

Vitamin D Beyond Bones in Chronic Obstructive Pulmonary Disease

Time to Act

Wim Janssens¹, An Lehouck¹, Claudia Carremans¹, Roger Bouillon², Chantal Mathieu², and Marc Decramer¹

¹Respiratory Division, University Hospital Gasthuisberg; and ²Clinic and Laboratory of Experimental Medicine and Endocrinology, Katholieke Universiteit Leuven, Leuven, Belgium

The discovery that the vitamin D endocrine system regulates a very large number of genes and their associated biological processes improves our insight into the fundamental role of vitamin D and sun exposure for human health. Accumulating epidemiological data are linking a low vitamin D nutritional status to highly prevalent diseases such as cancer, autoimmune diseases, and chronic infections. Approximately half of the world's elderly, and to a lesser extent the adult population, have insufficient to deficient 25-hydroxyvitamin D (25-OHD) serum levels, and several intervention studies are being undertaken to study the impact of adequate vitamin D supplementation in chronic diseases. In this perspective we claim that chronic obstructive pulmonary disease (COPD) is a candidate disease for which vitamin D supplementation might be beneficial. Epidemiological studies revealed a dose-dependent association between serum 25-OHD levels and pulmonary function so that adequate vitamin D supplementation may extend beyond its protection against osteoporotic fractures. In line with the novel insights on its immune function, it is tempting to speculate that vitamin D may down-regulate the inflammatory immune response in the airways while boosting innate immune defense against different microorganisms. Apart from its effects on osteoporosis, vitamin D may also interfere with other comorbidities of COPD such as skeletal muscle weakness, cardiovascular disease, and cancer. Because respiratory treatments in COPD fail to reverse disease progression, interventional trials that may exploit the broader potential of vitamin D are warranted. A further challenge of such studies is to define optimal serum 25-OHD levels for such noncalcemic endpoints.

Keywords: vitamin D; COPD; antiinflammatory; comorbidity; 25-OHD

Over the last decades considerable progress has been made in understanding the complex pathogenesis of chronic obstructive pulmonary disease (COPD) leading to the discovery of new molecular pathways and potentially important therapeutic targets. Apart from smoking cessation, no treatment has convincingly proven to modify COPD disease progression, although two large randomized controlled trials recently demonstrated some beneficial effects of long-acting bronchodilators on exacerbation rate, quality of life, and survival (1, 2). Most new therapeutics, small molecules, or recombinant antibodies, however, have not

fulfilled their promises. In view of the disappointing results of these specific and expensive drugs, more attention should be refocused on the potential of older drugs in new indications. Statins, angiotensin-converting enzyme (ACE)-inhibitors, and heparines all have a broader field of action than initially presumed and may become of interest in the future therapy of COPD (3, 4). In this perspective we will discuss the potential of another, even older molecule, vitamin D.

After the dual origin of vitamin D (by synthesis in the skin or by dietary intake) was understood, oral vitamin D supplementation almost fully eradicated endemic rickets. Many health care professionals thought the major health problems resulting from vitamin D deficiency had thus been resolved. However, it turned out that rickets was only the top of the iceberg and that less severe vitamin D deficiency is still very common and also contributes to osteopenia, osteoporosis, and increased risk for fractures. As such, the vitamin D hormonal system with its complex metabolism and tight regulation of its key hormone, the dihydroxylated 1,25-(OH)₂D, was largely unraveled and its central role in the calcium and bone homeostasis became clear.

The discovery in recent years of a widespread presence in almost all mammalian cells of key activating and inactivating enzymes of vitamin D and its intracellular receptor, VDR, provided new insights into the paracrine role of vitamin D. The observation that approximately 3% of the mouse and human genome is regulated via the vitamin D pathway is indicative for a much broader role than initially presumed (5). Of great interest is the growing evidence for the role vitamin D might play in controlling the risk of many chronic illnesses including common cancers, myopathy, autoimmune disease, diabetes and the metabolic syndrome, infections, and cardiovascular disease (6, 7). As patients with COPD often integrate all of these comorbid diseases in one, we will review the current knowledge on calcemic and noncalcemic or extracalcemic effects of vitamin D from a pulmonary perspective and speculate on its unexploited potential in the treatment of COPD.

