Chapter 11
Vitamin D and Chronic Obstructive Pulmonary Disease

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Abstract Vitamin D is an important regulator of calcium and bone homeostasis. It is also involved in the regulation of different genes and cellular functions, particularly in the context of inflammation, regeneration and immune control. Conversely, vitamin D deficiency which is often found in chronic, infectious and inflammatory diseases is thought to drive or enhance uncontrolled inflammation. Chronic obstructive pulmonary disease (COPD) is characterized by chronic inflammation of the airways most often because of cigarette smoking. It has been recognized that repetitive airway infections and systemic consequences or co-morbidities also contribute to the progressive nature of COPD. Vitamin D deficiency is known to sneak in from the early stages of COPD, to become highly prevalent at the more severe stages, and may thereby catalyse airway infection, inflammation and systemic consequences. Undoubtedly, vitamin D deficiency enhances bone resorption and osteoporosis in COPD for which appropriate vitamin D supplementation is recommended. However, conflicting evidence has emerged on the extra-calcemic effects of vitamin D in COPD. A recent intervention trial with high-dose supplementation in COPD was only able to reduce exacerbation frequency in the subgroup of patients with lowest baseline vitamin D levels. It confirms that severe vitamin D deficiency is a health hazard but that more clinical and experimental studies are needed to explore how

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vitamin D deficiency may affect airway biology and systemic effects in the context of smoke-induced lung diseases.

Keywords COPD • Vitamin D • Vitamin D deficiency • Osteoporosis • Exacerbations • Randomized trial

Introduction

Over the last years, there is an increasing interest in the role of vitamin D and vitamin D deficiency in various chronic diseases. Besides the well-known effect of vitamin D deficiency on bone loss in adults, accumulating evidence also links a low vitamin D nutritional status to highly prevalent chronic illnesses, including cancers, autoimmune diseases, infectious and cardiovascular diseases [1–3]. Vitamin D is now known to have an important influence on immunoregulation and on the expression of antimicrobial peptides. Since patients with chronic obstructive pulmonary disease (COPD) often integrate all of these co-morbid diseases in one and given that most of COPD exacerbations are triggered by bacterial and viral infection, vitamin D could play a key role in the pathogenesis of this disease. This chapter aims to discuss the prevalence and determinants of vitamin D deficiency in COPD, the well-known effect of vitamin D in the development and treatment of COPD-associated osteoporosis and its potential role in the uncontrolled inflammatory cascade and systemic consequences of the disease.

Chronic Obstructive Pulmonary Disease

Definition

COPD is a chronic disease characterized by airflow limitation that is progressive, not fully reversible and associated with an abnormal inflammatory response of the lungs to noxious particles or gases. In Western countries, tobacco smoke is the major cause for COPD, accounting for 90–95% of the cases. Since only 20% of smokers develop severe COPD, other factors (biological, hereditary, environmental) must be involved [4]. Narrowing of the airways by inflammation, mucus production, irreversible remodelling and emphysema results in a limitation of expiratory airflow and disturbed gas exchange [5]. Currently, it is estimated that 210 million people suffer from COPD worldwide, a number that is still increasing. By 2020, the World Health Organization predicts that COPD will rise from the sixth to the third leading cause of death, next to only cardiovascular disease and cancer [6]. According to the Global Obstructive Lung Disease (GOLD)

definition, diagnosis of COPD should be based on spirometry measurements with a post-bronchodilator forced expiratory volume in 1 s over forced vital capacity ratio (FEV_1/FVC) below 0.7. Subsequently, COPD can be categorized in different stages of severity (GOLD stages) going from mild, moderate and severe to very severe disease according to FEV_1 [7]. It should be noted, however, that the majority of COPD patients, especially in the early stages of the disease, report no complaints, do not perform spirometry and thus are unaware of their disease. Treatment for COPD focuses on minimizing symptoms and preventing exacerbations. With the exception of smoking cessation, so far, no treatment has clearly proven to significantly modify COPD disease progression. Recent data, however, indicate that pharmacological intervention with inhalation therapy may slow down the yearly decline of FEV_1 [8–10].

Pathophysiology

The pathophysiology of COPD is characterized by an increased inflammatory response in the airways and parenchyma. Besides an increase in number of neutrophils, macrophages and T-lymphocytes, COPD is associated with elevated concentrations of various cytokines, including interleukins (IL-1, IL-6 and IL-8), tumour necrosis factor alpha (TNF-α), oxidative stress and the release of proteolytic enzymes. Cigarette smoke is known to cause a direct injury of the airway epithelial cells leading to the release of endogenous intracellular molecules or danger-associated molecular patterns (DAMPs). These signals are recognized by Toll-like receptors on epithelial cells which initiate a non-specific inflammatory response. As reaction on the release of early cytokines (TNF-α, IL-1, IL-8), macrophages, neutrophils and dendritic cells are recruited to the site of inflammation [11]. Proteolytic enzymes and reactive oxygen species are released which may cause further damage to the lung. Next, self-antigens and antigens coming from pathogens bound to dendritic cells can activate naive T cells into Th1 cells [12] and may lead to antibody producing B cells. This adaptive immune response may then further enhance the inflammatory cascade. In addition, the observed reduction of regulatory T cells (Treg) in COPD lungs against the rise of pro-inflammatory Th17 cells is pointing towards an impaired immune regulation in COPD [13].

