0.078	0.002

FEV₁=forced expiratory volume in 1 second

Table 5. Cox proportional hazards for all-cause mortality in COPD subjects

	Hazard Ratio Estimate (95% CI)	p-value
Age, yrs	1.063 (1.036,1.091)	<0.001
Male versus Female	1.128 (0.802,1.587)	0.489
Bone attenuation, HU	0.998 (0.995,1.002)	0.282

DISCUSSION

Our data showed that bone attenuation of thoracic vertebrae 4, 7 and 10 measured on low-dose chest CT was lower in COPD subjects compared with smoker and non-smoker controls. In the COPD subjects, older age, lower FFMI and higher Agatston score were independently associated with lower CT-measured bone attenuation. In addition, lower CT-measured bone attenuation was associated with lower rate of decline in FEV₁ and higher exacerbation and hospitalization rates, but was not associated with all-cause mortality.

In line with previous data,^{8,17,30} COPD subjects had lower bone attenuation compared with smoker and non-smoker controls. However, the difference in bone attenuation between COPD subjects and smoker controls was not statistically significant after adjustment for age, sex and pack years of smoking. Since older age, female gender and smoking are well-established risk factors of osteoporosis,⁶ these factors may contribute to the difference in bone density between COPD subjects and smoker controls. Our data suggest that osteoporosis is a comorbidity rather than a systemic effect of COPD.

In the COPD subjects, higher bone attenuation of thoracic vertebrae 4, 7 and 10 was associated with higher FEV₁ and less severe emphysema. In line with these findings, Ohara and colleagues¹³ demonstrated that in 65 male COPD patients the average bone density of thoracic vertebrae 4, 7 and 10 correlated positively with FEV₁ ($r=0.286$) and correlated negatively with %LAA ($r=-0.522$). The higher correlation coefficients reported in their study may be due to differences in the study populations (e.g. race and sex) or the methods used (such as different slice thickness, emphysema quantification in a part of the lung rather than the whole lung, and assessment of bone attenuation with phantom CT). Several other studies have demonstrated a relationship between bone health and lung function parameters.^{8,31} It has even been suggested that the skeletal and pulmonary systems share a common underlying mechanism such as impairment of Wntless tail/ β -catenin signalling³² or disturbance of the RANK/RANKL/OPG pathway due to systemic inflammation.³³

In addition to its relation with lung function parameters, bone attenuation decreased with age in the COPD subjects. A previous study showed that bone density of the thoracic vertebrae correlated negatively with age in male COPD patients,¹³ and a cross-sectional study with 554 COPD patients showed that patients aged 55 years or older had an increased risk of osteoporosis compared with their younger peers.²⁹ In the general population, older age is a well-established risk factor of osteoporosis.^{6,34} In a healthy young skeleton, the rate of bone formation and matrix mineralization equals the rate of bone resorption and matrix degradation. However, during the aging process significant amounts of bone are lost due to enhanced resorption coupled with decreased formation, resulting in osteoporosis.³⁵

Bone attenuation correlated positively with BMI and FFMI. This finding is supported by a study in which overweight and obese COPD patients had a decreased risk of osteoporosis whereas cachectic COPD patients had an increased risk of osteoporosis compared with

their normal weight peers.²⁹ Low body weight, BMI and FFMI are well-known risk factors of osteoporosis in COPD patients^{8,36} and in the general population.^{6,34} Low body weight may lead to bone loss due to decreased mechanical loading or direct effects of loss of fat free mass or fat mass on bone metabolism. Loss of fat free mass may result in bone loss due to increased systemic inflammation and protein breakdown,³⁰ and loss of fat mass may result in reduced bone formation due to decreased secretion of bone active hormones from the pancreatic beta cells (e.g. insulin and amylin) and from adipocytes (e.g. leptin).³⁷

Moreover, bone attenuation correlated negatively with coronary artery calcification. Although the relationship between bone density and cardiovascular disease has been studied widely in non-COPD populations,^{15,38-40} only one previous study showed a relationship between low bone density and increased arterial stiffness in COPD patients.¹⁷ The relationship between the skeletal and cardiovascular systems may be due to common risk factors like older age and smoking, or a shared underlying mechanism such as systemic inflammation,¹⁷ disturbance of the RANK/RANKL/OPG system⁴¹ and reduced bone perfusion due to generalized atherosclerosis.¹⁵

In our study, bone attenuation was similar among the COPD subjects with and without systemic inflammation. Notably, bone attenuation was negatively correlated with IL-8, while positively correlated with CRP. The positive correlation between bone attenuation and CRP disappeared after adjustment for BMI, suggesting an interaction with BMI. A previous study in COPD patients indeed showed that an obese BMI was associated with elevated CRP levels.⁴²

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Although a meta-analysis demonstrated that the use of inhaled corticosteroids was associated with increased risk of fractures in COPD patients,⁹ our data did not show a relationship between bone attenuation and the use of inhaled corticosteroids. However, the lack of a relationship may be due to the design of our study since we did not record cumulative doses of inhaled corticosteroids.

Furthermore, no relationship was found between bone attenuation and the 6 minute walking distance. In line with this finding, a cross-sectional study with 95 COPD patients found no relationship between the 6 minute walking distance or the International Physical Activity Questionnaire total activity score and the T-score of the femoral neck or the lumbar spine.⁴³ Although research demonstrating a relationship between physical activity and bone density is sparse in COPD patients,⁴⁴ reductions in ground reaction forces, weight-bearing activities and muscular contraction are suggested to result in disuse osteoporosis⁴⁵ and physical exercise has shown to have a positive effect on bone density in postmenopausal women.⁴⁶

Regarding clinical outcomes, CT-measured bone attenuation correlated positively with rate of decline in FEV_1 , and correlated negatively with exacerbation and hospitalization rates, but was not associated with all-cause mortality. The positive correlation between bone attenuation and rate of decline in FEV_1 may be due to a higher rate of decline in FEV_1 in the subjects with a higher FEV_1 at baseline. Previous data have indeed demonstrated that the rate

of decline in FEV_1 is higher in subjects with less severe COPD.²⁷ Although bone attenuation was correlated with exacerbation and hospitalization rates, it was not associated with all-cause mortality. In the general population, data on the relationship between bone mineral density and mortality are conflicting^{47,48}.

This study has several limitations. First, bone health was assessed using bone attenuation on CT rather than bone density on DXA which is the gold standard to diagnose osteoporosis. However, CT-measured bone attenuation has been shown to be strongly correlated with DXA scanned bone mineral density in COPD patients.²² Second, vertebral fractures were not assessed although vertebral fractures can occur in COPD patients with normal bone density.⁴⁹ Third, bone attenuation was only assessed on the baseline CT scans. Since rate of bone loss has been associated with mortality in elderly men and women,⁴⁸ it would be interesting to correlate changes in bone attenuation to clinical parameters and outcomes in COPD patients. Acknowledging these limitations, this study is important for several reasons. First, we compared bone attenuation in a large cohort of COPD subjects, smoker and non-smoker controls, while previous studies reported comparisons of bone density in relatively small numbers of COPD subjects and control subjects.^{17,30} Second, our analyses were adjusted for age, sex and pack years of smoking, whereas previous data were not adjusted for these confounders.^{17,30} Third, our study contributes to the insight in the systemic complexity of COPD since it showed, as far as we know, for the first time a relationship between bone attenuation and coronary artery calcification in COPD subjects. Fourth, our study demonstrated that CT-measured bone attenuation was associated with clinical parameters in COPD subjects. These data suggest, in addition to our previous data,²² that CT-measured bone attenuation can be used to assess bone health in COPD subjects.

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Our data showed that bone density is lower in COPD subjects compared with control subjects. Chest physicians should be aware of the risk of poor bone health in their COPD patients. Since bone attenuation was independently associated with age, body composition and coronary artery calcification, these factors may contribute to or protect against poor bone health in COPD patients. However, longitudinal studies are needed to study the factors that contribute to osteoporosis or are protective against osteoporosis in COPD and to study their underlying mechanisms.

In conclusion, CT-measured bone attenuation of the thoracic vertebrae was lower in COPD subjects compared with smoker and non-smoker controls. However, bone attenuation was not significantly different between COPD subjects and smoker controls after adjustment for age, sex and pack years of smoking, suggesting osteoporosis may be a comorbidity rather than a systemic effect of COPD. In the COPD subjects, CT-measured bone attenuation was independently associated with age, body composition and coronary artery calcification, but not with all-cause mortality.

DISCLOSURES

The ECLIPSE study was supported by GlaxoSmithKline. Lisa D. Edwards is an employee of GlaxoSmithKline and owns stock in GlaxoSmithKline. Elisabeth A.P.M. was the recipient of a European Respiratory Society Fellowship (STRTF 381-2011). The work described in this manuscript was performed at the University of Edinburgh as part of this Fellowship.

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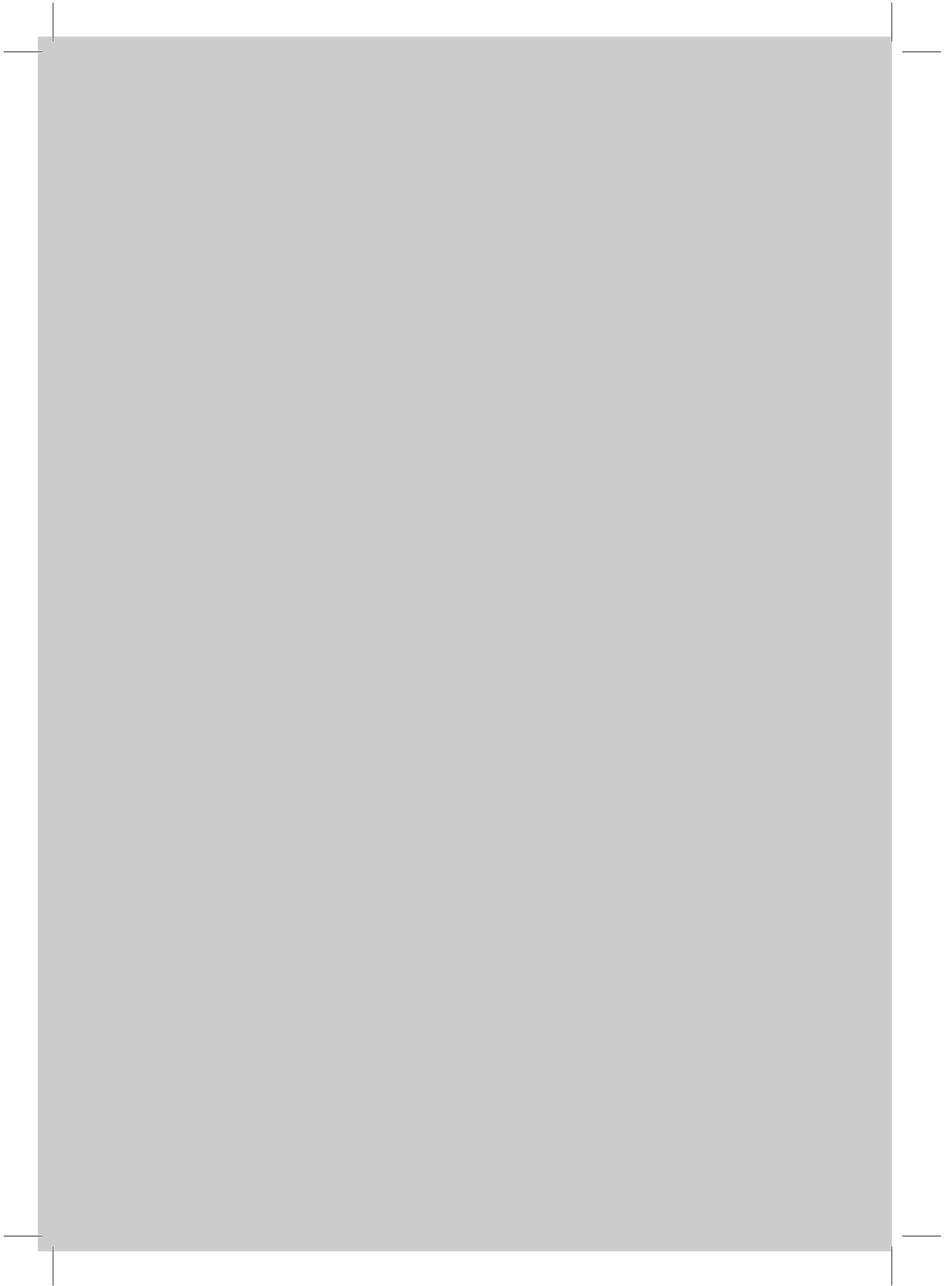
e-Table 1. Basic characteristics of the bone cohort and Agatston cohort compared with the total COPD cohort

	Total COPD Cohort	Bone Cohort	Agatston Cohort
N	2164	1634	672
Age, yrs	63.4±7.1	63.3±7.1	63.2±7.0
Male, n (%)	1412 (65%)	1045 (64%)	422 (63%)
Pack years, n	48.6±27.1	48.8±27.1	47.4±25.1
FEV ₁ , L	1.35±0.52	1.35±0.52	1.36±0.54
FEV ₁ , % predicted	48.3±15.8	48.5±15.9	48.7±16.1
FEV ₁ /FVC ratio	44.8±11.6	44.6±11.5	44.1±11.5
BMI, kg/m ²	26.5±5.7	26.5±5.8	26.5±5.6
Patient reported cardiovascular disease	1201 (55%)	876 (54%)	357 (53%)

Results are presented as mean±standard deviation unless otherwise indicated.

FEV₁=forced expiratory volume in 1 second, FVC=forced vital capacity, BMI=body mass index







Chapter 6

Associations between COPD-related manifestations: arterial calcification and stiffness, bone density, emphysema and all-cause mortality

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Respiratory Research 2013; 14: 129

ABSTRACT

Purpose

To examine associations between arterial stiffness, coronary artery calcium (CAC), thoracic aortic calcium (TAC), bone attenuation of the thoracic vertebrae, extent of emphysema and all-cause mortality in a COPD cohort.

Materials and Methods

The institutional review board approved the study protocol. We studied 119 COPD subjects (mean age 67.8 ± 7.3 years, 66% males and mean FEV₁ $46.0 \pm 17.5\%$ predicted), who were recruited from a university hospital between April 2003 and December 2005. We measured arterial stiffness as carotid-radial pulse wave velocity (PWV), and we assessed CAC, TAC, bone attenuation of the thoracic vertebrae and extent of emphysema on computed tomography of the chest. We identified deaths from the national register.

Results

Subjects with higher CAC were more likely to be older ($p < 0.001$) and male ($p = 0.03$), and more likely to have higher systolic blood pressure ($p = 0.001$) and a history of hypertension ($p = 0.002$) or ischemic heart disease ($p = 0.003$). Higher CAC was associated with higher PWV (OR 1.62, $p = 0.04$) and lower bone attenuation (OR 0.32, $p = 0.02$), but not with the extent of emphysema after adjustment for age, sex and pack years of smoking. In a Cox proportional-hazards model, CAC, TAC and extent of emphysema predicted all-cause mortality (HR 2.01, 2.09 and 0.66, respectively).

Conclusion

Increased CAC was associated with increased arterial stiffness and lower bone attenuation. In addition, CAC, TAC and extent of emphysema predicted all-cause mortality in a COPD cohort. Thus, quantitative assessment of CAC, TAC and emphysema on computed tomography of the chest might provide relevant prognostic information in COPD patients.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD), in addition to its pulmonary manifestations, is associated with significant extrapulmonary manifestations. Cardiovascular disease and osteoporosis are recognised extrapulmonary manifestations, whose prevalence is higher in COPD patients than in control subjects matched for age and sex.^{1,2}

In general population studies, a relationship has been suggested between cardiovascular disease and osteoporosis. Postmenopausal women with osteoporosis had a 3.9-fold increased risk of cardiovascular events compared with postmenopausal women with osteopenia.³ In 2348 postmenopausal women, increased aortic calcification, a marker of cardiovascular disease, was associated with lower bone density and an increased number of vertebral and hip fractures,⁴ and in a subpopulation studied longitudinally, progression of aortic calcification was associated with bone loss.⁴

Although cardiovascular disease and osteoporosis are common in COPD patients,^{1,2} there are few studies on the relationship between cardiovascular disease and osteoporosis in COPD. Sabit and colleagues⁵ found that COPD subjects with osteoporosis had increased arterial stiffness, another marker of cardiovascular disease, compared with COPD subjects without osteoporosis. In addition, arterial stiffness and osteoporosis have been shown to relate to the extent of emphysema.^{6,7} These data suggest associations between cardiovascular disease, osteoporosis and emphysema. Furthermore, COPD-related extrapulmonary manifestations are thought to contribute to morbidity and mortality.⁸

The objectives of this study were: 1) To determine the associations between markers of cardiovascular disease (coronary artery calcium [CAC], thoracic aortic calcium [TAC] and arterial stiffness), bone attenuation of the thoracic vertebrae, and extent of emphysema; and 2) To identify whether these factors predict all-cause mortality in a COPD cohort.