VITAMIN D: METABOLISM AND MECHANISM OF ACTION

Calcemic Effects and Bone Maintenance

Vitamin D is obtained by photosynthesis in the skin but can also be derived from nutrition (fatty fish, fish liver oils, and dairy products). Ultraviolet light catalyzes the first step in the vitamin D biosynthesis, which is the conversion of *de novo* synthesized 7-dehydrocholesterol into pre-vitamin D that undergoes an isomerization into vitamin D. The next step is a hydroxylation in the liver into 25-hydroxyvitamin D (25-OHD), which then circulates in serum with a long half-life, thereby reflecting a patient's

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Correspondence and requests for reprints should be addressed to Wim Janssens, M.D., Ph.D., Division of Respiratory Medicine, University Hospital Gasthuisberg (KUL) Herestraat 49, 3000 Leuven, Belgium. E-mail: wim.janssens@uz.kuleuven.be

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vitamin D status. Next, 25-OHD is hydroxylated into the active vitamin D metabolite 1,25-(OH)₂D by 1 α -hydroxylase (CYP27B1) in the kidney, which is under strict control of serum levels of calcium and phosphate and their regulating hormones such as parathyroid hormone (PTH), calcitonin, and phosphatonins. 1,25-(OH)₂D also induces the expression of a 24-hydroxylase (CYP24A1) that catabolizes both 25-OHD and 1,25-(OH)₂D into biologically inactive, water-soluble metabolites, thereby serving as its own negative feedback regulator. 1,25-(OH)₂D mediates its calcemic effects by binding to the nuclear vitamin D receptor (VDR), which, after binding to specific DNA sequences (VDREs) and recruiting a complex protein network, regulates the expression of a very large number of genes. The activation of the ligand-bound VDR in the intestine, bone, kidney, and parathyroid gland cells results in the maintenance of normal serum calcium and phosphorus levels and their related effects on mineralization and turnover of bone (8, 9). Serum levels of 25-OHD have been directly related to bone mineral density in various populations and low 25-OHD levels are inversely related to PTH levels, which, to maintain calcium homeostasis, further contribute to the breakdown of mineralized collagen matrix in bone, causing osteopenia, osteoporosis, and increased risk for bone fractures (9, 10). A significant reduction of the risk for fractures by vitamin D supplementation has been repeatedly demonstrated in randomized controlled trials indicating that a daily dose of 700 to 800 IU of vitamin D together with an adequate daily calcium intake (1000 mg) is probably the best strategy to prevent fractures in older subjects (11). Although most of these studies did not report 25-OHD levels, there is a broad consensus that in view of the calcemic effects, vitamin D deficiency is best defined as a 25-OHD level less than 20 ng/ml (50 nmol/L) (7, 12). Solely considering its effects on bone, a sensitive parameter to determine vitamin D deficiency are the serum levels of PTH. Older data have clearly demonstrated that levels of 25-OHD less than 20 ng/ml are experienced by the parathyroids as being insufficient (13).

Noncalcemic Effects and Chronic Diseases

1 α -Hydroxylase is also present in cells of several extrarenal tissues such as skin, bone, prostate, and many immune cells. 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 (14, 15). High local 1,25-(OH)₂D concentrations may, independently from serum concentrations, exert an autocrine and paracrine function as its nuclear receptor VDR is also widely present in many different cells and tissues. It is estimated that approximately 3% of the mouse/human genome is regulated by 1,25-(OH)₂D (5). Directly or indirectly, 1,25-(OH)₂D controls genes that are involved in the regulation of cellular proliferation, differentiation, and apoptosis of healthy and malignant cells. 1,25-(OH)₂D is also a potent immune modulator of the adaptive immune system and stimulates the innate immune response upon infection (16). As vitamin D is also involved in skeletal muscle function and the cardiovascular system, it is clear that these noncalcemic effects extend the therapeutic target of vitamin D supplementation from bone maintenance to many chronic diseases (see Figure 1).

Indeed, a positive association between 25-OHD and muscle strength or lower extremity function in elderly people has been described. A metaanalysis of five randomized clinical trials revealed that vitamin D supplementation reduces the risk of falls by 22% compared with placebo (10, 17). Several prospective and retrospective epidemiologic studies have also found a higher risk for different cancers with lower serum 25-OHD levels. Giovannucci demonstrated in a large U.S. pro-