Macrophages are believed to play a central role in the pathophysiology of COPD [14]. They are important sources of pro-inflammatory mediators but may also protect against infection by phagocytosis. In COPD, alveolar macrophages appear to be resistant to the anti-inflammatory effects of corticosteroids by the reduced activity of histone deacetylase 2 (HDAC2), a nuclear enzyme that switches off inflammatory genes activated by the nuclear factor NF-κB [15]. Additionally, Taylor and colleagues recently demonstrated that the phagocytotic capacity of macrophages of COPD patients is impaired, which may lead to bacterial colonization and increased

exacerbation frequency [16]. Overall, the complexity of the pathogenesis of COPD with different mechanisms and risk factors is reflected in the broad variation of clinical phenotypes.

COPD Exacerbations

With progression of the disease, as marked by a decline of forced expiratory volume in 1 s (FEV_1), COPD patients become more prone to exacerbations. An exacerbation of COPD is an acute worsening of respiratory symptoms which is associated with increased symptoms and worsening of lung function. Recent studies have shown that quality of life and health status of patients are mainly determined by the presence and frequency of such exacerbations which, in turn, may lead to a faster decline in FEV_1 [17]. Although viral and bacterial infections are assumed to be the major cause of exacerbations, other factors including environmental pollution and allergens have also been identified [18]. The exact role of bacterial infection in COPD exacerbations is often biased by bacterial colonization of the airways during stable state with the same organisms as those isolated at exacerbations: *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Different studies have shown that prevalence and load of organisms increases during an exacerbation [19], but recent evidence indicates that the acquisition of a new bacterial strain is likely the main trigger of an exacerbation [20, 21]. Besides bacterial infections, exacerbations may also be triggered by viral infections, including infections with *rhinoviruses*, *coronavirus*, *respiratory syncytial virus*, *influenza*, *parainfluenza* and *adenoviru*s. Moreover, recently, a frequent exacerbator phenotype has been identified suggesting that the innate and adaptive immune defence of the host also contributes to exacerbation susceptibility and that individualized therapy may become important in the nearby future [22].

Systemic Consequences/Co-Morbidities of COPD

COPD is not restricted to the lungs but also associated with systemic inflammation and increased co-morbidities which are now considered as important targets in the therapeutic approach of COPD. Increased systemic levels of TNF-α, IL-6 and C-reactive protein (CRP) are commonly found in patients with COPD [23]. Common co-morbidities of COPD include lung cancer, cardiovascular disease, osteoporosis, diabetes and skeletal muscle dysfunction [24, 25]. Whether these co-morbidities are caused by the underlying disease or just co-exist because of common risk factors such as smoking, ageing and inactivity is far from understood. Most likely, both mechanisms play together and the attractive hypothesis of inflammation in the lung "spilling over" into the systemic circulation and affecting other organs is corroborating this idea [26]. Whatever the mechanism may be, the presence of these co-morbidities clearly contributes to the poor outcome in COPD [27, 28].

COPD and Vitamin D

Vitamin D Metabolism

Vitamin D is generally obtained by photosynthesis in the skin but can also be derived from nutrition (fatty fish, fish liver oils and dairy products). Ultraviolet light catalyses the first step in the vitamin D biosynthesis, which is the conversion of 7-dehydrocholesterol into pre-vitamin D. The next step is a hydroxylation in the liver into 25-OHD, which then circulates in serum with a long half-life of 15 days. Next, 25-OHD is hydroxylated again into the active vitamin D metabolite $1,25(OH)_2D$ by 1α-hydroxylase (CYP27B1) in the kidney which is controlled by serum levels of calcium and phosphate and regulating hormones such as parathyroid hormone (PTH), calcitonin and phosphatonins. $1,25(OH)_2D$ also induces the expression of a 24-hydroxylase (CYP24A1) which catabolizes 25-OHD and $1,25(OH)_2D$ into biologically inactive, water-soluble metabolites, thereby serving as its own negative feedback. The majority of 25-OHD and $1,25(OH)_2D$ are bound to plasma proteins, of which more than 90% to the vitamin D binding protein (DBP), which carry out the delivery to their respective target organs [29]. $1,25(OH)_2D$ may thus bind to the nuclear vitamin D receptor (VDR) in the intestine, bone, kidney and parathyroid gland cells, resulting in the maintenance of normal serum calcium and phosphorus levels and their related effects on mineralization and turnover of bone [30, 31]. Since 1α-hydroxylase and the nuclear receptor VDR are widely present in cells of several extrarenal tissues such as skin, bone, prostate and immune cells, local $1,25(OH)_2D$ concentrations can also exert different autocrine and paracrine functions. Although the enzyme found here is identical to the one that is expressed in the kidney, its expression is regulated by immune signals instead of mediators of bone and calcium homeostasis [32, 33]. $1,25(OH)_2D$ mediates its effects by binding to the nuclear VDR The vitamin–VDR complex may then activate vitamin D response elements (VDRE) on genes involved in different cellular processes. It is estimated that about 3% of the mouse/human genome is regulated by vitamin D [34]. Directly or indirectly, vitamin D controls many genes that are involved in the regulation of cellular proliferation, differentiation and apoptosis of healthy and pathological cells.