6

MATERIALS AND METHODS

Our analysis was based on the data of a cohort study designed to identify prognostic markers in COPD.⁶ The study was conducted in accordance with the amended Declaration of Helsinki, the protocol was approved by the Lothian Research Ethics Committee (LREC/2003/8/28), and all subjects gave written informed consent.

Subjects

The inclusion and exclusion criteria have been described previously.⁶ In summary, all subjects were included between April 2003 and December 2005, had a clinical history compatible with COPD, a history of smoking for at least 10 pack years and evidence of chronic airflow limitation on spirometry. All subjects who had low-dose computed tomography (CT) of the chest were included in our analysis.

Height, weight and post-bronchodilator spirometry were measured according to American Thoracic Society/ European Respiratory Society standards. The subjects' self-reported respiratory symptoms, medications, smoking history, occupational exposure, and coexisting medical conditions were documented at study entry using structured interviews.

Arterial stiffness

Peripheral blood pressure was measured in all subjects, and arterial stiffness was assessed in 104 subjects. Arterial stiffness was measured as carotid-radial pulse wave velocity (PWV) as described previously.⁶ Briefly, we used the Q-wave of a simultaneously recorded electrocardiograph to identify the onset of the pressure wave, and used applanation tonometry of the carotid and radial arteries to record the pressure waveform at the peripheral site. The difference in wave transit time between the carotid and radial arteries was used to calculate carotid-radial PWV.

CT scanning

Low-dose CT scanning of the chest was performed without contrast media at full inspiration using a 16-slice multi-detector-row CT scanner (135 kV, 20 mAS; Toshiba Aquilion, Toshiba, Japan). Images were reconstructed with a slice thickness of 1 mm increment using an FC-O3 filter (Toshiba, Japan).

CAC and TAC were assessed on the standard images used for analysis of the lungs as previously described.⁹ Images were analysed on a dedicated post-processing workstation (VOXAR 3D) using calcium analysis software. CAC and TAC were quantified using the Agatston score.¹⁰ Calcification was defined as an area $\geq 1 \text{ mm}^2$ in the axial plane of a coronary artery or the thoracic aorta with an attenuation threshold of ≥ 130 Hounsfield units. Regions of interest were drawn, and CAC and TAC were calculated by multiplying by a weighting factor selected dependent on the peak signal within the region of interest. Total CAC was obtained by summing the weighted scores from each coronary artery, and total TAC was obtained by summing the weighted scores from the ascending aorta, aortic arch and descending aorta superiorly to the upper limit of the thoracic vertebrae 12 (T12). The CT images of a random sample of 25 patients were independently assessed by two observers and assessed by one observer twice. The intra-class correlation coefficients were high for inter-observer and intra-observer agreements for CAC (0.88 and 0.99 respectively) and TAC (both 0.99).

Emphysema was quantified by in-house software using the 15th percentile point of the frequency distribution of lung attenuation, and pixel index for -950 (PI-950) Hounsfield units as previously described.⁶ Bone attenuation of the thoracic vertebrae was measured according to a method described in detail previously.¹¹ The mean bone attenuation of thoracic vertebrae 4, 7 and 10 (T4, T7 and T10) were determined by placing circular regions of interest in the central parts of the vertebral bodies. The average bone attenuation of these three vertebrae T4, T7 and T10 was calculated and expressed in Hounsfield units.

Mortality

Deaths occurring anywhere in the United Kingdom were identified by obtaining records from the General Registry Office for Scotland. Survival time was calculated in number of days from date of CT scan until date of death with a census cut-off date of 31 December 2011.

Statistical analysis

CAC and TAC were log transformed (normalising/ linearising transformations). For CAC, subjects were classified into three pre-specified groups: CAC=0, $0 < \text{CAC} \leq 400$ and $\text{CAC} > 400$. Comparisons among the three groups were made using one way analysis of variance (ANOVA) or Kruskal-Wallis test. Univariate and multinomial logistic regression analyses were performed to estimate associations between CAC, TAC, PWV, bone attenuation and 15th percentile. Time to death was compared using Kaplan Meier curves, and Cox proportional-hazards analysis was used to estimate associations between all-cause mortality and CAC, TAC, PWV, bone attenuation and 15th percentile.

All statistical analyses were performed in SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). Two-sided p-values ≤ 0.05 were considered statistically significant.

RESULTS

One hundred nineteen COPD subjects (aged 67.8 ± 7.3 , 66% were males, mean forced expiratory volume in 1 second [FEV₁] % predicted was 46.0 ± 17.5) were included in our analysis. Subjects with higher CAC were more likely to be older ($p < 0.001$), male ($p = 0.03$), and to have higher systolic blood pressure ($p = 0.001$), a history of hypertension ($p = 0.002$) or ischemic heart disease ($p = 0.003$), higher TAC ($p < 0.001$) and lower bone attenuation ($p = 0.006$) (Table 1). As expected there was a significant correlation between CAC and TAC (Spearman's $r = 0.57$, $p < 0.001$). Higher CAC was associated with higher PWV (OR 1.62, $p = 0.04$) and lower bone attenuation (OR 0.32, $p = 0.02$), but was not associated with FEV₁, 15th percentile and PI-950 after adjustment for age, sex and pack years of smoking (Table 2). As described previously, PWV correlated with 15th percentile and PI-950 ($r = 0.47$, $p < 0.001$).⁶ Bone attenuation was not associated with PWV, 15th percentile or PI-950 (data not shown).

Mortality

The median follow-up was 65 (0-83) months. During the observation period, 30 subjects (25%) died. A respiratory cause of death was the primary aetiology in 18 subjects (60%), and cardiovascular cause of death was the primary aetiology in 7 subjects (23%). In a Cox proportional-hazards model, CAC predicted all-cause mortality after adjustment for age, sex, FEV₁ and pack years of smoking (HR 2.01, 95% CI 1.13-3.58, $p = 0.02$, Table 3). Figure 1 and Table 4 show the Kaplan-Meier curves and numbers at risk. TAC predicted all-cause mortality similarly to CAC (see supplement, e-Table 1). Lower 15th percentile (more emphysema) was associated with increased all-cause mortality after adjustment for age and sex (HR 0.65, CI 0.45-0.95, $p = 0.03$), but not after adjustment for age, sex, FEV₁ and pack years of smoking ($p = 0.06$) (see supplement, e-Table 2). PWV and bone attenuation were not associated with all-cause mortality (see supplement, e-Table 2).

Table 1. Clinical characteristics of the total cohort and after stratification for CAC

	Total cohort	CAC=0	0<CAC≤400	CAC>400	p-value
Number of subjects	119	14	41	64	
Age, yrs	67.8±7.3	58.6±6.3	66.1±6.2	70.8±6.2	<0.001
Male, n (%)	79 (66)	7 (50)	24 (59)	48 (75)	0.03
FEV ₁ , % predicted	46.0±17.5	44.2±13.7	43.8±17.4	47.9±18.3	0.47
FVC, % predicted	74.4±20.6	72.6±14.2	74.4±21.0	74.8±21.7	0.94
FEV ₁ /FVC ratio	47.1±12.3	46.9±10.7	44.9±13.5	48.6±11.9	0.33
BMI, kg/m ²	25.8±5.5	25.6±5.9	25.7±5.2	25.9±5.6	0.98
Distance walked, m	369.1±112.2	406.6±105.2	385.9±105.0	349.8±116.1	0.16
Pack years of smoking, n	45.4±20.5	44.4±20.2	44.6±21.7	46.2±20.0	0.91
Heart rate, beats/min	74.0±13.0	71.5±10.1	73.4±12.0	74.9±14.2	0.65
Blood pressure systolic, mmHg	142.2±23.9	127.7±16.5	136.2±20.3	149.2±25.0	0.001
Blood pressure diastolic, mmHg	79.9±11.3	76.6±11.5	78.0±9.2	81.9±12.1	0.11
Hypertension, n (%)	30 (25)	0 (0)	7 (17)	23 (36)	0.002
Ischemic heart disease, n (%)	22 (19)	0 (0)	4 (10)	18 (28)	0.003
Diabetes, n (%)	7 (6)	0 (0)	2 (5)	5 (8)	0.25
TAC, median (min-max)	1540 (0-20828)	262 (0-4237)	1125 (3-8606)	3475 (0-20828)	<0.001
PWV, m/s	8.90±1.63	8.35±1.36	9.18±1.54	8.86±1.72	0.31
PI-950, median in % (min-max)	6.89 (0.12-43.2)	17.1 (0.12-39.0)	5.32 (0.12-43.2)	6.86 (0.27-38.6)	0.81
15 th percentile, HU	-921.9±27.8	-919.9±38.3	-924.2±29.7	-920.8±24.1	0.82
Bone attenuation, HU	138.1±35.5	162.2±37.6	141.8±31.9	130.4±35.0	0.006

Results are presented as mean ±standard deviation unless otherwise indicated. PWV was assessed in 104 subjects.

BMI=body mass index, CAC=coronary artery calcium, FEV₁=forced expiratory volume in 1 second, FVC=forced vital capacity, HU=Hounsfield unit, PI=pixel index, PWV=pulse wave velocity, TAC=thoracic aortic calcium

Table 2. Multinomial regression for CAC

	0<CAC≤400		CAC>400		p-value
	Odds ratio	95% CI	Odds ratio	95% CI	
PWV ^a	1.92	1.08 - 3.44	1.62	0.91 - 2.91	0.05
PWV ^b	2.03	1.10 - 3.74	1.62	0.87 - 3.02	0.04
Bone attenuation/ SD ^a	0.46	0.21 - 1.03	0.33	0.14 - 0.77	0.02
Bone attenuation/ SD ^b	0.43	0.19 - 1.00	0.32	0.13 - 0.76	0.02
FEV ₁ ^a	0.82	0.22 - 3.09	0.84	0.21 - 3.29	0.96
FEV ₁ ^b	0.80	0.21 - 3.05	0.82	0.21 - 3.25	0.95
15 th percentile/ SD ^a	0.80	0.45 - 1.45	0.64	0.45 - 1.63	0.76
15 th percentile / SD ^b	0.80	0.43 - 1.48	0.84	0.43 - 1.64	0.77

Reference category CAC=0

^a after adjustment for age and sex^b after adjustment for age, sex and pack years of smokingCI=confidence interval, FEV₁=forced expiratory volume in 1 second, PWV=pulse wave velocity, SD=standard deviation**Table 3.** Cox proportional-hazards for all-cause mortality

	CAC=0	0<CAC≤400	CAC>400	Per 10-fold increase in CAC	p-value
Number of subjects	14	41	64	-	-
Mortality, n (%)	1 (7)	4 (10)	25 (39)	-	-
CAC	-	1.33	6.46	2.17 (1.29 - 3.65)	0.004
CAC ^a	-	1.18	5.15	2.02 (1.13 - 3.59)	0.02
CAC ^b	-	1.14	5.09	1.94 (1.11 - 3.41)	0.02
CAC ^c	-	1.11	4.98	2.01 (1.13 - 3.58)	0.02

^a after adjustment for age and sex^b after adjustment for age, sex and FEV₁^c after adjustment for age, sex, FEV₁ and pack years of smokingCAC=coronary artery calcium, FEV₁=forced expiratory volume in 1 second

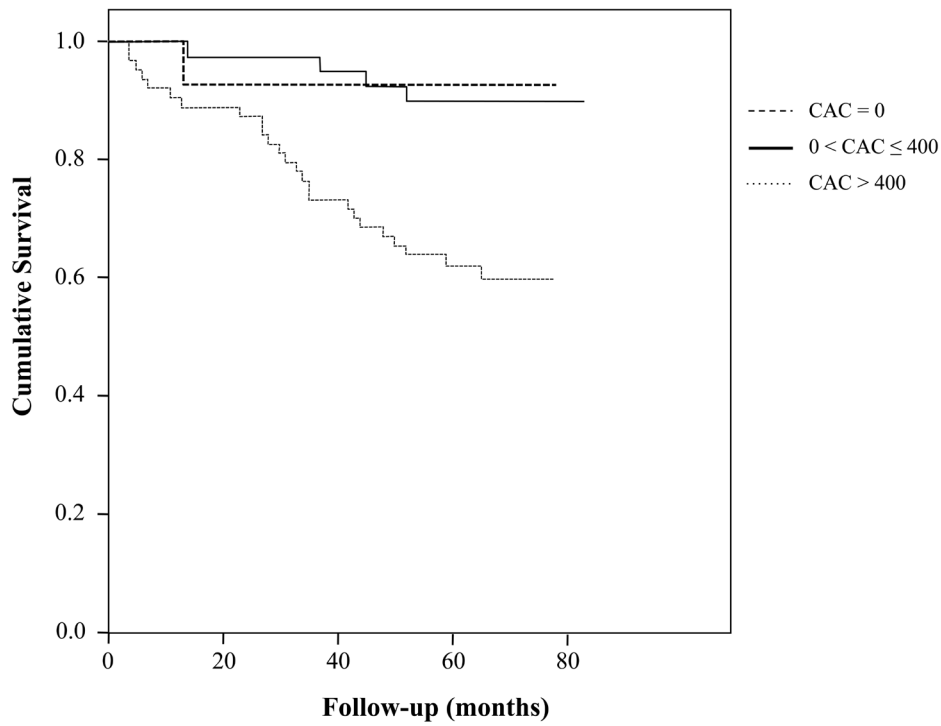


Figure 1. Kaplan-Meier

CAC=coronary artery calcium

Table 4. Numbers at risk

	CAC=0	0<CAC≤400	CAC>400
0 months	14	41	64
30 months	13	40	52
60 months	10	31	32

CAC=coronary artery calcium

DISCUSSION

We found that increased CAC was associated with increased arterial stiffness and lower bone attenuation in COPD subjects, but was not associated with extent of emphysema. CAC, TAC and extent of emphysema predicted all-cause mortality in our COPD cohort, while arterial stiffness and bone attenuation were not associated with all-cause mortality.

In line with previous studies,^{4,5} our data suggest a relationship between cardiovascular disease and osteoporosis in COPD patients. In our study, the association between CAC and bone attenuation was independent of age, sex and pack years of smoking. In a prospective study in 2442 postmenopausal women, the association between osteoporosis and cardiovascular events was independent of traditional cardiovascular risk factors such as age, cigarette smoking, hypertension and hyperlipidemia.³ These data suggest that, in addition to common risk factors, other factors might be involved in the vascular-bone relationship, including systemic inflammation,⁵ disturbance of the receptor activator of NF- κ B/ receptor activator of NF- κ B ligand/ osteoprotegerin system or reduced bone perfusion due to generalised atherosclerosis.