Determinants of Vitamin D Deficiency

Because of its long half-life, 25-OHD is typically used to determine vitamin D status. It reflects vitamin D synthesized in the skin as well as that acquired from the diet and vitamin D degradation by catabolizing enzymes. When focusing on the calcemic effects, vitamin D insufficiency is best defined as a 25-OHD level below 20 ng/ml (50 nmol/l) [2, 35]. A sensitive parameter to determine vitamin D deficiency is serum levels of PTH. Older data have clearly demonstrated that levels of 25-OHD below 20 ng/ml are associated with an increase in PTH expression [36]. Based on

observational studies, several experts have suggested that, for non-calcemic effects, serum levels of at least 30 ng/ml (75 nmol/l) are required, but so far, intervention studies to support this are lacking.

Dietary sources of vitamin D are limited, and food fortification is mostly inadequate or nonexistent. Although sunlight is the most important source of vitamin D, several other factors can influence the amount of vitamin D that can be synthesized: season, latitude, clothing, the use of sunscreen, darker skin pigmentation and age. For example, ageing is associated with decreased concentrations of 7-dehydrocholesterol in the skin, thereby reducing the capacity to synthesize vitamin D. Even if regularly exposed to sunlight, elderly people produce 75% less cutaneous vitamin D than compared to young adults [36]. Due to cultural habits and clothing, even those who live in sunny climates are commonly found to be deficient in vitamin D. Data from the Third National Health and Nutrition Examination Survey (NHANES III) revealed that in US adults, only 30% of the white population and 5% of the African Americans had levels of vitamin D of at least 30 ng/ml [37]. According to the current definitions, it is estimated that more than one billion people worldwide have impaired serum levels of vitamin D. As current supplementation regimens with a daily dose of 800–1,000 IU of vitamin D restore deficient serum 25-OHD levels in a general adult population to concentrations above 20 ng/ml, higher doses are probably required to increase 25-OHD levels to even higher levels that may be needed for non-calcemic diseases in a population at risk [38, 39]. At present, we can only speculate on what such ideal target range of 25-OHD levels is to maximally exploit these extra-calcemic effects [40]. We should also acknowledge that an extensive expert analysis of the potential effects of vitamin D supplementation on the health outcome of North-American subjects concluded that there is presently insufficient evidence for extraskeletal benefits of vitamin D therapy and that only new randomized controlled trials will be able to define such effect [41].

Vitamin D Deficiency in COPD

COPD patients should be considered at high risk to become vitamin D deficient for a variety of reasons: lower food intake, reduced capacity for vitamin D synthesis of the skin by ageing and smoking, the absence of outdoor activity and sun exposure, impaired activation by renal dysfunction and a lower storage capacity in muscles or fat by wasting may all contribute to a defective vitamin D status in COPD [2].

In 2005, Black and colleagues who examined spirometric data from the Third National Health and Nutrition Examination Survey, a cross-sectional survey on 14,091 US civilians over 20 years of age, discovered an important link between vitamin D and spirometric data [42]. After adjustment for potential confounders, a strong relationship between serum levels of 25-OHD and pulmonary function, as assessed by FEV_1 and FVC, was found. Although a significant correlation with airway obstruction could not be found, the observed dose–response relationship suggested a causal link [43]. The observation that smoking African-Americans
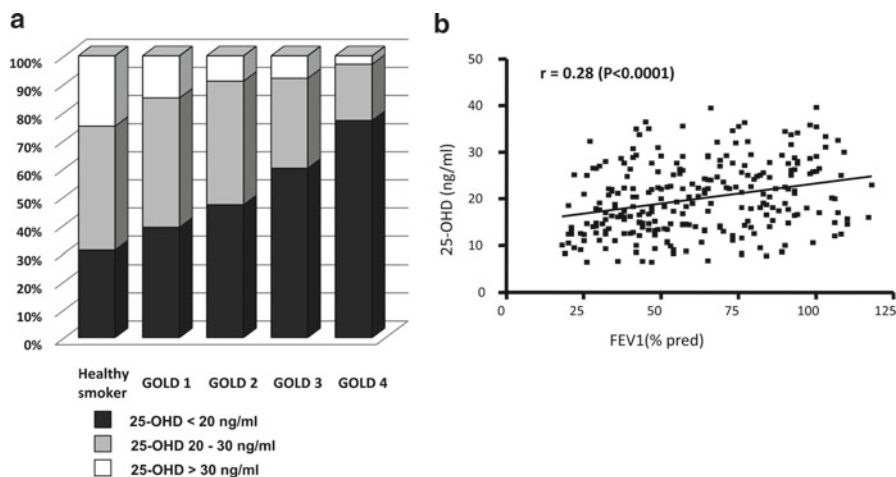
Fig. 11.1 (**a**) Cross-sectional assessment of 25-OHD levels in COPD patients and smoking controls. (**b**) Relationship between 25-OHD levels and FEV_1 (% pred) in COPD patients. Reprinted with permission from Janssens et al. [49]