Our data showed a weak association between CAC and arterial stiffness in a COPD cohort after adjustment for age, sex and pack years of smoking. Previous studies in older populations have found associations between CAC and arterial stiffness after adjustment for confounders.¹² Thus, in addition to common risk factors, atherosclerosis may cause arterial stiffening,¹³ while increased arterial stiffness in turn may promote atherosclerotic changes due to greater shear and intraluminal stresses.¹⁴

In line with previous research,^{15,16} CAC was not associated with the degree of airflow obstruction or the extent of emphysema. CAC was not associated with the severity of airflow obstruction or the extent of emphysema in 1159 smokers of the Multicentre Italian Lung Detection (MILD) study,¹⁶ and CAC and proximal aortic calcification were not associated with the severity of airflow obstruction in subjects without clinical cardiovascular disease of the Multi-Ethnic Study of Atherosclerosis (MESA) study.^{15,17} Notably, as reported previously in this cohort, arterial stiffness did correlate with the extent of emphysema in COPD subjects.⁶ The relationship between arterial stiffness and emphysema might be due to connective tissue degradation⁶ or elastin degradation.¹⁸

Bone attenuation was not associated with the extent of emphysema. In contrast, a recent review stated that more severe emphysema is associated with reduced bone mineral density.¹⁹ Bon and colleagues⁷ showed that the extent of emphysema was independently associated with bone mineral density in 190 current and former smokers, and Ohara and colleagues²⁰ demonstrated that the extent of emphysema was independently associated with CT-measured bone density of the thoracic and lumbar vertebrae in 65 male COPD subjects. The discrepancy between our data and their data might be due to differences in the study population (e.g. smokers versus COPD patients) and methods used (e.g. attenuation threshold of low attenuation areas).

CAC and TAC predicted all-cause mortality after adjustment for age, sex, FEV₁ and pack years of smoking. Several studies have shown that CAC is a predictor of cardiovascular events and mortality in smokers.^{21,22} Here we show that CAC was a strong predictor of all-cause mortality in a COPD cohort. The hazard ratios reported in our COPD subjects were comparable with those reported in smokers and subjects without known coronary artery diseases. In 1159 smokers, the hazard ratio of CAC>400 was 4.00 (CI 1.17-13.7) for all-cause mortality compared with CAC≤400 after adjustment for age, sex, body mass index and history of diabetes or hypertension.¹⁶ In our study, the hazard ratio of CAC>400 was 4.6 (CI 1.63-13.12, $p=0.004$, data not shown) compared with CAC≤400 after adjustment for age, sex, FEV₁ and pack years of smoking. In 3966 subjects without known coronary artery diseases, the crude hazard ratio of CAC≥400 was HR 6.54 (CI 3.51-12.21) for all-cause mortality,²³ and in our study the crude hazard ratio of CAC>400 was 6.46.

Although CAC and TAC were associated with all-cause mortality, arterial stiffness was not associated with all-cause mortality in our COPD cohort. This finding is in contrast to previous studies that have demonstrated a relationship between increased arterial stiffness and all-cause mortality in subjects with chronic kidney disease.^{24,25} The lack of a relationship between increased arterial stiffness and mortality in our study might be explained by the fact that we measured carotid-radial PWV rather than carotid-femoral PWV which is the gold standard.²⁶ A study in 305 end-stage renal disease patients showed indeed that carotid-femoral PWV was an independent predictor of cardiovascular mortality, whereas carotid-radial and femoral-posterior tibial PWV were not associated with mortality.²⁷

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In addition, the extent of emphysema was associated with all-cause mortality after adjustment for age and sex, but not after adjustment for age, sex and FEV₁. As such, it may be that emphysema causes increased mortality indirectly through reducing lung function. Our findings are in line with previous studies that have shown associations between the extent of emphysema and all-cause mortality in COPD subjects.²⁸

Although lower bone attenuation was associated with increased CAC, bone attenuation was not associated with all-cause mortality in our COPD cohort. In contrast, previous studies have shown that bone density and rate of bone loss are related to mortality in elderly men and women.^{29,30} The Rotterdam Study demonstrated that in elderly men the risk of mortality increased when bone density was below average, and that the relationship between bone density and mortality was nonlinear.²⁹ In addition, Szulc and colleagues³⁰ showed in 781 elderly men that bone resorption markers predicted mortality more strongly than bone mineral density. The lack of a relationship between bone attenuation and mortality in our study might be due to the study population (e.g. COPD subjects rather than elderly subjects) and the methods used (e.g. bone attenuation of the thoracic vertebrae rather than bone mineral density of the hip, lumbar spine or whole body).

Our study has several limitations. First, bone attenuation was assessed on low-dose chest CT while dual energy X-ray absorptiometry is the gold standard. However, previous data

have demonstrated that bone attenuation measured on CT is strongly correlated with bone mineral density assessed on dual energy X-ray absorptiometry.¹¹ Second, CAC and TAC were measured on non-gated scans, however, it has been shown previously that measurements of CAC and TAC on non-gated chest CT scans show good agreement with measurements from electrocardiographically gated chest CT scans.⁹ Third, arterial stiffness was measured as carotid-radial PWV rather than carotid-femoral PWV which is the gold standard.²⁶ Although our study has several limitations, we measured several COPD-related manifestations such as CAC, TAC, bone attenuation and extent of emphysema in a well-characterised COPD cohort.

Our data showed that CAC, TAC and emphysema which were measured on low-dose chest CT predicted all-cause mortality in COPD subjects. We suggest that low-dose chest CT might contribute to early diagnosis of COPD-related manifestations and improved risk stratification, although further evidence, ideally from randomised controlled trials, are required to determine the benefits of this screening approach in COPD patients.

In conclusion, our study showed that increased CAC was associated with increased arterial stiffness and lower bone attenuation in COPD subjects. CAC, TAC and emphysema predicted all-cause mortality in our COPD cohort, suggesting that quantitative assessment of CAC, TAC and emphysema provide relevant prognostic information in COPD subjects.

DISCLOSURES

Elisabeth A.P.M. Romme was the recipient of a European Respiratory Society Fellowship (STRTF 381-2011). The work described in this manuscript was performed at the University of Edinburgh as part of this Fellowship.

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e-Table 1. Cox proportional-hazards for all-cause mortality

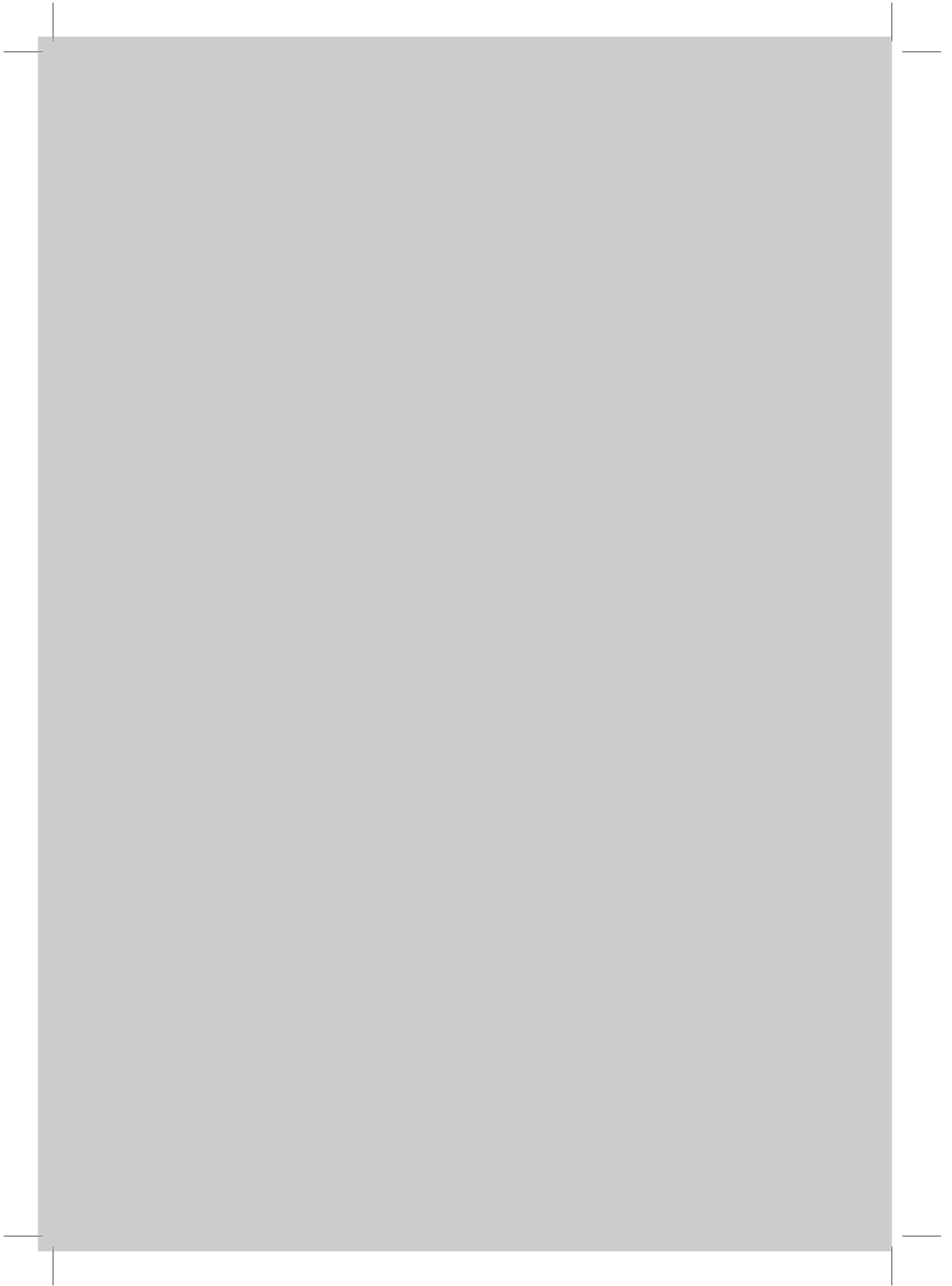
	Per 10-fold increase in TAC	95% CI	p-value
TAC	2.20	1.20 - 4.03	0.01
TAC ^a	2.08	0.99 - 4.38	0.06
TAC ^b	1.97	0.93 - 4.19	0.08
TAC ^c	2.09	0.95 - 4.59	0.07

^a after adjustment for age and sex^b after adjustment for age, sex and FEV₁^c after adjustment for age, sex, FEV₁ and pack years of smokingCI=confidence interval, FEV₁=forced expiratory volume in 1 second, TAC=thoracic aortic calcification**e-Table 2.** Cox proportional-hazards for all-cause mortality

	Hazard ratio	95% CI	p-value
PWV	0.91	0.72 - 1.16	0.44
PWV ^a	0.86	0.67 - 1.10	0.23
PWV ^b	0.85	0.67 - 1.08	0.18
PWV ^c	0.81	0.62 - 1.06	0.13
Bone attenuation/ SD	0.98	0.68 - 1.40	0.90
Bone attenuation/ SD ^a	1.04	0.72 - 1.50	0.84
Bone attenuation/ SD ^b	1.10	0.76 - 1.57	0.62
Bone attenuation/ SD ^c	1.11	0.77 - 1.60	0.58
15 th percentile/ SD	0.70	0.49 - 1.00	0.05
15 th percentile/ SD ^a	0.65	0.45 - 0.95	0.03
15 th percentile/ SD ^b	0.69	0.46 - 1.04	0.07
15 th percentile/ SD ^c	0.66	0.43 - 1.01	0.06

^a after adjustment for age and sex^b after adjustment for age, sex and FEV₁^c after adjustment for age, sex, FEV₁ and pack years of smokingCI=confidence interval, FEV₁=forced expiratory volume in 1 second, PWV=pulse wave velocity, SD=standard deviation







Chapter 7

Bone stiffness and failure load are related with clinical parameters in men with chronic obstructive pulmonary disease

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ABSTRACT

Osteoporosis is frequently seen in patients with chronic obstructive pulmonary disease (COPD). Since research on bone structure and bone strength in COPD patients is limited, the objectives of this pilot study were: 1) To compare bone structure, stiffness and failure load, measured at the peripheral skeleton, between men with and without COPD after stratification for areal bone mineral density (aBMD); and 2) To relate clinical parameters with bone stiffness and failure load in men with COPD. We included 30 men with COPD (normal aBMD n=18, osteoporosis n=12) and 17 men without COPD (normal aBMD n=9, osteoporosis n=8). We assessed pack years of smoking, body mass index (BMI), fat free mass index (FFMI), pulmonary function (FEV_1 , FEV_1/FVC , DLCO and KCO) and extent of emphysema. Bone structure of the distal radius and tibia was assessed by high resolution peripheral quantitative computed tomography (HR-pQCT), and bone stiffness and failure load of the distal radius and tibia were estimated from micro-finite element analysis (μ FEA). After stratification for aBMD and COPD, men with osteoporosis showed abnormal bone structure ($p<0.01$), lower bone stiffness ($p<0.01$) and lower failure load ($p<0.01$) compared with men with normal aBMD, and men with COPD had comparable bone structure, stiffness and failure load compared with men without COPD. In men with COPD, lower FFMI was related with lower bone stiffness and failure load of the radius and tibia and lower DLCO and KCO were related with lower bone stiffness and failure load of the tibia after normalization with respect to femoral neck aBMD. Thus, this pilot study could not detect differences in bone structure, stiffness and failure load between men with and without COPD after stratification for aBMD. FFMI and gas transfer capacity of the lung were significantly related with bone stiffness and failure load in men with COPD after normalization with respect to femoral neck aBMD.

INTRODUCTION

Osteoporosis and vertebral fractures are frequently seen in patients with chronic obstructive pulmonary disease (COPD) and related with the severity of airflow obstruction.¹⁻³ The relationship between COPD and osteoporosis is assumed to be due to common risk factors, such as older age and cigarette smoking, or to COPD-specific mechanisms, such as systemic inflammation,⁴ the use of corticosteroids⁵ and vitamin D deficiency.⁶

The current gold standard for diagnosing osteoporosis is areal bone mineral density (aBMD) on dual energy X-ray absorptiometry (DXA).⁷ Although low aBMD is a well-established risk factor of fragility fractures,⁸ COPD subjects with a normal aBMD can have vertebral fractures,⁹ suggesting that other factors are involved. Indeed, in addition to aBMD, bone strength is influenced by several structural and material properties of bone.¹⁰

Recently, high resolution peripheral quantitative computed tomography (HR-pQCT) has been introduced to assess structural parameters of bone.¹¹ In addition, HR-pQCT images can be used to estimate mechanical parameters of bone, such as bone stiffness and failure load, from micro-finite element analysis (μ FEA).^{12,13} Previous data have shown that structural parameters assessed on HR-pQCT and mechanical parameters estimated from μ FEA are related with fragility fractures.¹¹ Vilayphiou and colleagues¹⁴ showed that bone structure, stiffness and failure load were associated with all types of fractures in postmenopausal women, and Graeff and colleagues¹⁵ demonstrated that structural and mechanical parameters of bone were superior to aBMD in discriminating men with and without vertebral fractures.

Although previous studies have shown that lung function parameters and radiographic emphysema are related with aBMD and vertebral fractures,¹⁶⁻¹⁸ research on structural and mechanical parameters of bone in COPD patients is sparse. A previous study using histomorphometry and micro computed tomography (μ CT) showed that structural parameters of bone in bone biopsies were different in postmenopausal women with COPD compared with control subjects.¹⁹ However, the COPD and control groups were not matched for aBMD.

Since research on structural and mechanical parameters of bone in COPD patients is limited, the objectives of this pilot study were: 1) To compare bone structure, stiffness and failure load, measured at the peripheral skeleton, between men with and without COPD after stratification for aBMD; and 2) To relate clinical parameters with bone stiffness and failure load in men with COPD.

MATERIALS AND METHODS

Subjects

This study included men with moderate to very severe COPD and men without COPD matched for age, who were enrolled in a clinical trial at the Catharina hospital (Eindhoven, the Netherlands) between February 2010 and September 2011. The inclusion and exclusion

criteria of this clinical trial have been published previously.²⁰ Women were excluded from our analysis, because their number was relatively small and previous data showed differences in bone structure between men and women.²¹

The study was approved by the medical ethical committee of the Catharina hospital (MO9-1971) and registered at www.clinicaltrials.gov (NCT01067248). All subjects gave written informed consent.

Clinical parameters

At study entry, structured interviews were used to document the subjects' self-reported smoking history, medications (e.g. use of oral or inhaled corticosteroids) and coexisting medical conditions. Total body weight and height were measured to calculate body mass index (BMI). Fat free mass (FFM) was assessed by bio-impedance analysis (Bodystat 1500, Bodystat Ltd., Onchan, Isle of Man) and FFM index (FFMI) was calculated as FFM divided by height².

Pulmonary function was measured with standardized equipment (MasterScreen™ Body, Carefusion, San Diego, California, USA) according to the guidelines of the American Thoracic Society (ATS)/ European Respiratory Society (ERS).²² Measurements included forced expiratory volume in 1 second (FEV₁), forced vital capacity (FVC), vital capacity (VC), total lung capacity (TLC), residual volume (RV), inspiratory capacity (IC) and expiratory reserve volume (ERV). Following the ERS recommendations, the single-breath technique was used to determine the diffusion capacity for carbon monoxide (DLCO) and transfer coefficient for carbon monoxide (KCO).²³

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Chest CT examinations were performed using a single-energy 256 multidetector row scanner (Philips Brilliance intelligent CT, Philips Healthcare, Eindhoven, The Netherlands) with technical parameters of 120 kVp, 350-mm field of view, 2.5 mm slice thickness and ECG gated. The scanner was calibrated daily to ensure accurate CT attenuation numbers. All subjects were scanned in supine position, during deep inspiration and without administration of contrast. Emphysema was quantified by in-house software using the 15th percentile point of the frequency distribution of lung density and pixel index for -950 (PI-950) Hounsfield units, as previously described.²⁴⁻²⁷

Bone density, structure, stiffness and failure load

Areal BMD (aBMD) of the lumbar spine (L1 to L4), femoral neck and total hip were measured using a Delphi upgraded to a discovery W (S/N70991) DXA scanner (Tromp Medical Engineering BV, Castricum, The Netherlands). Diagnosis of osteoporosis was based on the lowest T-score of the lumbar spine, femoral neck and total hip, and defined according to the criteria of the World Health Organization (WHO) (osteoporosis: T-score ≤ -2.5 ; osteopenia: T-score < -1.0 and > -2.5 ; and normal aBMD: T-score ≥ -1.0).⁷

High-resolution pQCT (HR-pQCT) images of the non-dominant (or non-fractured) distal radius and tibia were taken using a HR-pQCT device (XtremeCT, Scanco Medical AG, Brüttisellen, Switzerland) with standard *in vivo* parameters of 60 kVp, 900 μ A and 100 ms integration time. Each measurement took approximately 3 minutes and resulted in a 9.02 mm thick stack of parallel images (110 slices, voxel size of 82 μ m). Quality control was performed by daily scans of a phantom containing rods of hydroxyapatite (HA) embedded in a soft-tissue equivalent resin (QRM, Moehrendorf, Germany).

The HR-pQCT images were evaluated using standard software of the manufacturer to assess total bone density (Dt_{tot}), trabecular density (D_{trab}), relative bone volume (BV/TV), trabecular number (Tb.N), trabecular thickness (Tb.Th), trabecular separation (Tb.Sp), cortical density (D_{cort}) and cortical thickness (Ct.Th), as described previously.^{28,29} In addition, μ FEA was performed to calculate bone stiffness in kiloNewton per millimeter (kN/mm) and failure load in kiloNewton (kN), as described previously.^{13,29} Bone stiffness is the resistance against deformation, and failure load is the estimated load at which bone failure will occur.

Statistical analysis

Subjects were classified into: COPD subjects with normal aBMD, COPD subjects with osteoporosis, control subjects with normal aBMD and control subjects with osteoporosis. Comparisons among groups were made using Mann-Whitney U and Chi-square analyses. Bonferroni correction was used to adjust for multiple comparisons. Two-sided p-values ≤ 0.0125 ($0.05/4$) were considered statistically significant.

Standard simple and multiple regression models were used to assess relationships between clinical parameters and bone stiffness and failure load. Preliminary analyses were conducted to ensure no violation of the assumptions of normality, linearity, multicollinearity and homoscedasticity. Since the study group is relatively small en femoral neck aBMD is a strong predictor of osteoporosis-related fractures,³⁰ multiple regression models were adjusted for femoral neck aBMD only.

All statistical analyses were performed in SPSS version 17.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

We included 30 men with COPD (normal aBMD n=18, osteoporosis n=12) and 17 men without COPD (normal aBMD n=9, osteoporosis n=8). Table 1 shows the clinical characteristics. COPD subjects with osteoporosis had lower BMI ($p=0.007$), FFMI ($p=0.01$), FEV₁ ($p=0.008$), FEV₁/FVC ($p=0.005$), DLCO ($p=0.001$) and KCO ($p<0.001$) compared with COPD subjects with normal aBMD, and control subjects with osteoporosis had similar clinical characteristics compared with control subjects with normal aBMD. No differences were found in the use of corticosteroids between COPD subjects with and without osteoporosis.

Table 2 shows the structural and mechanical parameters of bone after stratification for COPD and aBMD. COPD subjects and control subjects with osteoporosis had lower total bone

density, lower trabecular density, lower relative bone volume, lower trabecular number, higher trabecular separation, lower cortical thickness, lower bone stiffness and lower failure load compared with COPD subjects and control subjects with normal aBMD, respectively. In addition, COPD subjects had comparable bone structure, stiffness and failure load compared with control subjects after stratification for aBMD.

In the total cohort, BMI, FFMI, FVC, VC, DLCO, KCO, PI-950, 15th percentile and aBMD were significantly related with bone stiffness and failure load of the radius and tibia, and FEV₁, TLC and IC were significantly related with bone stiffness and failure load of the radius or tibia (see supplement, e-Table 1 and e-Table 2). In the COPD subjects, BMI, FFMI, DLCO, KCO, PI-950, 15th percentile and aBMD were significantly related with bone stiffness and failure load of the radius and tibia, and FEV₁ and FEV₁/FVC were significantly related with bone stiffness and failure load of the radius or tibia (see supplement, e-Table 3 and e-Table 4). In the COPD subjects, lower FFMI was significantly related with lower bone stiffness and failure load of the radius and tibia and DLCO and KCO were significantly related with lower bone stiffness and failure load of the tibia, after adjustment for femoral neck aBMD (Table 3). Figure 1 shows the relationship between DLCO and failure load of the tibia in the COPD subjects after adjustment for femoral neck aBMD.

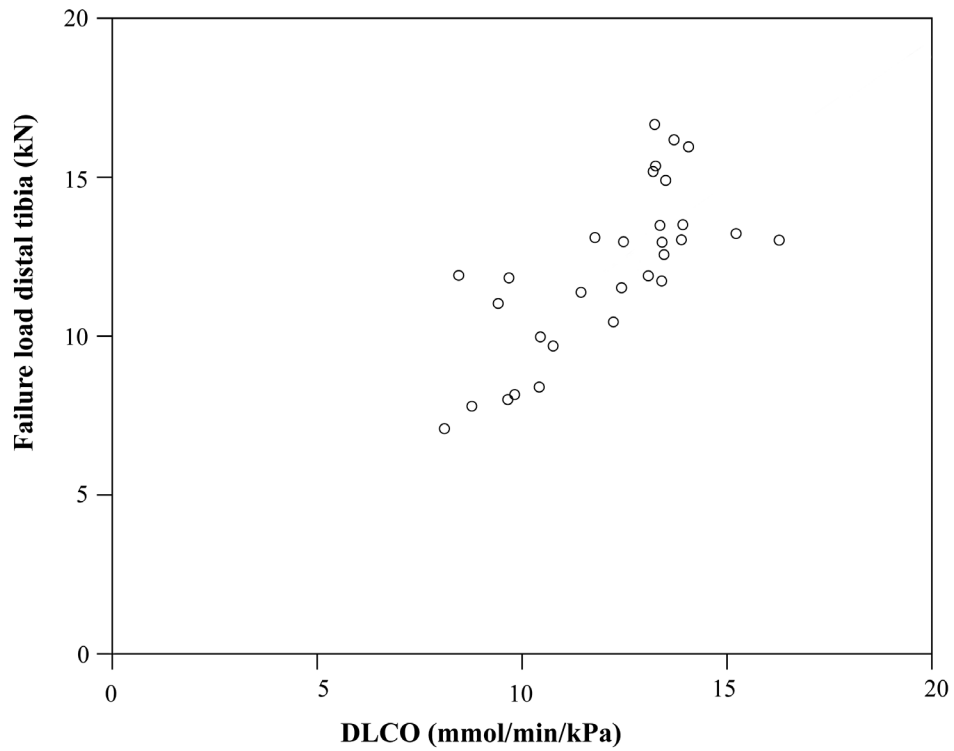


Figure 1. Diffusion capacity for carbon monoxide related with failure load of the distal tibia in COPD subjects after adjustment for femoral neck aBMD (g/cm^2)

aBMD=areal bone mineral density; DLCO=diffusion capacity for carbon monoxide.

Table 1. Clinical characteristics

	Group 1 COPD subjects Normal aBMD N=18	Group 2 COPD subjects Osteoporotic aBMD N=12	Group 3 Control subjects Normal aBMD N=9	Group 4 Control subjects Osteoporotic aBMD N=8	1 vs. 2 p	3 vs. 4 p	1 vs. 3 p	2 vs. 4 p
Age, yrs	64.0 (28.0)	64.5 (16.0)	65.0 (17.0)	68.0 (13.0)	0.82	0.21	0.70	0.14
BMI, kg/m ²	26.7 (19.2)	23.3 (14.6)	27.5 (9.9)	25.2 (7.5)	0.007	0.27	0.80	0.14
FFMI, kg/m ²	18.6 (8.8)	17.3 (7.1)	19.3 (4.5)	18.0 (2.7)	0.01	0.41	0.61	0.19
Pack years, n	37.0 (105.5)	37.2 (100.0)	11.3 (37.5)	6.8 (90.0)	0.77	0.71	0.001	0.08
Oral corticosteroids								
Number (%)	8 (44)	6 (50)	0 (0)	0 (0)	0.77	1.00	0.02	0.02
Dose, mg	0 (4500)	150 (3650)	0 (0)	0 (0)	0.59	1.00	0.02	0.02
Inhaled corticosteroids								
Number (%)	9 (50)	8 (67)	0 (0)	0 (0)	0.37	1.00	0.009	0.003
Dose, mg	46 (7862)	326 (2920)	0 (0)	0 (0)	0.45	1.00	0.01	0.005
FEV ₁ , L	2.01 (1.50)	1.35 (2.33)	3.47 (1.66)	3.34 (2.06)	0.008	0.16	<0.001	<0.001
FEV ₁ , % pred	67.5 (36.0)	51.5 (52.0)	108.0 (29.0)	114.5 (59.0)	0.01	0.74	<0.001	<0.001
FVC, L	3.66 (4.37)	3.18 (3.89)	4.73 (2.58)	4.49 (2.59)	0.11	0.21	0.004	0.01
FVC, % pred	93.1 (88.0)	91.0 (67.0)	114.0 (36.0)	117.0 (60.0)	0.67	0.92	0.001	0.004
FEV ₁ /FVC ratio	56.0 (30.8)	41.9 (32.7)	74.7 (5.6)	74.6 (13.1)	0.005	0.92	<0.001	<0.001
DLCO, mmol/min/kPa	6.78 (5.56)	3.80 (5.43)	8.98 (5.61)	7.86 (2.52)	0.001	0.04	0.001	0.001
DLCO, % pred	78.0 (59.0)	46.0 (42.0)	98.0 (27.0)	88.5 (18.0)	<0.001	0.19	<0.001	<0.001
KCO, mmol/min/kPa/L	1.23 (1.00)	0.78 (0.48)	1.38 (0.55)	1.24 (0.45)	<0.001	0.15	0.009	<0.001
KCO, % pred	94.5 (67.0)	58.0 (36.0)	104 (32.0)	97.0 (32.0)	<0.001	0.21	0.003	<0.001

Results are presented as median (range) unless otherwise indicated. After Bonferroni correction, two-sided p-values ≤ 0.0125 (0.05/4) are considered statistically significant.

Table 2. Bone structure, stiffness and strength of the radius and tibia

	Group 1		Group 2		Group 3		Group 4		1 vs. 2		3 vs. 4		1 vs. 3		2 vs. 4	
	COPD subjects	Normal aBMD	COPD subjects	Osteoporotic aBMD	Control subjects	Normal aBMD	Control subjects	Osteoporotic aBMD	p		p		p		p	
	N=18		N=12		N=9		N=8									
Radius																
Dtot, mg HA/cm ³	346.0 (268.2)		247.2 (127.3)		363.6 (146.2)		287.6 (154.9)		0.004		0.04		0.36		0.12	
Dtrab, mg HA/cm ³	184.4 (157.8)		142.0 (124.4)		199.7 (90.4)		137.9 (38.2)		0.002		0.001		0.61		0.82	
BV/TV, %	15.4 (13.2)		11.8 (10.3)		16.6 (7.6)		11.5 (3.2)		0.002		0.001		0.61		0.82	
Tb.N, mm ⁻¹	2.27 (1.34)		1.86 (1.24)		2.12 (0.71)		1.86 (0.46)		0.001		0.007		0.27		0.94	
Tb.Th, mm	0.070 (0.040)		0.063 (0.036)		0.082 (0.030)		0.063 (0.033)		0.13		0.02		0.11		0.97	
Tb.Sp, mm	0.366 (0.379)		0.471 (0.572)		0.388 (0.181)		0.479 (0.137)		0.001		0.007		0.57		0.94	
Dcort, mg HA/cm ³	859.6 (274.0)		788.7 (161.1)		861.4 (118.9)		830.3 (259.0)		0.07		0.53		0.76		0.19	
Ct.Th, mm	0.950 (0.870)		0.595 (0.470)		1.110 (0.550)		0.785 (0.680)		0.02		0.09		0.68		0.18	
Stiffness, kN/mm	120.3 (84.1)		87.1 (73.3)		132.6 (81.9)		97.2 (23.1)		0.003		0.009		0.30		0.49	
Failure load, kN	5.69 (4.00)		4.14 (3.27)		6.27 (3.72)		4.62 (0.87)		0.003		0.007		0.33		0.44	
Tibia																
Dtot, mg HA/cm ³	299.4 (140.4)		227.5 (88.9)		337.7 (148.6)		227.4 (148.3)		<0.001		0.003		0.24		0.64	
Dtrab, mg HA/cm ³	184.8 (122.8)		129.2 (112.9)		214.0 (137.3)		134.5 (37.0)		<0.001		0.005		0.21		0.46	
BV/TV, %	15.4 (10.3)		10.8 (9.5)		17.8 (11.5)		11.3 (3.1)		<0.001		0.005		0.21		0.46	
Tb.N, mm ⁻¹	2.11 (1.18)		1.55 (0.97)		2.16 (0.85)		1.50 (0.66)		<0.001		0.002		0.84		0.94	
Tb.Th, mm	0.074 (0.044)		0.070 (0.031)		0.084 (0.047)		0.074 (0.029)		0.16		0.36		0.32		0.28	
Tb.Sp, mm	0.409 (0.318)		0.579 (0.519)		0.378 (0.218)		0.595 (0.285)		<0.001		0.001		0.59		0.94	
Dcort, mg HA/cm ³	863.0 (215.6)		807.7 (143.3)		853.6 (102.9)		799.1 (199.6)		0.03		0.15		0.68		0.88	

Ct.Th, mm	1.325 (0.610)	0.890 (0.630)	1.450 (0.850)	1.030 (0.900)	<0.001	0.009	0.05	0.59
Stiffness, kN/mm	278.8 (126.1)	206.3 (118.9)	313.1 (176.0)	211.9 (51.6)	<0.001	0.001	0.17	0.54
Failure load, kN	13.1 (6.21)	9.83 (6.01)	14.73 (7.98)	10.15 (2.48)	<0.001	0.001	0.15	0.54

Results are presented as median (range) unless otherwise indicated. After Bonferroni correction, two-sided p-values ≤ 0.0125 (0.05/4) are considered statistically significant.

aBMD=areal bone mineral density; BV/TV=relative bone volume; Ct.Th=cortical thickness; Dcort=cortical density; Dtot=total density; Dtrab=trabecular density; Tb.N=trabecular number; Tb.Sp=trabecular separation; Tb.Th=trabecular thickness.