more rapidly develop severe airflow obstruction as compared to Caucasians is also in agreement with the idea that a presumed lower vitamin D status in African-Americans correlates with an increased susceptibility to COPD [44]. Furthermore, different genetic variants involved in the vitamin D signalling pathway are shown to determine 25-OHD levels [45], and some of these variants have repeatedly been associated with COPD. For instance, variants of the DBP gene (*GC*) have been shown to be protective or risk factors for COPD [46], and a more recent robust candidate gene study in two large data sets identified the *GC* genes as susceptibility loci for COPD [47]. In a study of Forli and colleagues, vitamin D deficiency (<20 ng/ml) was found in more than 50% of a cohort waiting for lung transplantation [48], but they failed to compare vitamin D serum levels with a matched control group. However, we recently demonstrated in a group of 414 smoking individuals that patients with COPD were more likely to suffer from vitamin D deficiency than aged and gender-matched healthy control smokers without COPD [49]. In COPD patients, we found a significant association between vitamin D serum levels and severity of disease assessed by FEV_1. The prevalence of vitamin D deficiency defined by 25-OHD levels below 20 ng/ml increased to, respectively, 60% and 75% in severe (GOLD 3) and very severe COPD patients (GOLD 4) (Fig. 11.1). Interestingly, we also showed that 25-OHD levels were determined by genetic variants in the vitamin D binding gene (GC) after correcting for age, gender, smoking history and disease severity and that homozygous carriers of the rs7041 T allele with lowest vitamin D levels exhibited an increased risk for COPD. Although the risk effect of certain GC alleles may relate to a lower bioavailability of vitamin D, other authors have suggested that protein variants of DBP may directly affect inflammation in the airways [50]. Wood and colleagues, for instance, demonstrated that local DBP expression in sputum of COPD patients correlates with macrophage phagocytosis capacity

suggesting that the risk effect of DBP may be found in a different activation of macrophages [51].

A recent population based study in 2,943 individuals living in Hertfordshire (UK) found reduced vitamin D intake in the COPD subgroup of 521 individuals compared to the non-COPD subjects but was not able to confirm the positive association between 25-OHD serum levels and FEV_1 or FVC [52]. Surprisingly, Shaheen et al. found that patients with highest vitamin D levels were more likely to have COPD. They concluded that in contrast to a prudent dietary pattern with the intake of high amounts of antioxidants [53], vitamin D was not an important determinant for adult pulmonary function and risk of COPD. Unfortunately, more than 50% of their population was taking dietary vitamin D supplements for unspecified reasons, which may have affected their analysis and biased their conclusions. Finally, in a small sub-study of the Lung Health Study III conducted in 198 selected individuals, mean 25-OHD levels of COPD patients with a rapid FEV_1 decline were found to be similar to mean 25-OHD levels of patients with a slow decline, suggesting again that vitamin D deficiency does not contribute to COPD progression [54]. Together, from these conflicting data, it is clear that more prospective studies are needed to determine causal relationships between vitamin D deficiency and pulmonary function in COPD. But even if causality cannot be found for pulmonary function variables, vitamin D deficiency may still alter the disease course by affecting other outcomes such as respiratory tract infections or co-morbidities.

Vitamin D, Calcemic Effects and Osteoporosis

Low levels of vitamin D result in low bioavailability of calcium which stimulates parathyroid glands to increase secretion of PTH. In the kidneys, PTH reduces the reabsorption of phosphate from the proximal tubule and increases calcium reabsorption in the distal tubule, resulting in a net increase in calcium/phosphate ratio. PTH also induces renal 1α-hydroxylase expression which then leads to an increased production of active $1,25(OH)_2D$. $1,25(OH)_2D$ enhances intestinal calcium absorption and acts on the immature osteoblastic cells to stimulate osteoclastogenesis through the RANKL/RANK regulatory system, with enhanced bone resorption and mobilization of calcium from the bone compartment, causing osteopenia, osteoporosis and increased risk for bone fractures [55]. This results in higher levels of calcium and $1,25(OH)_2D$ with a negative feedback on PTH and a subsequent limitation of bone resorption. Osteoporosis is a skeletal disorder which is characterized by compromised bone strength resulting in a higher susceptibility to fractures. Bone strength is determined by the structural quality of the bone and by bone mineral density, the latter measured by dual X-ray absorptiometry (DXA) and used to define osteoporosis. Osteoporosis is a major health problem as osteoporotic fractures are a frequent cause of significant and long-lasting morbidity in older individuals. Hip fractures and other types of non-vertebral fractures account for most of the burden of osteoporosis, with increased mortality, functional decline, loss of quality of life and need for institutionalization [56]. Female gender, advancing age, a history of fragility fractures, current or former
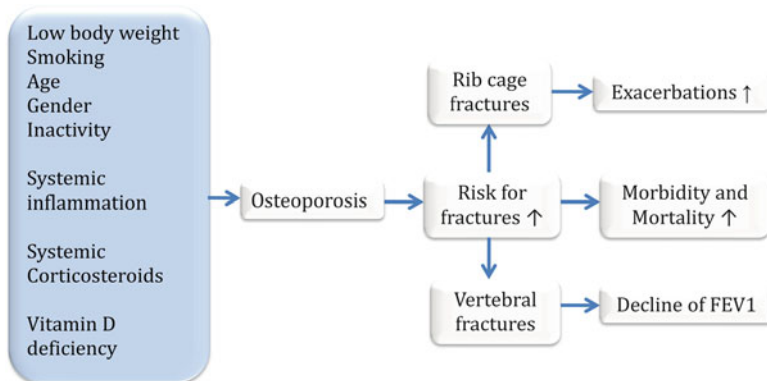
Fig. 11.2 COPD-related risk factors for osteoporosis and its functional consequences. Reprinted with permission from Lehouck et al. [58]