Table 3. Clinical parameters related with bone stiffness and failure load in COPD subjects after adjustment for femoral neck aBMD (g/cm²)

	Radius					Tibia				
	Stiffness, kN/mm		Failure load, kN		p	Stiffness, kN/mm		Failure load, kN		p
	B (SE)	95% CI	B (SE)	95% CI		B (SE)	95% CI	B (SE)	95% CI	
BMI, kg/m ²	1.33 (0.85)	-0.41, 3.07	0.13	0.06 (0.04)	0.15	2.43 (1.24)	-0.12, 4.97	0.11 (0.06)	-0.01, 0.23	0.07
FFMI, kg/m ²	4.04 (1.92)	0.10, 7.99	0.05	0.19 (0.09)	0.04	6.81 (2.81)	1.03, 12.6	0.33 (0.13)	0.06, 0.60	0.02
FEV ₁ , L	1.65 (8.06)	-14.9, 18.2	0.84	0.17 (0.37)	0.65	5.67 (12.0)	-19.0, 30.3	0.35 (0.57)	-0.81, 1.52	0.54
FEV ₁ /FVC ratio	-0.13 (0.44)	-1.04, 0.78	0.78	0.00 (0.02)	0.87	0.26 (0.66)	-1.10, 1.61	0.01 (0.03)	-0.05, 0.08	0.74
DLCO, mmol/min/kPa	4.01 (2.75)	-1.64, 9.65	0.16	0.21 (0.13)	0.11	8.15 (3.98)	-0.01, 16.3	0.40 (0.19)	0.02, 0.78	0.04
KCO, mmol/min/kPa/L	21.3 (18.1)	-15.9, 58.4	0.25	1.04 (0.84)	0.23	55.9 (25.6)	3.35, 108	2.56 (1.22)	0.05, 5.06	0.05
PI-950, %	-0.59 (0.76)	-2.18, 1.00	0.45	-0.03 (0.04)	0.38	-1.45 (1.06)	-3.65, 0.75	-0.07 (0.05)	-0.18, 0.03	0.18
15 th percentile, HU	0.32 (0.25)	-0.20, 0.85	0.22	0.02 (0.01)	0.20	0.49 (0.36)	-0.25, 1.24	0.02 (0.02)	-0.01, 0.06	0.19

Two-sided p-values ≤0.05 are considered statistically significant.

aBMD=areal bone mineral density; B=unstandardized regression coefficient; BMI=body mass index; CI=confidence interval; DLCO=diffusion capacity for carbon monoxide; FEV₁=forced expiratory volume in 1 second; FFMI=fat free mass index; HU=Hounsfield units; KCO=transfer coefficient for carbon monoxide; PI-950=pixel index for 950 Hounsfield units; SE=standard error.

DISCUSSION

This study could not detect differences in bone structure, stiffness and failure load, measured at the peripheral skeleton, between men with and without COPD after stratification for aBMD. FFMI and gas transfer capacity of the lung were significantly related with bone stiffness and failure load in men with COPD after normalization with respect to femoral neck aBMD.

Our data showed that men with osteoporosis had impaired bone structure and lower bone stiffness and failure load compared with men with normal aBMD. These findings are in line with previous data demonstrating associations between aBMD, bone structure, stiffness and failure load.^{14,28,31} In addition, previous data have shown that structural and mechanical parameters of bone are even better predictors of vertebral fractures than aBMD,^{15,28} suggesting that structural and mechanical parameters of bone might improve the prediction of vertebral fractures.

After stratification for COPD and aBMD, men with COPD had comparable bone structure, stiffness and failure load compared with men without COPD. To the best of our knowledge, only one previous study has investigated differences in bone structure between subjects with and without COPD.¹⁹ This study showed that postmenopausal women with COPD had abnormal bone structure compared with control subjects.¹⁹ However, the COPD and control groups were not matched for aBMD. These findings suggest that structural parameters of bone are more impaired in COPD patients than in control subjects, whereas structural and mechanical parameters of bone are similar in COPD patients and control subjects after matching for aBMD.

Several pulmonary parameters, including FEV₁, FVC, VC, TLC, IC, DLCO, KCO, 15th percentile and PI-950, were significantly related with bone stiffness and failure load. Although research on associations between pulmonary function and mechanical parameters of bone is lacking, previous studies have shown associations between pulmonary function and bone density or fragility fractures.^{18,32} In 85 subjects with moderate to very severe COPD, lower VC and DLCO and more severe emphysema were associated with osteoporosis defined as a T score <-2.5, whereas lower VC and FEV₁ were associated with vertebral fractures.¹⁷ In addition, a longitudinal study in 70 subjects with emphysema showed that lung volume reduction surgery improved pulmonary function and aBMD, compared with respiratory rehabilitation therapy.³³ These findings suggest associations between the pulmonary and skeletal system.

FFMI was significantly related with bone stiffness and failure load of the radius and tibia and DLCO and KCO were significantly related with bone stiffness and failure load of the tibia, after normalization with respect to femoral neck aBMD. These data suggest that FFMI and gas transfer capacity of the lung are related with properties of bone that are only partially related with aBMD, such as bone structure, micro damage burden, collagen type and cross-linking.¹⁰

FFMI might interact with properties of bone via physical activity. Reduced physical activity has been related with bone loss and osteoporosis-related fractures,^{34,35} whereas, on the other hand, exercise interventions have been shown to increase aBMD³⁶ and reduce the number of fractures.³⁷ In addition to physical activity, decreased mechanical loading might influence bone strength.

In addition to FFMI, gas transfer capacity of the lung might interact with properties of bone. The gas transfer capacity of the lung is associated with several factors that have already been related with properties of bone. First, a lower gas transfer capacity of the lung is associated with emphysema,²³ which has been related with osteoporosis.¹⁸ The relationship between emphysema and osteoporosis might be due to a common mechanism, such as impaired Wnt/ β -catenin signaling.³⁸ Second, a lower gas transfer capacity of the lung is associated with anemia,²³ which has been related with osteoporosis and vertebral fractures.^{39,40} Animal studies have demonstrated that anemia-induced hypoxia might be responsible for the effects on bone remodeling.⁴¹ However, additional research is needed to further elucidate the interaction between hypoxia and bone remodeling. Third, a lower gas transfer capacity of the lung is associated with thoracic deformity,²³ which has been related with vertebral fractures.⁴² These data suggest a mechanical relationship between lung function and osteoporosis. Fourth, a higher gas transfer capacity of the lung is associated with obesity,²³ which has been shown to be protective against osteoporosis.¹⁶ Previous research has indeed shown beneficial effects of adipose tissue on bone density.^{43,44} Although several potential mechanisms have been described, additional research is warranted to further investigate the relationship between gas transfer capacity of the lung and mechanical parameters of bone.

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Some limitations should be mentioned. First, no causal relationship could be established due to the cross-sectional design of the study. Second, a relatively small number of men was included. Third, subjects with osteopenia were excluded, as described previously.²⁰ Fourth, our bone analyses were limited to the peripheral skeleton, because high resolution computed tomography is only possible at peripheral sites. Acknowledging these limitations, our study is the first to show that disease-specific parameters, such as FFMI and gas transfer capacity of the lung, are related with structural and mechanical parameters of bone in COPD subjects.

Since FFMI and gas transfer capacity of the lung were related with bone stiffness and failure load independent of aBMD, we suggest that FFMI and gas transfer capacity of the lung can improve risk stratification of fragility fractures in COPD patients. A combination of clinical features and structural and mechanical parameters of bone is likely to be a better predictor of fragility fractures than aBMD alone.⁴⁵ Longitudinal studies are needed to investigate which clinical features and structural and mechanical parameters of bone are related with future fractures.

This pilot study could not detect differences in bone structure, stiffness and failure load between men with and without COPD after stratification for aBMD. FFMI and gas transfer capacity of the lung were related with bone stiffness and failure load in men with COPD after

normalization with respect to femoral neck aBMD. These data suggest that FFMI and gas transfer capacity of the lung might interact with structural and mechanical parameters of bone. Longitudinal studies are needed to further investigate associations between clinical features and structural and mechanical parameters of bone in COPD patients.

DISCLOSURES

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e-Table 1. Predictors of bone stiffness and failure load of the distal radius in the total cohort

	Radius					
	Stiffness, kN/mm			Failure load, kN		
	B (SE)	95% CI	p	B (SE)	95% CI	p
Age, yrs	-0.97 (0.65)	-2.29, 0.35	0.15	-0.05 (0.03)	-0.11, 0.02	0.15
BMI, kg/m ²	2.52 (0.77)	0.97, 4.07	0.002	0.12 (0.04)	0.05, 0.19	0.002
FFMI, kg/m ²	6.65 (1.68)	3.26, 10.0	<0.001	0.31 (0.08)	0.16, 0.47	<0.001
Pack years, n	-0.17 (0.15)	-0.48, 0.13	0.25	-0.01 (0.01)	-0.02, 0.01	0.28
FEV ₁ , L	7.49 (3.92)	-0.41, 15.4	0.06	0.36 (0.18)	0.00, 0.73	0.05
FVC, L	8.37 (3.60)	1.11, 15.6	0.03	0.40 (0.17)	0.07, 0.74	0.02
FEV ₁ /FVC ratio	0.25 (0.27)	-0.30, 0.79	0.37	0.01 (0.01)	-0.01, 0.04	0.33
VC, L	8.97 (3.75)	1.42, 16.5	0.02	0.43 (0.17)	0.09, 0.78	0.02
TLC, L	6.59 (3.29)	-0.05, 13.2	0.05	0.33 (0.15)	0.03, 0.63	0.03
RV, L	0.72 (4.36)	-8.08, 9.51	0.87	0.05 (0.20)	-0.35, 0.46	0.80
RV/TLC ratio	-0.42 (0.41)	-1.23, 0.40	0.31	-0.02 (0.02)	-0.06, 0.02	0.31
IC, L	6.78 (4.73)	-2.76, 16.3	0.16	0.35 (0.22)	-0.09, 0.79	0.12
ERV, L	9.11 (6.15)	-3.30, 21.5	0.15	0.41 (0.28)	-0.17, 0.98	0.16
DLCO, mmol/ min/kPa	6.01 (1.63)	2.73, 9.28	0.001	0.29 (0.07)	0.14, 0.44	<0.001
KCO, mmol/ min/kPa/L	38.4 (12.8)	12.6, 64.3	0.004	1.82 (0.59)	0.63, 3.01	0.004
PI-950, %	-1.51 (0.68)	-2.88, -0.14	0.03	-0.07 (0.03)	-0.14, -0.01	0.02
15 th percentile, HU	0.46 (0.18)	0.10, 0.81	0.01	0.02 (0.01)	0.01, 0.04	0.01
Areal BMD, g/ cm ²						
Femoral neck	120 (22.7)	74.5, 166	<0.001	5.65 (1.04)	3.56, 7.75	<0.001
Total hip	92.5 (15.7)	60.9, 124	<0.001	4.31 (0.72)	2.86, 5.77	<0.001
L1-L4	79.6 (14.9)	49.6, 110	<0.001	3.69 (0.69)	2.31, 5.08	<0.001

Two sided p-values ≤0.05 are considered statistically significant.

B=unstandardized regression coefficient; BMD=bone mineral density; BMI=body mass index; CI=confidence interval; DLCO=diffusion capacity for carbon monoxide; ERV=expiratory reserve volume; FEV₁=forced expiratory volume in 1 second; FFMI=fat free mass index; FVC=forced vital capacity; HU=Hounsfield units; IC=inspiratory capacity; KCO=transfer coefficient for carbon monoxide; PI-950=percentile index for -950 Hounsfield units; RV=residual volume; TLC=total lung capacity; VC=vital capacity.

e-Table 2. Predictors of bone stiffness and failure load of the distal tibia in the total cohort

	Tibia					
	Stiffness, kN/mm			Failure load, kN		
	B (SE)	95% CI	p	B (SE)	95% CI	p
Age, yrs	0.06 (1.39)	-2.75, 2.86	0.97	0.00 (0.06)	-0.13, 0.13	0.98
BMI, kg/m ²	5.69 (1.57)	2.53, 8.85	0.001	0.27 (0.07)	0.12, 0.41	0.001
FFMI, kg/m ²	13.4 (3.54)	6.27, 20.5	<0.001	0.63 (0.16)	0.31, 0.96	<0.001
Pack years, n	-0.56 (0.31)	-1.17, 0.06	0.08	-0.03 (0.01)	-0.05, 0.00	0.09
FEV ₁ , L	17.5 (8.07)	1.27, 33.8	0.04	0.81 (0.37)	0.06, 1.56	0.04
FVC, L	15.4 (7.59)	0.10, 30.7	0.05	0.74 (0.35)	0.04, 1.45	0.04
FEV ₁ /FVC ratio	0.83 (0.55)	-0.28, 1.94	0.14	0.04 (0.03)	-0.02, 0.09	0.16
VC, L	16.3 (7.91)	0.34, 32.2	0.05	0.78 (0.36)	0.05, 1.52	0.04
TLC, L	11.9 (6.83)	-1.89, 25.7	0.09	0.58 (0.31)	-0.05, 1.22	0.07
RV, L	1.99 (8.94)	-16.0, 20.0	0.83	0.11 (0.41)	-0.72, 0.94	0.79
RV/TLC ratio	-0.68 (0.83)	-2.36, 1.01	0.42	-0.03 (0.04)	-0.11, 0.05	0.42
IC, L	19.8 (9.47)	0.70, 38.9	0.04	0.91 (0.44)	0.03, 1.79	0.04
ERV, L	1.99 (12.9)	-24.1, 28.1	0.88	0.17 (0.60)	-1.04, 1.37	0.78
DLCO, mmol/ min/kPa	13.2 (3.32)	6.53, 19.9	<0.001	0.62 (0.15)	0.31, 0.92	<0.001
KCO, mmol/ min/kPa/L	92.2 (25.8)	40.2, 144	0.001	4.25 (1.20)	1.84, 6.65	0.001
PI-950, %	-3.53 (1.43)	-6.42, -0.63	0.02	-0.16 (0.07)	-0.30, -0.03	0.02
15 th percentile, HU	0.80 (0.39)	0.02, 1.59	0.05	0.04 (0.02)	0.00, 0.07	0.04
Areal BMD, g/ cm ²						
Femoral neck	318 (37.0)	243, 392	<0.001	14.7 (1.71)	11.3, 18.1	<0.001
Total hip	236 (25.4)	185, 288	<0.001	10.9 (1.17)	8.57, 13.3	<0.001
L1-L4	196 (26.6)	143, 250	<0.001	9.11 (1.23)	6.64, 11.6	<0.001

Two sided p-values ≤0.05 are considered statistically significant.

B=unstandardized regression coefficient; BMD=bone mineral density; BMI=body mass index; CI=confidence interval; DLCO=diffusion capacity for carbon monoxide; ERV=expiratory reserve volume; FEV₁=forced expiratory volume in 1 second; FFMI=fat free mass index; FVC=forced vital capacity; HU=Hounsfield units; IC=inspiratory capacity; KCO=transfer coefficient for carbon monoxide; PI-950=pixel index for -950 Hounsfield units; RV=residual volume; TLC=total lung capacity; VC=vital capacity.

e-Table 3. Predictors of bone stiffness and failure load of the distal radius in the COPD subjects

	Radius					
	Stiffness, kN/mm			Failureload, kN		
	B (SE)	95% CI	p	B (SE)	95% CI	p
Age, yrs	-0.69 (0.76)	-2.25, 0.86	0.37	-0.03 (0.04)	-0.11, 0.04	0.37
BMI, kg/m ²	2.33 (0.83)	0.62, 4.03	0.009	0.11 (0.04)	0.03, 0.19	0.01
FFMI, kg/m ²	6.13 (1.83)	2.38, 9.89	0.002	0.29 (0.09)	0.12, 0.47	0.002
Pack years, n	0.05 (0.21)	-0.38, 0.49	0.81	0.00 (0.01)	-0.02, 0.02	0.86
FEV ₁ , L	12.6 (8.29)	-4.38, 29.6	0.14	0.68 (0.38)	-0.11, 1.47	0.09
FVC, L	6.60 (5.11)	-3.86, 17.1	0.21	0.35 (0.24)	-0.14, 0.84	0.16
FEV ₁ /FVC ratio	0.51 (0.47)	-0.44, 1.46	0.28	0.03 (0.02)	-0.02, 0.07	0.23
VC, L	7.54 (5.08)	-2.87, 17.9	0.15	0.39 (0.24)	-0.09, 0.88	0.11
TLC, L	5.45 (3.98)	-2.73, 13.6	0.18	0.29 (0.18)	-0.09, 0.67	0.13
RV, L	2.47 (5.94)	-9.73, 14.7	0.68	0.13 (0.28)	-0.44, 0.70	0.64
RV/TLC ratio	-0.37 (0.62)	-1.64, 0.89	0.55	-0.02 (0.03)	-0.08, 0.04	0.50
IC, L	4.77 (6.13)	-7.84, 17.4	0.44	0.29 (0.29)	-0.30, 0.87	0.33
ERV, L	7.34 (7.44)	-7.95, 22.6	0.33	0.33 (0.35)	-0.38, 1.05	0.35
DLCO, mmol/ min/kPa	7.45 (2.41)	2.52, 12.4	0.004	0.37 (0.11)	0.14, 0.60	0.002
KCO, mmol/ min/kPa/L	45.0 (16.6)	11.1, 78.9	0.01	2.18 (0.77)	0.60, 3.76	0.009
PI-950, %	-1.44 (0.82)	-3.14, 0.25	0.09	-0.07 (0.04)	-0.15, 0.01	0.07
15 th percentile, HU	0.57 (0.27)	0.01, 1.14	0.05	0.03 (0.01)	0.00, 0.05	0.04
Areal BMD, g/ cm ²						
Femoral neck	106 (29.2)	45.7, 166	0.001	5.10 (1.36)	2.32, 7.88	0.001
Total hip	88.2 (20.3)	46.5, 130	<0.001	4.21 (0.95)	2.27, 6.15	<0.001
L1-L4	74.4 (20.1)	33.3, 116	0.001	3.51 (0.94)	1.57, 5.44	0.001

Two sided p-values ≤0.05 are considered statistically significant.