smoking, low body weight or weight loss and the use of systemic glucocorticoids are well-established risk factors for osteoporosis and osteoporotic fractures. As many of these risk factors are present in COPD patients, especially at the more severe stages, it should be no surprise that osteoporosis and COPD are strongly linked. A recent review of Graat-verboom et al. confirmed low body mass, disease severity, use of corticosteroids, age and female gender to be independent risk factors for osteoporosis in COPD [57]. The majority of studies have reported an increased risk for osteoporosis with decreasing FEV_1 (Fig. 11.2) [59–61].

The prevalence of osteoporosis in COPD varies between 9% and 59% depending on the diagnostic methods used, the population studied and the severity of the underlying respiratory disease [57]. Sin and colleagues used the NHANES III data to demonstrate that airflow obstruction is independently associated with reduced bone mineral density [59]. In their population-based cohort of 9,502 non-Hispanic White participants, 33% of all women with severe COPD had osteoporosis whereas almost all women with mild airway obstruction had osteopenia. In comparison, men were at lower risk than women but still, in men with severe COPD, the prevalence of osteoporosis and osteopenia was 11% and 60%, respectively, which was approximately three times higher than expected. Most studies looking at prevalence of osteoporosis have used DEXA scans which measure bone mineral density but do not evaluate micro-architectural changes of the bone. It is known that these microarchitectural changes may equally cause fragility fractures, even with normal bone density, and should therefore be considered to be osteoporotic as well. When taking DEXA measures and vertebral fragility fractures into account, Graat-Verboom et al. found that prevalence of osteoporosis almost doubled in 250 COPD outpatients [62]. It indicates that prevalence of osteoporosis in COPD might be much higher than the current prevalence data suggest [63].

Interesting relationships are also found with emphysema which is associated with reduced bone mineral density and lower body mass index and which may represent a clinical phenotype at risk for osteoporosis [64, 65]. Visual emphysema as assessed by CT scan was found to be an independent risk factor for osteopenia/osteoporosis

[66], and different bone turnover markers are increased in COPD. Recent data also show that osteoprotegerin, which is critically involved in bone turnover by blocking RANK–RANKL interaction, may become a useful marker for parenchymal lung destruction in COPD [67, 68]. It is currently not known whether the vitamin D pathway is involved in the specific development of emphysema, but studies in laboratory animals certainly corroborate this idea [69, 70].

The consequences of osteoporotic fragility fractures in a COPD population may be detrimental. In hip-fracture patients, mortality is close to 20% within 1 year, and of those who do survive the fracture, again, some 20% will have to be institutionalized because of its functional consequences [71]. The exact prevalence of hip fractures in COPD patients has not been studied in detail, but it is probable that the impact of such events in disabled COPD patients will be even worse. Additionally, vertebral compression fractures can lead to back pain, functional impairments, increased kyphosis with reduced rib cage mobility and decline of pulmonary function [72–74]. The impact of loss of vertebral height on pulmonary deterioration in COPD has been demonstrated by Leech and colleagues who found that vital capacity and total lung capacity incrementally declined as the number of thoracic vertebral fractures increased [72]. In the EOLO study, a large COPD cohort of up to 3,000 participants, more than 40%, had one or more vertebral fractures and the prevalence significantly correlated with severity of disease [75]. Kyphosis related to osteoporosis may also cause limitation in rib mobility and inspiratory muscle dysfunction and was also correlated with loss of FEV_1 and FVC [76].

There is no doubt that vitamin D protects against osteoporosis and osteoporotic fractures, and therefore, sufficient vitamin D supplementation should be encouraged. The fact that the majority of COPD patients are of older age, have many common risk factors for osteoporosis and are more likely to be deficient in vitamin D supports standard supplementation, especially at the more severe stages of disease. A daily dose of 700–800 IU of vitamin D together with an adequate daily calcium intake (1,000 mg) is probably the best strategy to prevent fractures in older subjects. Such supplementation is known to restore low serum 25-OHD levels in a general adult population to concentrations above the 20 ng/ml (50 nmol/l) threshold. Patients with COPD, particularly those on systemic corticosteroids, should also be considered for a DEXA scan and if needed, osteoporosis medication [58]. Even though causality and therapeutic benefits of vitamin D remain to be established for pulmonary inflammation and other co-morbidities, prevention of vertebral fractures will positively affect pulmonary function [75].

Extra-Calcemic Effects of Vitamin D

Exacerbations

Along with a progressive loss of pulmonary function, COPD patients become more prone to acute COPD exacerbations which are an important cause of hospitalization, impaired quality of life and mortality [77]. Appropriate antimicrobial treatment is

essential in the treatment of acute bacterial exacerbations whereas in case of colonization, repetitive and long-term antibiotic treatments are still avoided as they contribute to the multi-resistance of colonizing strains. Anti-inflammatory treatments different from inhaled and systemic corticosteroids are currently validated in COPD to reduce exacerbations on top of bronchodilator therapy. PDE4 inhibitors and neo-macrolides are the most promising agents from this perspective and seem to be beneficial for a subgroup of patients with repetitive exacerbations [78–80]. An attractive alternative approach might be the up-regulation of the innate immune defence system with vitamin D, particularly with regard to antimicrobial polypeptides [81]. Wang and colleagues demonstrated that in different cell types such as epithelial cells and white blood cells, the genes encoding for antimicrobial polypeptides such as cathelicidin (LL-37) and β-defensin are driven by VDR elements containing promoters [82]. In human monocytes, TLR activation up-regulates expression of the VDR and the 1-α-hydroxylase genes, leading to induction of LL-37 and killing of intracellular *Mycobacterium tuberculosis* [83]. LL-37 is also found to be very effective in the killing of a number of antibiotic-resistant strains such as *Pseudomonas* and *S. aureus*, different viruses and *Chlamydia* [84, 85]. As LL-37 is diffusely expressed in the surface epithelia of human airways, in the submucosal glands and in macrophages and neutrophils [86], substitution of local vitamin D insufficiency may reduce bacterial load and concomitant airway inflammation [87]. Apart from its potential benefit on bacterial eradication, vitamin D may also down-regulate the complex inflammatory cascade at several levels. In vitro vitamin D can reduce the expression of TLRs which are critical in the induction of the early immune response [88]. High levels of vitamin D also inhibit dendritic cell maturation with lower expression of MHC class II molecules, down-regulation of co-stimulatory molecules and lower production of pro-inflammatory cytokines such as IL-2, IL-12, IFN-γ and IL-23 [33, 89]. In several mouse models, vitamin D also leads to a switch from a Th1/Th17 responses towards a Th2 and regulatory T cell answer [1, 90–92]. Low serum levels of vitamin D have also been correlated with a decreased phagocytic activity of macrophages in patients with rickets [93] whereas antimicrobial activity of macrophages against *M. tuberculosis* could be increased by vitamin D supplementation [94]. Overall, the potential of vitamin D in reducing pro-inflammatory processes of the innate and adaptive immune system, together with an increased bacterial eradication by self antimicrobial peptides and enhanced macrophage phagocytosis, may offer great potential in the treatment of exacerbations.

Indirect clinical evidence for such hypothesis may be found in the observation that exacerbations of COPD are most common in winter, when 25-OHD levels are lowest. In addition, data from NHANES III showed that upper respiratory tract infections were most frequent in patients with lowest vitamin D levels. To further investigate such intriguing hypothesis, a randomized placebo-controlled intervention trial was performed to evaluate the effect of vitamin D supplementation in COPD patients, prone to exacerbations [95]. One hundred and eighty-two patients with moderate to very severe COPD and a history of recent exacerbations were supplemented with 100,000 IU vitamin D or placebo every 4 weeks over one year. Because of high-dose supplementation mean, 25-OHD serum levels increased significantly in the intervention arm and reached stable mean serum levels of 50 ng/ml,

which is in the therapeutic range of the hypothesized extra-calcemic effects [2]. However, despite effective supplementation, no significant difference in time to first exacerbation, time to first hospitalization and exacerbation rate could be observed between the intervention and the control group. The absence of a therapeutic effect of vitamin D may relate to the fact that most of the patients presented with severe disease and were on maximal inhalation therapy. As all these treatments are known to reduce exacerbations [96, 97], it is likely that any additional effect of vitamin D on top of regular treatment is more difficult to obtain. Intervention within the more early COPD stages taking less medications might therefore be more effective which is in line with the idea that such milder stages are also more sensitive to disease modification [98].

Interestingly, a significant baseline vitamin level by treatment interaction was observed for exacerbation rates. When performing a post hoc analysis in the subgroup of patients with very deficient vitamin D levels at baseline (<10 ng/ml), a significant 43% reduction of the number of exacerbations was observed in the intervention group. As one out of six COPD patients in the trial presented with such asymptomatic low baseline 25-OHD levels which persisted during the entire course of the study, further focus and future studies on this important subgroup may be warranted, eventually resulting in better patient-tailored interventions. Recently, a frequent exacerbator phenotype has been indentified suggesting that individualized therapy—including appropriate vitamin D substitution—may become important [22].