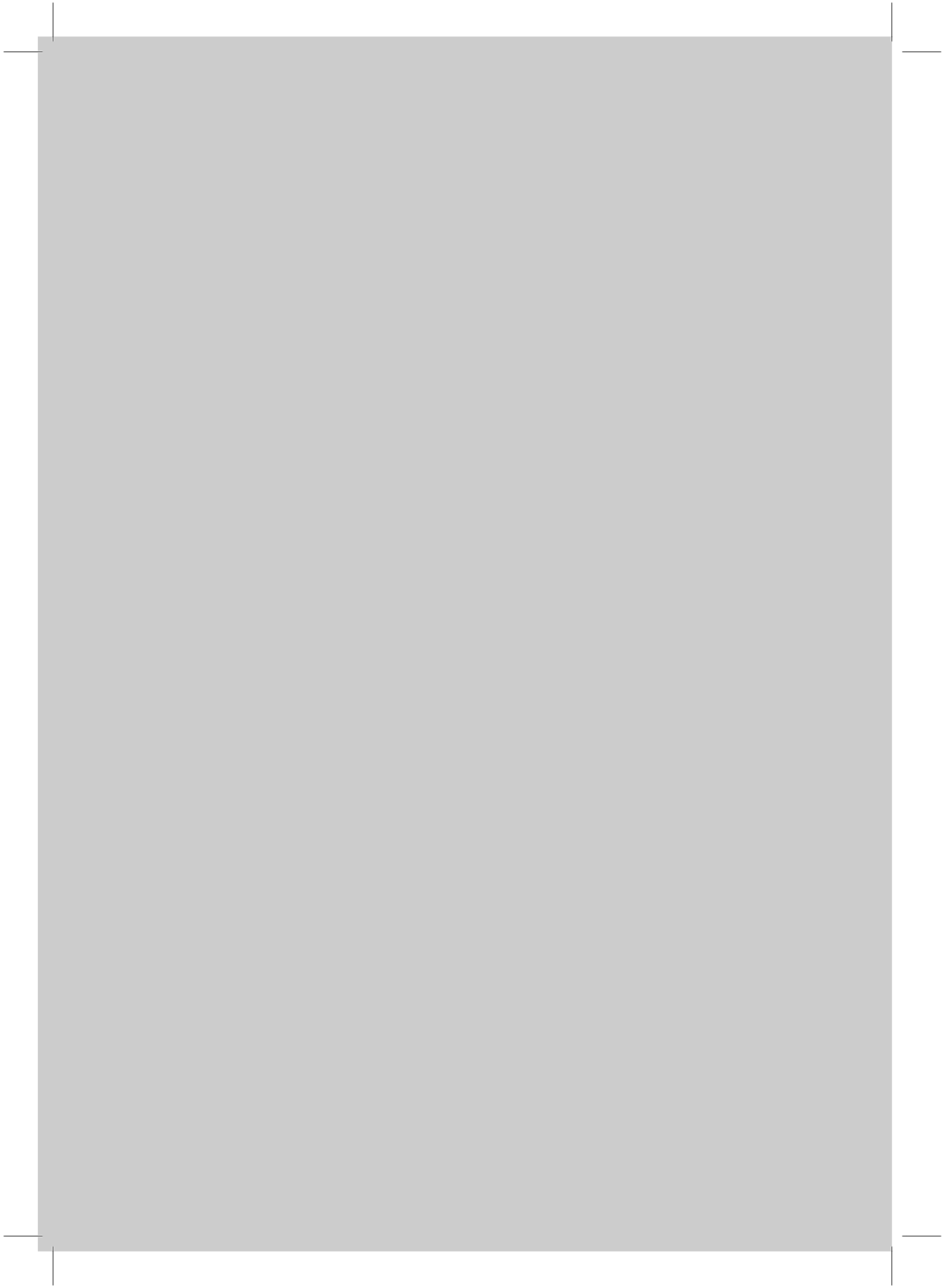
B=unstandardized regression coefficient; BMD=bone mineral density; BMI=body mass index; CI=confidence interval; DLCO=diffusion capacity for carbon monoxide; ERV=expiratory reserve volume; FEV₁=forced expiratory volume in 1 second; FFMI=fat free mass index; FVC=forced vital capacity; HU=Hounsfield units; IC=inspiratory capacity; KCO=transfer coefficient for carbon monoxide; PI-950=pixel index for -950 Hounsfield units; RV=residual volume; TLC=total lung capacity; VC=vital capacity.

e-Table 4. Predictors of bone stiffness and failure load of the distal tibia in the COPD subjects

	Tibia					
	Stiffness, kN/mm			Failureload, kN		
	B (SE)	95% CI	p	B (SE)	95% CI	p
Age, yrs	0.35 (1.47)	-2.65, 3.36	0.81	0.01 (0.07)	-0.13, 0.15	0.85
BMI, kg/m ²	5.18 (1.50)	2.10, 8.25	0.002	0.24 (0.07)	0.10, 0.39	0.002
FFMI, kg/m ²	13.1 (3.33)	6.22, 19.9	0.001	0.62 (0.16)	0.30, 0.94	<0.001
Pack years, n	-0.23 (0.40)	-1.05, 0.60	0.58	-0.01 (0.02)	-0.05, 0.03	0.59
FEV ₁ , L	33.5 (15.1)	2.50, 64.5	0.04	1.63 (0.71)	0.19, 3.07	0.03
FVC, L	9.70 (9.84)	-10.5, 29.9	0.33	0.52 (0.46)	-0.42, 1.46	0.27
FEV ₁ /FVC ratio	1.78 (0.84)	0.07, 3.50	0.04	0.08 (0.04)	0.00, 0.16	0.05
VC, L	12.0 (9.78)	-8.05, 32.0	0.23	0.62 (0.46)	-0.32, 1.55	0.19
TLC, L	8.93 (7.33)	-6.14, 24.0	0.23	0.47 (0.34)	-0.23, 1.17	0.18
RV, L	5.56 (10.8)	-16.7, 27.9	0.61	0.29 (0.51)	-0.75, 1.33	0.57
RV/TLC ratio	-0.42 (1.13)	-2.75, 1.90	0.71	-0.02 (0.05)	-0.13, 0.09	0.68
IC, L	20.2 (10.6)	-1.70, 42.1	0.07	0.96 (0.50)	-0.06, 1.98	0.06
ERV, L	-8.98 (13.8)	-37.2, 19.3	0.52	-0.32 (0.64)	-1.64, 1.00	0.62
DLCO, mmol/ min/kPa	17.7 (4.12)	9.25, 26.2	<0.001	0.84 (0.19)	0.44, 1.23	<0.001
KCO, mmol/ min/kPa/L	116 (27.8)	59.6, 173	<0.001	5.38 (1.31)	2.69, 8.07	<0.001
PI-950, %	-3.82 (1.54)	-7.02, -0.62	0.02	-0.18 (0.07)	-0.33, -0.03	0.02
15 th percentile, HU	1.23 (0.54)	0.11, 2.35	0.03	0.06 (0.03)	0.01, 0.11	0.03
Areal BMD, g/ cm ²						
Femoral neck	272 (43.8)	182, 361	<0.001	12.6 (2.07)	8.37, 16.9	<0.001
Total hip	215 (29.4)	154, 275	<0.001	9.95 (1.40)	7.08, 12.8	<0.001
L1-L4	178 (32.5)	111, 244	<0.001	8.29 (1.53)	5.17, 11.4	<0.001

Two sided p-values ≤0.05 are considered statistically significant.

B=unstandardized regression coefficient; BMD=bone mineral density; BMI=body mass index; CI=confidence interval; DLCO=diffusion capacity for carbon monoxide; ERV=expiratory reserve volume; FEV₁=forced expiratory volume in 1 second; FFMI=fat free mass index; FVC=forced vital capacity; HU=Hounsfield units; IC=inspiratory capacity; KCO=transfer coefficient for carbon monoxide; PI-950=pixel index for -950 Hounsfield units; RV=residual volume; TLC=total lung capacity; VC=vital capacity.





Chapter 8

General discussion and future perspectives

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Previous chapters of this thesis gave an overview of the current literature on osteoporosis in COPD, described an algorithm for measuring bone attenuation on chest CT, associated CT-measured bone attenuation with clinical features of COPD, and compared structural and mechanical parameters of bone between men with and without COPD. In this chapter, we will discuss the main findings of this thesis and future perspectives.

VITAMIN D AND COPD

Vitamin D deficiency was found in the majority of COPD patients and related with airflow obstruction (chapter 3). Several factors might contribute to increased vitamin D deficiency in COPD patients, including poor diet, less exposure to sun light, renal dysfunction, accelerated skin aging or increased catabolism by corticosteroids.¹ On the other hand, vitamin D deficiency might contribute to impaired lung function, due to osteoporosis-related vertebral fractures, an altered host defense of the lung resulting in COPD exacerbations, or direct effects on the extracellular matrix homeostasis within the lung.²⁻⁴ Recently, vitamin D supplementation was shown to reduce COPD exacerbations in subjects with vitamin D concentrations below 10 ng/mL.⁵

Lower plasma vitamin D concentrations were related with lower bone mineral density and poor functional exercise capacity in a COPD cohort (chapter 3). Although the role of vitamin D in bone health is well-established,¹ its role in skeletal muscle function is less clear. Previous cross-sectional and longitudinal data on the effects of vitamin D on skeletal muscle function have been conflicting, probably due to heterogeneity in vitamin D doses, duration of treatment, or methods used for assessing skeletal muscle function.⁶⁻¹⁰ A review of the literature indicated that vitamin D might affect skeletal muscle function through the binding of 1,25-hydroxyvitamin D to vitamin D receptor, resulting in muscle growth and other adaptations.^{11,12}

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Since vitamin D deficiency might influence lung function and several COPD-related comorbidities,^{4,10,13} additional research on the role of vitamin D in COPD is warranted. Future randomised controlled trials in COPD patients should be focussed on the effects of vitamin D supplementation on lung function, skeletal muscle function, bone strength, cardiovascular disease, COPD exacerbations and mortality. In addition, these trials should explore interactions between baseline plasma vitamin D concentrations, polymorphisms in the vitamin D receptor and clinical outcomes. Trials investigating the effects of vitamin D supplementation on skeletal muscle function, exacerbations, lung function and pneumonia are underway (clinicaltrials.gov).

CT SCANNING OF THE CHEST

CT scans of the chest are frequently performed in COPD patients. In addition to information on pulmonary diseases, chest CT might provide useful information on markers of cardiovascular

disease (e.g. coronary artery calcium and thoracic aortic calcium) and osteoporosis.¹⁴ Chapter 4 described an algorithm for measuring bone attenuation of the thoracic vertebrae on routine chest CT in a COPD cohort. This study showed that simple attenuation measurement of the thoracic vertebrae on chest CT had a good reproducibility and correlated strongly with bone mineral density measurement on DXA.

In chapters 5 and 6, routine chest CT was used to assess extent of emphysema, markers of cardiovascular disease and bone attenuation of the thoracic vertebrae in two large cohorts. In the ECLIPSE cohort, older age, lower fat free mass index and higher coronary artery calcium were independently associated with lower CT-measured bone attenuation (chapter 5). In a Scottish cohort, higher coronary artery calcium was independently associated with lower CT-measured bone attenuation, and, additionally, all-cause mortality was predicted by coronary artery calcium, thoracic aortic calcium and extent of emphysema (chapter 6).

Since chest CT provides useful information on several COPD-related comorbidities, chest CT might contribute to identification of various CT phenotypes.^{14,15} Previous studies have already demonstrated that chest CT provides useful information on extent of emphysema, airway wall dimensions, pulmonary nodules, markers of cardiovascular disease, bone density of the thoracic vertebrae, vertebral fractures and kyphotic angle.^{14,16-19} This information might lead to a more accurate phenotyping of individuals with COPD and, hence, to better personalised treatment.

Although information on COPD-related comorbidities seems to be readily available on chest CT without additional patient time or radiation exposure, radiological evaluation will be extended, which will add a modest amount of costs. In addition, variation across scanners, scanning protocols, evaluation techniques and software is likely to lead to a high variability in outcome measures. Therefore, additional research is needed to develop automated computer-aided evaluation tools and to standardise assessment methods before integrated imaging on chest CT can be implemented in clinical practice.

BONE IMAGING AND STRENGTH

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A strong predictor of non-traumatic fractures is bone mineral density, which nowadays is considered the gold standard for diagnosing osteoporosis.^{20,21} However, other properties of bone might contribute to non-traumatic fractures, since vertebral fractures can also occur in COPD patients with normal bone density or osteopenia.²² Indeed, bone strength is influenced by several material and structural properties of bone, including bone mineral density, composition and number of collagen cross-links, micro- and macrostructure of bone and burden of micro damages.²³

Several other methods have been developed to assess bone strength and predict non-traumatic fractures.²⁴ Vertebral fracture assessment on X-rays of the spine was shown to reflect microarchitectural deterioration²⁵ and predict incidental vertebral fractures,²⁶ and can therefore be used to predict future fractures. One of the most promising techniques is

High-Resolution peripheral Quantitative Computed Tomography (HR-pQCT). With HR-pQCT, structural parameters of bone can be assessed and mechanical parameters of bone can be estimated using micro-finite element analysis (μ FEA).²⁴ These structural and mechanical parameters have been shown to be superior to bone mineral density in discriminating between subjects with and without fractures.²⁷

Previous studies on osteoporosis in COPD patients have mainly used bone mineral density measurement and vertebral fracture assessment for diagnosing osteoporosis and predicting future fractures.²⁸ In chapter 7, structural and mechanical parameters of bone were assessed on HR-pQCT images in men with and without COPD. Since this pilot study could not detect any differences in structural or mechanical parameters of bone between men with and without COPD after adjustment for bone mineral density, bone structure and strength appear to be comparable between subjects with and without COPD. However, after adjustment for bone mineral density, mechanical parameters of bone were related with fat free mass index and gas transfer capacity of the lung. These findings might suggest that disease-specific factors contribute to loss of bone strength in COPD patients.

Since bone strength is influenced by several properties of bone, future research on osteoporosis in COPD should not be focussed on bone mineral density alone. Structural and mechanical parameters assessed on HR-pQCT have already shown promising results in non-COPD patients.²⁹ Therefore, future research on osteoporosis in COPD should be focussed on structural and mechanical parameters of bone. Hopefully, this will lead to more insight into the pathophysiologic mechanisms of osteoporosis in COPD and, consequently, to improved treatment of osteoporosis in COPD.