We also assessed for the presence and load of pathogenic bacteria in cultures of morning sputa during the trial but found no difference in eradication between both study arms. However, monocyte phagocytosis capacity in peripheral blood monocytes of patients receiving vitamin D was significantly increased compared to the placebo group, an effect which was more pronounced in the subgroup with lowest baseline levels. It is therefore tempting to speculate that the significant reduction of exacerbations in the vitamin D deficient subgroup is explained by an important up-regulation of impaired phagocytosis capacity [51]. So far, hard evidence for this mechanism is lacking. Finally, it should be noted that the lack of an overall effect could also relate to local vitamin D insensitivity because of epigenetic modifications. In line with the known corticosteroid resistance in COPD [99], recent studies in cancer have shown that epigenetic silencing of key enzymes of the vitamin D pathway may occur leaving tumour cells insensitive to vitamin D therapy [100, 101]. At least, epigenetic modifications especially in the context of smoking or poor diet may explain why many observations suggest causal relationships between vitamin D deficiency and inflammatory diseases whilst supplementation later on in the disease cannot reverse this process [102].

Peripheral Muscle Function

Skeletal muscle weakness is common in moderate to severe COPD and is an independent predictor of respiratory failure and death [103]. Although the underlying mechanisms of skeletal muscle dysfunction in COPD are not entirely understood,

it is generally accepted that the combination of disuse because of respiratory limitation, with elevated oxidative stress, systemic inflammation, hypoxia and frequent steroid intake, is the main cause of deterioration [25]. Rehabilitation programmes in COPD are proven successful, but there is still a large variability in training effectivity [104, 105]. Since muscle weakness is a prominent feature in rickets and chronic renal failure, and epidemiological studies found a positive association between 25-OHD levels and lower extremity function in older persons, vitamin D could be an important factor in muscle health [106]. In elderly individuals, vitamin D status predicts physical performance and consequent decline during long-term follow-up [107]. Several double-blind randomized controlled trials demonstrated that vitamin D supplementation increased muscle strength and balance and reduced the risk of falling in elderly [108]. Although a recent meta-analysis looking at the effect of vitamin D supplementation on muscle strength was negative, positive effects were still found in very deficient patients [109]. Moreover, the cross-sectional analysis from NHANES indicated that muscle strength continued to increase throughout 25-OHD serum levels of 9–37 ng/ml, indicating that for obtaining beneficial effects on the muscle, higher dose supplementation might be necessary [106].

On the pathological level, adults with vitamin D deficiency show predominantly type II muscle fibre atrophy [110] with several muscle abnormalities such as enlarged interfibrillar spaces, infiltration of fat, fibrosis and glycogen granules [111]. Conversely, increase in relative fibre composition and type II fibre dimensions has been reported in elderly after treatment with vitamin D [112]. These type II fibres are also the first to be recruited to prevent falling [113], which may explain why vitamin D supplementation is shown to reduce falling [114]. In COPD, limb muscle adaptation leads to a decrease of the proportion of slow oxidative type I fibres with a relative increase towards glycolytic type II fibres [115, 116], those fibres that are preferentially affected by vitamin D deficiency. Therefore, vitamin D deficiency may be of particular concern in COPD patients with muscle weakness and dysfunction.

The exact mechanisms by which vitamin D affect muscle function are not fully understood. However, $1,25(OH)_2D$ may impair muscle function by altering calcium regulation. In particular, $1,25(OH)_2D$ is responsible for the active calcium transportation into the sarcoplasmic reticulum by Ca-ATPase. It is known to regulate Ca-ATPase by phosphorylation of proteins in the sarcoplasmic reticulum membrane; it can increase phosphate transport across the membrane and interacts with calmodulin [110, 117]. Interestingly, calmodulin is highly sensitive to oxidative stress [118], a typical feature of COPD, and $1,25(OH)_2D$ may yield antioxidant properties. Thus, both vitamin D deficiency and increased oxidative stress through, e.g. smoking may act synergistically impairing calmodulin function, muscle structure and contractility. $1,25(OH)_2D$ has also an important role in protein synthesis in the muscle cell, mediated through nuclear receptor-mediated gene transcription [113]. For example, it can affect actin and troponin C content, two major contractile proteins in skeletal muscle [119], or may up-regulate gene expression of muscular growth factors, for instance, IGF-I [120].

Although it is tempting to extrapolate these vitamin D-mediated actions in skeletal muscles of healthy or elderly subjects [108, 121] to a specific population of COPD patients, it is still to be shown that vitamin D deficiency contributes to the observed muscle weakness in COPD. At present, there is no direct evidence for such causal relationship but the observation that VDR genotypes may influence quadriceps strength in COPD patients is in line with this assumption [122]. Recent data also show that vitamin D deficient COPD patients referred for rehabilitation have a higher risk for dropout and reduced benefit on walking endurance [123]. In a post hoc analysis in moderate to severe COPD, we also found a significant effect of high-dose vitamin D supplementation on top of 3 months of rehabilitation in terms of improved exercise capacity [124]. Therefore, randomized controlled trials investigating if supplementation of vitamin D deficiency may positively affect muscle force, muscle function and general COPD outcomes are urgently needed.