FINAL CONCLUSIONS AND RECOMMENDATIONS

This thesis has resulted in the following conclusions and recommendations:

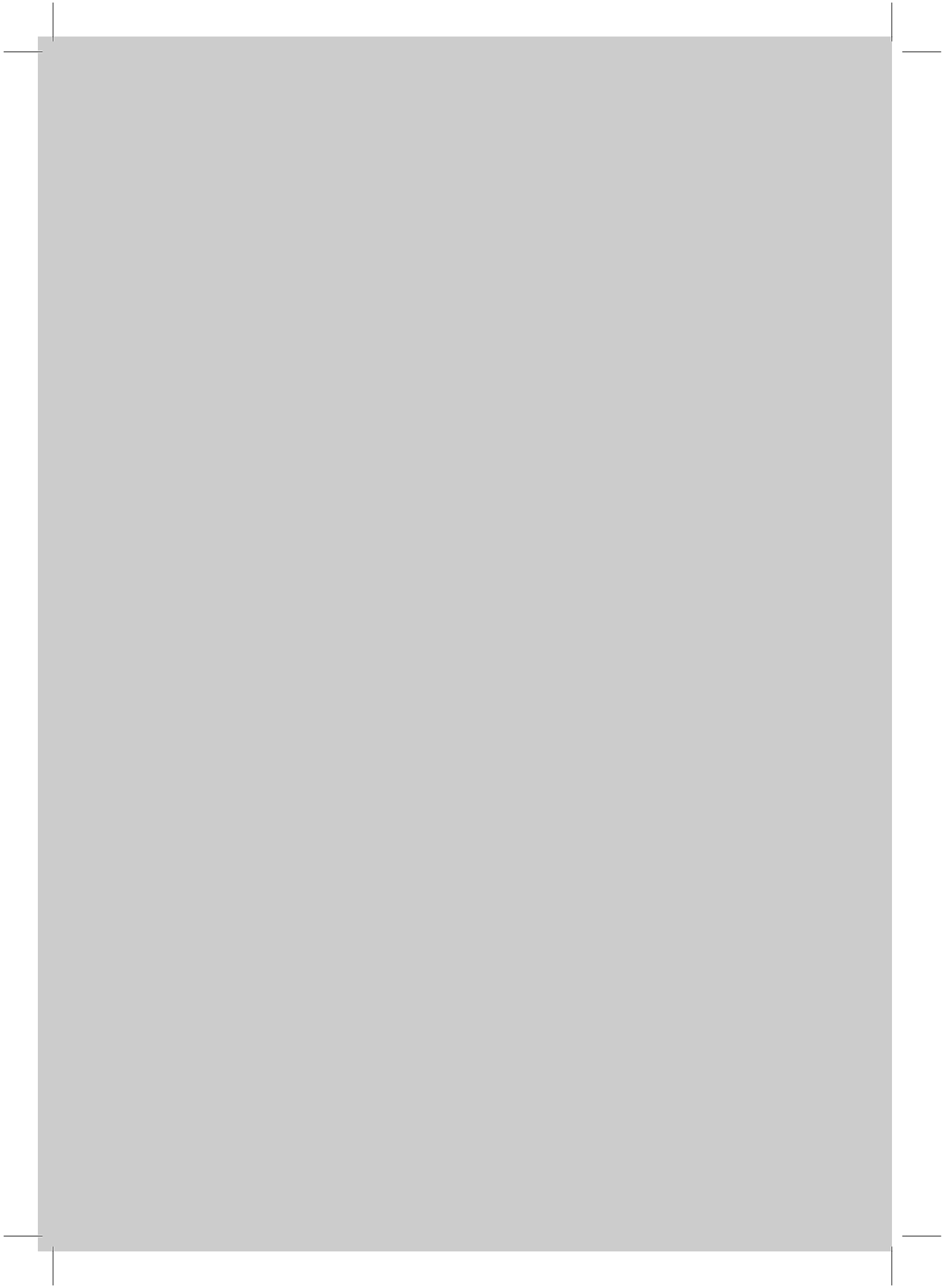
1. Osteoporosis is highly prevalent and largely under-diagnosed in COPD patients. COPD patients at risk for osteoporosis include older patients, patients with low body or muscle mass, patients who are less physically active, patients who use corticosteroids, patients with vitamin D deficiency, patients with a high number of pack years smoked and patients with high alcohol consumption.
2. Vitamin D deficiency is found in the majority of COPD patients and is related with impaired lung function, osteoporosis and poor physical activity. Future research on COPD should be focussed on vitamin D as the target of treatment for both pulmonary and extrapulmonary manifestations of COPD.
3. A new algorithm was introduced to assess bone attenuation of the thoracic vertebrae on routine chest CT. This algorithm had a good reproducibility and was strongly correlated with bone mineral density measurement on DXA.
4. Chest CT provides useful information on COPD and several related comorbidities, such as markers of cardiovascular disease, emphysema, pulmonary nodules and bone health. Therefore, chest CT might be useful for integrated imaging in COPD patients.

5. Future research on osteoporosis in COPD should be focussed on structural and mechanical parameters of bone. Although in our pilot study structural and mechanical parameters of bone were similar in men with and without COPD, mechanical parameters of bone were related with disease-specific features, including fat free mass index and gas transfer capacity of the lung.

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Chapter 9

Summary of this thesis / Samenvatting van dit proefschrift

SUMMARY OF THIS THESIS

This thesis primarily focused on diagnostic imaging and risk factors of osteoporosis in COPD. The main objectives of this thesis were 1) to give an overview of the current literature on osteoporosis in COPD; 2) to develop a new algorithm for measuring bone density on routine chest CT; 3) to study associations between CT-measured bone attenuation and clinical features of COPD; and 4) to study structural and mechanical parameters of bone in subjects with and without COPD. In this chapter, we will provide an overview of the main findings of this thesis.

Chapter 2 gives an overview of the current literature on osteoporosis in COPD. Osteoporosis is frequently seen in COPD patients. The prevalence of osteoporosis is around 33% in COPD patients, compared with 11% in controls matched for age. Risk factors of osteoporosis in COPD patients include older age, low body or muscle mass, physical inactivity, tobacco smoking, alcohol use and vitamin D deficiency. In addition to these risk factors, COPD-specific factors, such as the use of corticosteroids and systemic inflammation, might contribute to the development of osteoporosis in COPD patients.

The gold standard for diagnosing osteoporosis is dual energy X-ray absorptiometry (DXA). In addition to DXA, vertebral fracture assessment might be helpful to identify COPD patients at risk of fracture. Vertebral fractures reflect the severity of microarchitectural deterioration and are related with a high annual number of incidental vertebral fractures. The clinical technique of choice for diagnosing vertebral fractures is the Genant visual semi-quantitative method.

Management of osteoporosis is primarily focused on preventing osteoporosis-related fractures. Since osteoporosis is frequently seen in COPD patients, (chest) physicians should inform all COPD patients about the benefits of a healthy diet, physical activity and smoking cessation. In addition, COPD patients at risk of osteoporosis, but preferably all COPD patients, should be screened for osteoporosis using DXA and vertebral fracture assessment, and, if necessary, treatment of osteoporosis should be initiated (e.g. calcium and vitamin D supplementation, bisphosphonates). Moreover, all COPD patients who use corticosteroids should be treated according to the guidelines for management of corticosteroid-induced osteoporosis.

Chapter 3 describes associations between vitamin D, bone mineral density, skeletal muscle strength and functional exercise capacity in patients with moderate to very severe COPD entering pulmonary rehabilitation. Vitamin D deficiency was found in the majority of COPD patients and increased with more severe airflow obstruction. In addition, plasma vitamin D concentrations were related with bone mineral density and functional exercise capacity.

Chapter 4 describes an algorithm for measuring bone attenuation of the thoracic vertebrae on routine chest CT in COPD patients. This algorithm had a good reproducibility. In addition,

bone attenuation of the thoracic vertebrae on chest CT was strongly correlated with bone mineral density of the hip and lumbar spine on DXA. Therefore, bone attenuation measurement on routine chest CT might be useful for assessing bone density.

In **chapters 5 and 6**, routine chest CT was used to assess bone attenuation of the thoracic vertebrae in two large cohorts. In the ECLIPSE cohort (chapter 5), CT-measured bone attenuation was lower in COPD subjects than in smoker and non-smoker controls. In the COPD subjects, older age, lower fat free mass index and higher coronary artery calcium were independently associated with lower CT-measured bone attenuation. In addition, lower CT-measured bone attenuation was associated with a lower rate of decline in FEV₁ and higher exacerbation and hospitalisation rates, but was not associated with all-cause mortality. In a Scottish cohort (chapter 6), increased coronary artery calcium was associated with increased arterial stiffness and lower CT-measured bone attenuation. In addition, coronary artery calcium, thoracic aortic calcium and extent of emphysema were associated with all-cause mortality, while arterial stiffness and bone attenuation were not associated with all-cause mortality.

Chapter 7 describes a pilot study on structural and mechanical parameters of bone in men with and without COPD. This study could not detect any differences in bone structure, stiffness and failure load between men with and without COPD after stratification for bone mineral density. In men with COPD, fat free mass index and gas transfer capacity of the lung were related with bone stiffness and failure load after adjustment for bone mineral density.

Chapter 8 discusses the main findings of this thesis and future perspectives. The main conclusions of this thesis can be summarised as follows:

1. Osteoporosis is highly prevalent and remains largely under-diagnosed in COPD patients.
2. Vitamin D deficiency is found in the majority of COPD patients and is associated with several COPD-related features.
3. Routine chest CT provides opportunities for measuring bone density in COPD patients.
4. Although structural and mechanical parameters of bone appear to be similar in men with and without COPD, mechanical parameters of bone might be related with disease specific features such as fat free mass index and gas transfer capacity of the lung.

SAMENVATTING VAN DIT PROEFSCHRIFT

Dit proefschrift is gericht op de diagnostiek van en risicofactoren voor osteoporose bij COPD patiënten. De doelstellingen van het proefschrift zijn: 1) het samenvatten van de huidige literatuur over osteoporose bij COPD patiënten; 2) het ontwikkelen van een algoritme voor het meten van de botdichtheid op een CT scan van de thorax; 3) het bestuderen van verbanden tussen de botdichtheid, gemeten op een CT scan van de thorax, en klinische uitkomstmaten van COPD; en 4) het bestuderen van de structurele en mechanische botparameters in deelnemers met en zonder COPD. In dit hoofdstuk worden de belangrijkste bevindingen van het proefschrift beschreven.

Hoofdstuk 2 geeft een overzicht van de huidige literatuur over osteoporose bij COPD. Osteoporose komt frequent voor bij patiënten met COPD. De prevalentie van osteoporose is ongeveer 33% bij COPD patiënten en ongeveer 11% bij gezonde leeftijdgenoten. Er zijn bij COPD patiënten verschillende risicofactoren voor osteoporose beschreven, zoals oudere leeftijd, laag lichaamsgewicht, weinig lichaamsbeweging, roken, alcoholgebruik en vitamine D deficiëntie. Behalve deze algemene risicofactoren, zijn er ook verschillende COPD gerelateerde risicofactoren beschreven, zoals het gebruik van corticosteroïden en systemische inflammatie.

De gouden standaard voor het diagnosticeren van osteoporose is dual energy X-ray absorptiometry (DXA). Het beoordelen van wervelfracturen op beeldvorming van de wervelkolom kan als aanvulling op DXA worden gebruikt. Wervelfracturen geven de ernst van de microarchitecturale beschadiging weer en zijn gerelateerd aan een hoog aantal nieuwe wervelfracturen in het eerste jaar na het ontstaan van een wervelfractuur. De gouden standaard voor het beoordelen van wervelfracturen is de visuele semikwantitatieve methode van Genant.

De behandeling van osteoporose is hoofdzakelijk gericht op het voorkómen van fracturen. Omdat osteoporose frequent voorkomt bij COPD patiënten, zouden alle COPD patiënten moeten worden voorgelicht over de positieve effecten van een gezond dieet rijk aan eiwitten en vitamine D, voldoende lichaamsbeweging en stoppen met roken. Bovendien zouden alle COPD patiënten met risicofactoren voor osteoporose, maar bij voorkeur alle COPD patiënten, moeten worden gescreeend op osteoporose door gebruik te maken van DXA scans en beeldvorming van de wervelkolom. Indien nodig moet gestart worden met een behandeling tegen osteoporose. De medicamenteuze behandeling van osteoporose kan bestaan uit calcium en vitamine D suppletie en een bisfosfonaat. Bovendien zouden alle COPD patiënten die corticosteroïden gebruiken, behandeld moeten worden volgens de richtlijn voor de preventie en behandeling van corticosteroïden geïnduceerde osteoporose.

Hoofdstuk 3 beschrijft de verbanden tussen vitamine D, botdichtheid, spierkracht en inspanningsvermogen bij patiënten met een matig tot zeer ernstig COPD die deelnemen aan een longrevalidatieprogramma. Vitamine D deficiëntie werd gevonden in het merendeel van de COPD patiënten. Het aantal patiënten met een vitamine D deficiëntie nam toe met de

ernst van de COPD. De plasma vitamine D concentratie was gerelateerd aan de botdichtheid en het inspanningsvermogen.

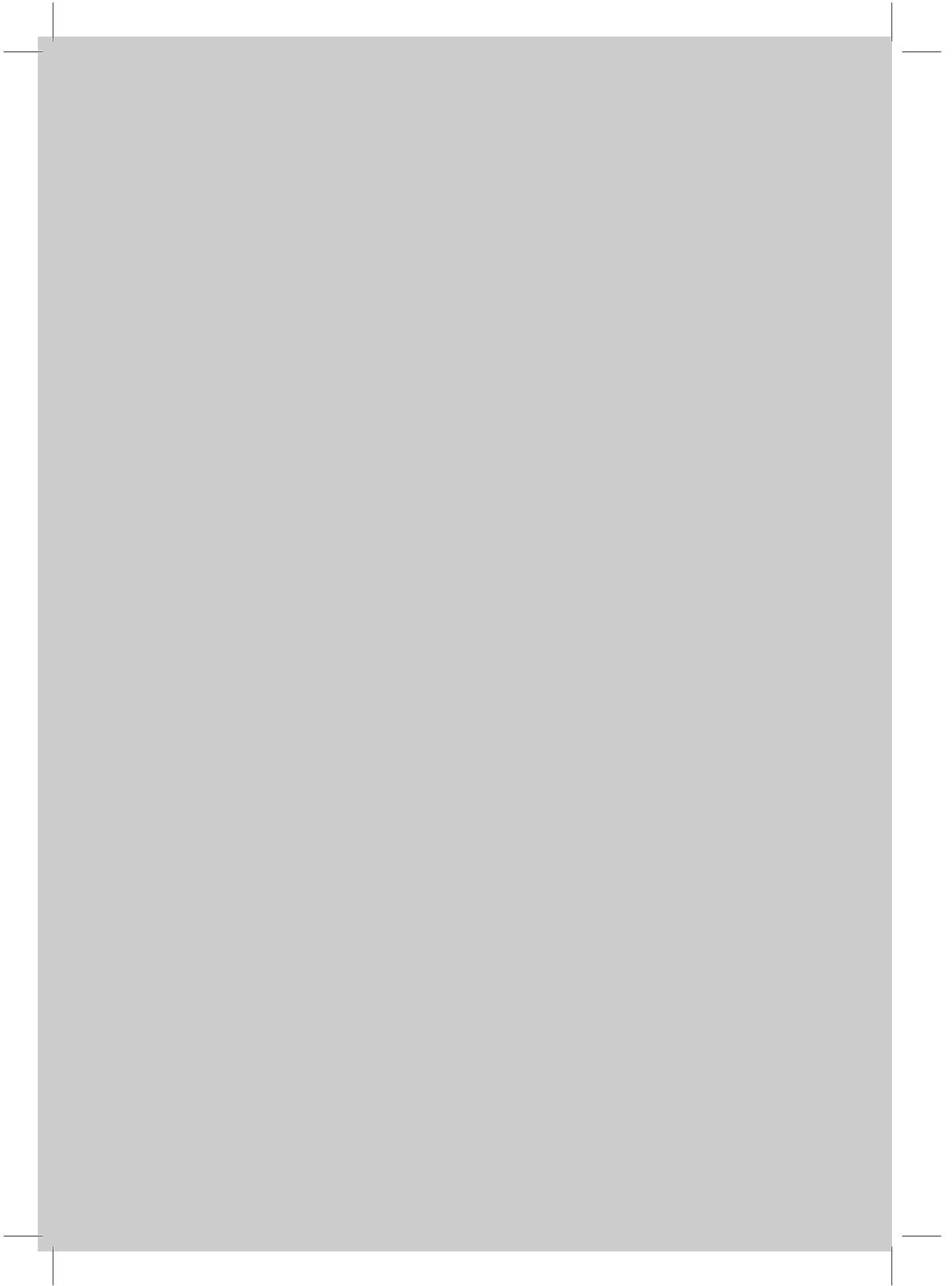
Hoofdstuk 4 beschrijft een algoritme voor het meten van de botdichtheid van de thoracale wervels op een CT scan van de thorax bij patiënten met COPD. Het algoritme had een goede reproduceerbaarheid. Daarnaast was de botdichtheid van de thoracale wervels op een CT scan sterk gecorreleerd met de botdichtheid van de heup en lumbale wervels op een DXA scan. Deze resultaten tonen dat een botdichtheidsmeting op een CT scan van de thorax kan worden gebruikt voor het bestuderen van botweefsel.