Systemic Consequences

In the last years, many clinical studies have associated low vitamin D levels to prevalence and incidence of cancer, including lung cancer [125, 126]. Several studies associate vitamin D deficiency with autoimmune diseases like type I diabetes, multiple sclerosis and rheumatoid arthritis [127–129]. Deficient vitamin D levels have been linked to chronic infections such as tuberculosis and acute viral infections like influenza or upper tract respiratory infections [130–133]. Similar data are also available which link vitamin D deficiency to cardiovascular diseases, arterial hypertension and even all cause mortality [134]. It is beyond the scope of this book chapter to review all evidence on vitamin D in these different chronic diseases, but it is striking that many of them are currently considered to be co-morbid conditions of COPD and accepted as important determinants of COPD outcome and prognosis [23, 25]. Tackling vitamin D-mediated effects in these co-morbid conditions may therefore indirectly improve COPD status [135]. It should be stressed, however, that the above mentioned relationships between vitamin D deficiency and different chronic diseases are speculative and most often rely on cross-sectional and retrospective observations or on evidence of in vitro and animal research. In humans, placebo-controlled intervention studies and observational studies with prospective long-term follow-up specifically designed to demonstrate causal relationships are often lacking. Moreover, recent intervention studies with vitamin D supplementation in multiple sclerosis, diabetes, influenza and tuberculosis have reported disappointing results, most often by their limitation of statistical power or insufficient supplementation [136–139]. Recent expert analysis therefore concluded that there is yet insufficient evidence for extra-calcemic benefits of vitamin D therapy and that more randomized placebo-controlled interventions trials are needed to define such effects [41]. For COPD in particular, intervention studies targeting co-morbid conditions to improve COPD-specific outcomes will be needed and in analogy with the

ongoing trial on statins in COPD patients (www.clinicaltrials.gov), one may think about a large intervention study with vitamin D supplements.

Lung Tissue Remodelling

Indirectly or directly, vitamin D is also believed to regulate extracellular matrix homeostasis in other tissues than bone, within particular lung and skin tissue via the control of transforming growth factor-β, matrix metalloproteinase and plasminogen activator systems [140–143]. There is compelling evidence that vitamin D plays a key role in foetal lung growth, development and maturation [144, 145]. Although 1.25 (OH)$_2$D toxicity in Klotho-null mice results in a phenotype of skin atrophy, osteoporosis and emphysema [146], recent data in mice show that severe vitamin D deficiency from early life also results in a impaired lung function by differences in lung volume and growth [69]. Evidence from human epidemiological studies also suggests that higher prenatal uptake of vitamin D protects against childhood wheezing [147]. As impaired lung growth and childhood asthma are known risk factors for COPD at later age [148, 149], the causal link between vitamin D deficiency and COPD may therefore already exist from early childhood on. Again, recent evidence from animal studies corroborates this idea. VDR knockout mice develop emphysematous airspace enlargement which is associated with the up-regulation of matrix metalloproteinases in the lung, an increased influx of inflammatory cells and the development of typical lymphoid aggregates around the peripheral airways [70].

Conclusion

The evidence that the vitamin D pathway plays a pivotal role in the biology of healthy and diseased lungs is compelling. As with many chronic diseases, vitamin D deficiency is highly prevalent in COPD and occurs more frequently with increasing disease severity. Such deficiency may not only enhance local airway inflammation but may also induce or accelerate ongoing co-morbid diseases and subsequently impair the general prognosis of the disease (Fig. 11.3). So far, there is only hard evidence for a causal role of vitamin D deficiency in the pathogenesis of COPD-related osteoporosis. For extra-calcemic effects, a recent randomized controlled trial demonstrated no overall effect of high-dose supplementation on exacerbations but was supportive for an important effect in a limited subgroup of patients highly deficient for vitamin D. Before embarking on new intervention trials with vitamin D in COPD targeting subgroups, more fundamental research is needed to learn how vitamin D and its deficiency interact with smoking in the development of COPD. Only then we will be able to understand why so far most intervention trials with vitamin D have failed to yield important health benefits in chronic diseases including COPD.
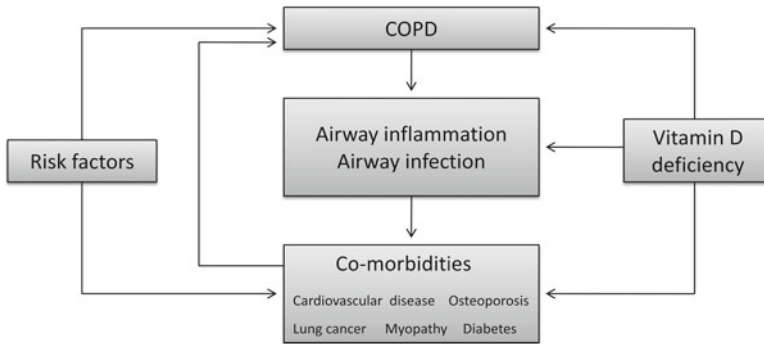
Fig. 11.3 Schematic representation of potential relationship between vitamin D and COPD. Reprinted with permission from Janssens et al. [150]

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