In **hoofdstuk 5 en 6** werden botdichtheidsmetingen verricht op CT scans van de thorax in twee verschillende onderzoeksgroepen. De data van de ECLIPSE studie (hoofdstuk 5) toonden dat COPD patiënten een lagere botdichtheid hadden dan gezonde rokers of niet-rokers. Bij de COPD patiënten waren een hogere leeftijd, lagere vet vrije massa index en hogere calciumscore van de coronairen geassocieerd met een lagere botdichtheid. Vervolgens was een lagere botdichtheid geassocieerd met een verminderde afname van de FEV₁, meer exacerbaties en meer ziekenhuisopnames. Een lagere botdichtheid was echter niet gerelateerd aan een hogere mortaliteit. Een studie in Schotland (hoofdstuk 6) toonde dat een verhoogde calciumscore van de coronairen geassocieerd was met een verhoogde stijfheid van de vaten en een lagere botdichtheid. Vervolgens waren de mate van emfyseem en de calciumscores van de coronairen en thoracale aorta gerelateerd aan de mortaliteit, terwijl de stijfheid van de vaten en de botdichtheid niet waren gerelateerd aan de mortaliteit.

Hoofdstuk 7 beschrijft een studie naar de verschillen in structurele en mechanische botparameters tussen mannen met en zonder COPD. In deze studie werden geen verschillen gevonden in de structuur, stijfheid en draagkracht van bot tussen mannen met en zonder COPD na stratificatie voor botdichtheid. Bij de mannen met COPD was de vet vrije massa index en diffusie capaciteit van de longen gerelateerd met de stijfheid en draagkracht van bot na correctie voor botdichtheid.

In **hoofdstuk 8** worden de belangrijkste bevindingen van dit proefschrift beschreven en bediscussieerd. De belangrijkste conclusies die op basis van dit proefschrift kunnen worden getrokken zijn:

1. Osteoporose komt frequent voor bij patiënten met COPD en wordt vaak niet, of pas laat, gediagnosticeerd.
2. Vitamine D deficiëntie wordt gevonden bij een groot deel van de COPD patiënten en is geassocieerd met verschillende COPD gerelateerde comorbiditeiten.
3. Een CT scan van de thorax kan gebruikt worden voor het meten van de botdichtheid bij COPD patiënten.
4. Ondanks dat de structurele en mechanische botparameters bij mannen met en zonder COPD vergelijkbaar zijn, blijken de mechanische botparameters toch gerelateerd te zijn aan ziekte specifieke factoren, zoals vet vrije massa index en diffusie capaciteit van de longen.



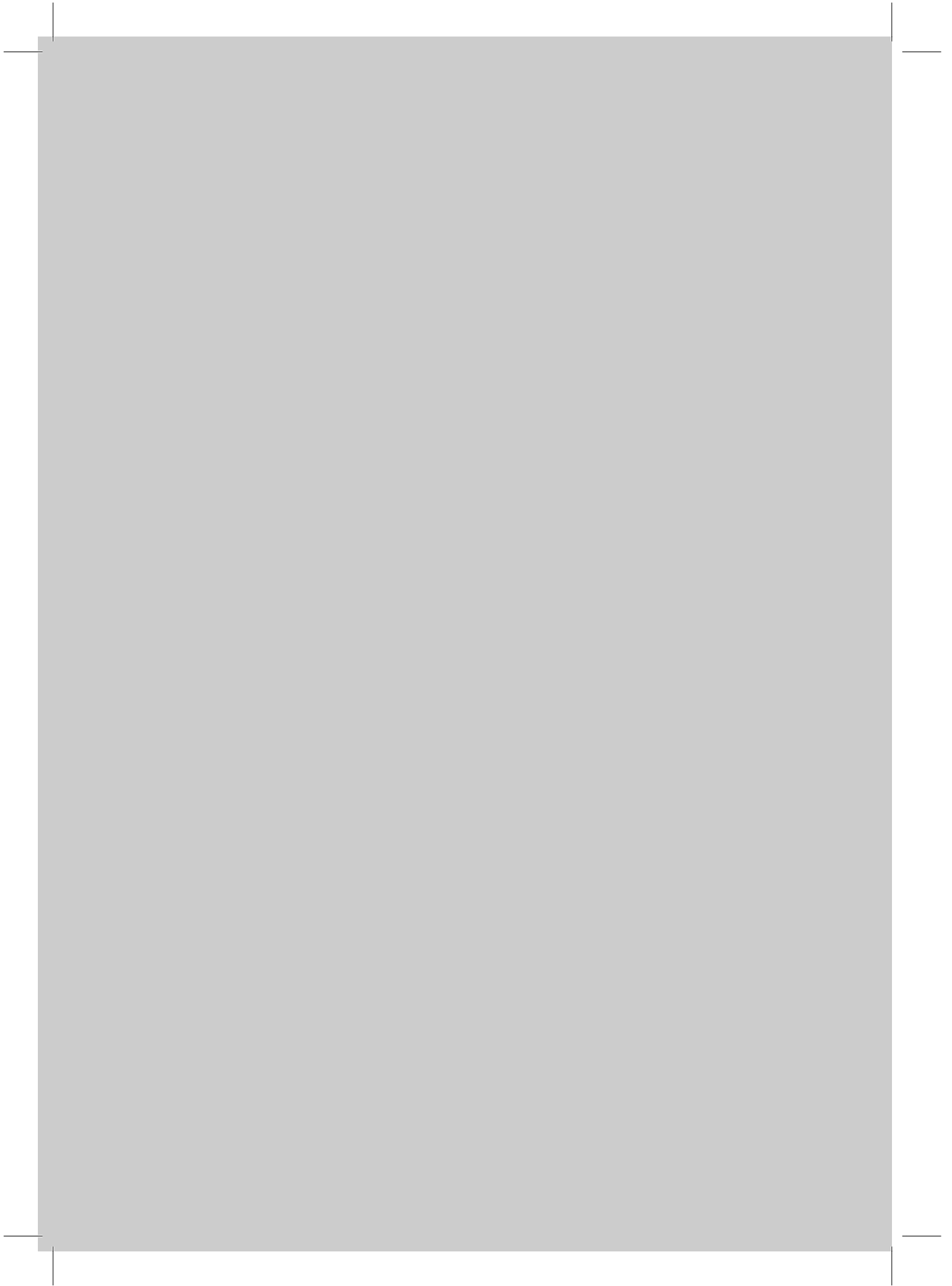


List of publications



List of publications

1. van de Schoot L, **Romme EA**, van der Sangen MJ, Creemers GJ, van Lijnschoten G, van Driel OJ, Rutten HJ, Nieuwenhuijzen GA. A highly active and tolerable neoadjuvant regimen combining paclitaxel, carboplatin, 5-FU, and radiation therapy in patients with stage II and III esophageal cancer. *Ann Surg Oncol* 2008; 15: 88-95.
2. **Romme EA**, Murchison JT, Phang KF, Jansen FH, Rutten EP, Wouters EF, Smeenk FW, Van Beek EJ, Macnee W. Bone attenuation on routine chest CT correlates with bone mineral density on DXA in patients with COPD. *J Bone Miner Res* 2012; 27: 2338-43.
3. **Romme EA**, Rutten EP, Smeenk FW, Spruit MA, Menheere PP, Wouters EF. Vitamin D status is associated with bone mineral density and functional exercise capacity in patients with chronic obstructive pulmonary disease. *Ann Med* 2013; 45: 91-6.
4. **Romme EA**, Murchison JT, Edwards LD, van Beek EJ, Murchison DM, Rutten EP, Smeenk FW, Williams MC, Wouters EF, Macnee W; on behalf of the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study investigators. CT-measured bone attenuation in patients with chronic obstructive pulmonary disease: relation to clinical features and outcomes. *J Bone Miner Res* 2013; 28: 1369-77.
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Dankwoord

DANKWOORD

Het is zover! Mijn proefschrift is klaar. Ondanks dat ik er met veel plezier aan heb gewerkt, ben ik blij dat het eindresultaat voor u ligt. Op deze plaats wil ik graag een aantal personen in het bijzonder bedanken.

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M. Connell. Dear Martin, many thanks for your great help and the lovely porridge meal you served me.

In de loop van het onderzoek werd de onderzoeksgroep uitgebreid met de volgende personen: prof. dr. J.P.W. van den Bergh, prof. dr. P. Geusens en dr. ir. B. van Rietbergen. Beste heren, bedankt voor jullie enthousiasme en kritische blik. Onze samenwerking heeft tot een mooie publicatie in Journal of Bone and Mineral Research geleid. Ik hoop dat er nog een paar mooie publicaties mogen volgen.

Het onderzoek is uitgevoerd met grote steun van de maatschap longgeneeskunde in het Catharina ziekenhuis.

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Een aantal data, die tijdens mijn onderzoeksperiode zijn verzameld, zijn nog niet geanalyseerd of gepubliceerd. Via deze weg wil ik de personen die hebben geholpen bij het includeren van proefpersonen en verzamelen van gegevens bedanken. De volgende personen wil ik graag in het bijzonder noemen.

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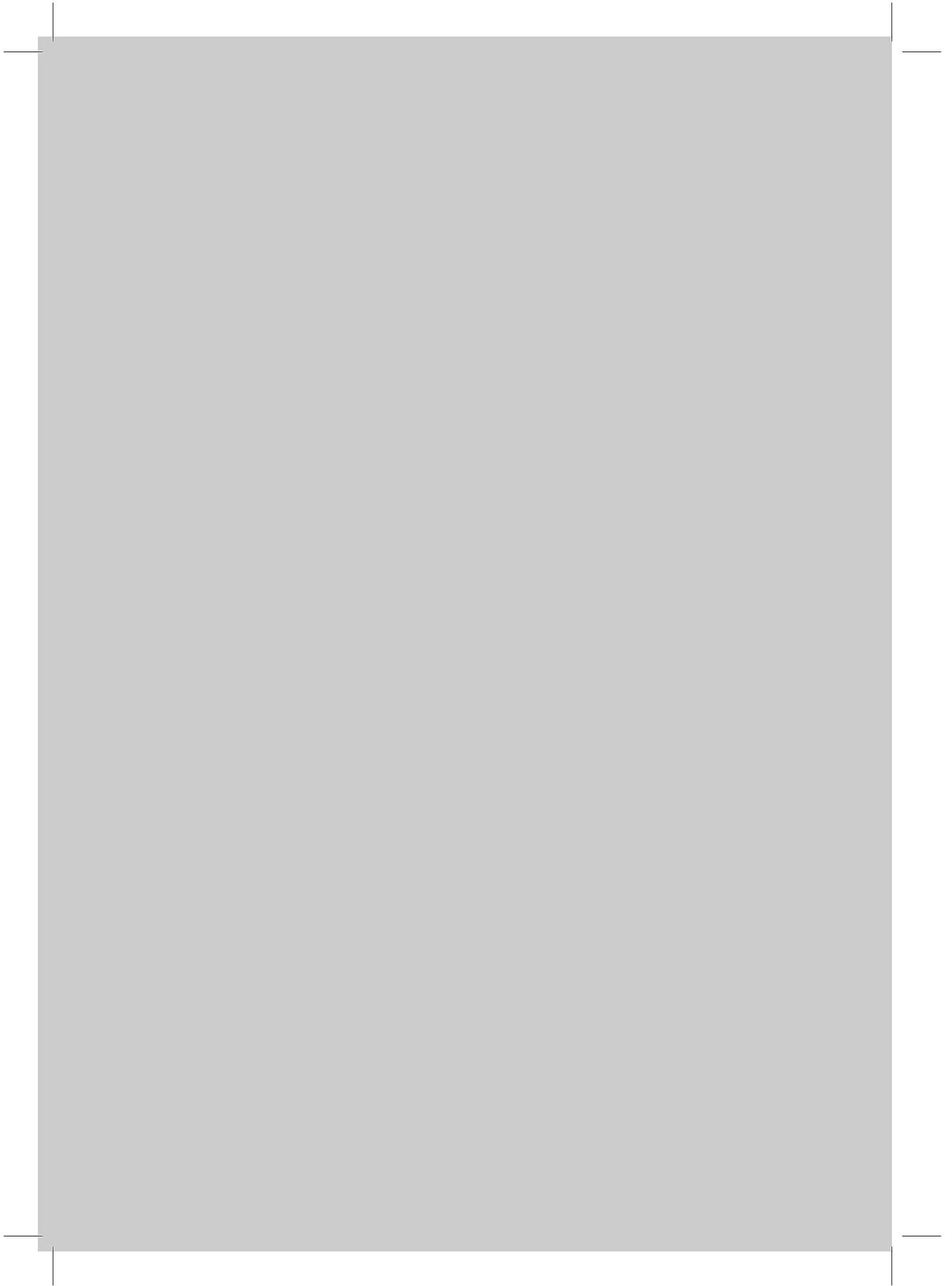
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Curriculum Vitae

De auteur van dit proefschrift werd geboren op 27 januari 1983 in Hooge Zwaluwe. In 2001 behaalde zij haar eindexamen Atheneum aan het Newmancollege in Breda en ging zij geneeskunde studeren aan de Universiteit Maastricht.

Tijdens haar opleiding geneeskunde was zij actief lid van de Maastrichtse Studenten Roeivereniging Saurus en werkte zij als student-assistent bij de capaciteitsgroep onderwijsontwikkeling en -research van de Universiteit Maastricht onder leiding van prof. dr. Lambert Schuwirth. In het laatste jaar van haar opleiding deed zij een wetenschappelijke stage op de afdeling chirurgie van het Catharina ziekenhuis onder leiding van prof. dr. Harm J.T. Rutten en publiceerde zij haar eerste artikel. In oktober 2007 behaalde zij haar artsdiploma en werkte zij achtereenvolgens als arts-assistent niet in opleiding tot specialist op de afdelingen intensive care, inwendige geneeskunde en longgeneeskunde van het Catharina ziekenhuis.

In mei 2009 begon zij met haar promotieonderzoek op de afdeling longgeneeskunde van het Catharina ziekenhuis. Zij werd begeleid door prof. dr. Emiel F.M. Wouters (Maastricht University Medical Centre*), prof. dr. Frank W.J.M. Smeenk (Catharina ziekenhuis) en dr. Erica P.A. Rutten (CIRO+ Horn). Tijdens haar promotieonderzoek ontving zij een ERS Short-Term Research Training Fellowship. Hiermee ging zij gedurende 3 maanden naar Edinburgh en werkte zij onder leiding van prof. dr. William MacNee (University of Edinburgh). De resultaten van haar promotie onderzoek werden gepresenteerd op verschillende nationale en internationale congressen en resulteerden in het winnen van verschillende prijzen (travel grant for best abstract on COPD tijdens ERS 2012, trainee research prize tijdens RSNA 2012 en de "Dr. Henk C. van Paassen prijs" tijdens de IWO bijeenkomst 2013) en dit proefschrift.

In december 2012 begon zij met haar opleiding tot longarts in het Catharina ziekenhuis onder leiding van prof. dr. Frank W.J.M. Smeenk.

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