spective male cohort that an increment of 10 ng/ml in estimated 25-OHD was associated with a 17% reduction in total cancer incidence, a 28% reduction in total cancer mortality, and a 45% reduction in digestive cancer mortality (18). The supplementation of a small group of postmenopausal women with vitamin D (1,100 IU/d) and calcium significantly reduced the overall cancer risk during follow-up (19). Similar beneficial effects were shown in a variety of Th1-mediated autoimmune diseases. The risk for multiple sclerosis was found to be approximately 50% greater when 25-OHD serum levels were less than 20 ng/ml, and the intake of vitamin D has been inversely related to the risk for developing multiple sclerosis (20, 21). Comparable observations have been made for rheumatoid arthritis (22). In addition, the Third National Health and Nutrition Survey (NHANES III), showed a dose-dependent inverse association between serum 25-OHD and the prevalence of diabetes (23). Different studies reported that supplementing children with up to 2,000 IU of vitamin D per day early in life reduced their risk for type I diabetes by approximately 30% on average (see Reference 24). Another study showed that a combined daily intake of calcium and 800 IU of vitamin D lowered the risk for type II diabetes by 33% (25). Furthermore, vitamin D deficiency has been linked to arterial hypertension, congestive heart failure, and the metabolic syndrome (26–28). According to a recent metaanalysis, low serum levels of 25-OHD were also associated with a higher risk of active tuberculosis (29). Given such abundant epidemiological data in humans, and supported by increasing evidence in animal models, placebo-controlled interventional studies are being undertaken to examine a causal relationship between vitamin D deficiency and different chronic diseases. Such studies are indeed needed to delineate the therapeutic potential as well as the optimal dosage for vitamin D supplementation in the context of noncalcemic effects. We will demonstrate that COPD is a good candidate disease for such explorative study.

COPD AND VITAMIN D PATHWAY

Epidemiological and Genetic Evidence

Black and colleagues examined spirometric data from the NHANES III (cross-sectional survey of 14,091 U.S. civilians greater than 20 yr of age) (30). After adjustment for potential confounders, a strong relationship between serum levels of 25-OHD and pulmonary function, as assessed by FEV₁ and FVC, was found (30). Although a significant correlation with airway obstruction could not be found, the observed dose–response relationship may suggest a causal link (31). Since then, no other survey has confirmed or further examined this interesting association. The observation that smoking African Americans develop severe airflow obstruction more rapidly than Caucasians is, however, in agreement with the idea that a presumed lower vitamin D status in African Americans correlates with an increased susceptibility to COPD (32). Furthermore, other genetic variants involved in the vitamin D pathway have been linked to COPD. For instance, a single nucleotide polymorphism (SNP) of the vitamin D binding protein was shown to be protective for COPD by a mechanism that is currently unclear (33). As similar SNPs in the vitamin D binding protein may also influence the level of circulating 25-OHD and 1,25-(OH)₂D (34, 35), we hypothesize that their protective role might be mediated by the bioavailability of 1,25-(OH)₂D. In addition, different variants of VDR were associated with skeletal muscle strength in COPD (36), and although no studies have linked the common variants of this important gene regulator to COPD (37), we believe that the absence of well-designed genetic studies with sufficient power in COPD may explain this.

Vitamin D Deficiency in COPD

Few studies have reported on 25-OHD serum levels in COPD patients. Forli and colleagues found vitamin D deficiency (<20 ng/ml) in more than 50% of a cohort waiting for lung transplantation (38). Similarly, in a study on community-dwelling patients with COPD in Denmark, 68% of the participants had osteoporosis or osteopenia that was not adequately treated (39). It should be emphasized that insufficient or deficient vitamin D levels are not a unique finding in COPD. According to the current definitions, it is estimated that more than one billion people worldwide have impaired serum levels of vitamin D. Several studies indicate that 40 to 100% of the elderly in the U.S. and Europe still living in the community are mildly or severely vitamin D deficient (12, 40, 41). However, patients with COPD should be considered at high risk for a variety of reasons. A lower food intake, a reduced capacity of aging skin for vitamin D synthesis, the absence of outdoor activity and sun exposure, an increased catabolism by glucocorticoids, impaired activation because of renal dysfunction, and a lower storage capacity in muscles or fat due to wasting, may all contribute to a defective vitamin D status in patients with COPD (7). Although current supplementation with a daily dose of 800 to 1,000 IU of vitamin D restores deficient levels of serum 25-OHD in a general adult population to concentrations greater than 20 ng/ml, higher doses are probably required to increase 25-OHD levels to even higher levels that may be needed for noncalcemic diseases in a population at risk (10, 42). At present we can only speculate on the ideal target range for 25-OHD levels to maximally exploit these extracalcemic effects.

Mechanisms of Action in COPD

Calcemic effects. Sin and colleagues used the NHANES III data to demonstrate that airflow obstruction is independently associated with reduced bone mineral density (43). 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 less-severe airway obstruction had osteopenia. In comparison, men were less at risk than women, but, in men with severe COPD, the prevalence of osteoporosis and osteopenia was 11 and 60%, respectively, which was approximately three times higher than expected. The impact of the 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 (44). Kyphosis related to osteoporosis caused limitation in rib mobility and inspiratory muscle function and correlated with a loss of FEV₁ and FVC (45). There is no doubt that vitamin D protects against osteoporosis and osteoporotic fractures, and therefore, sufficient vitamin D supplementation, at least to levels greater than 20 ng/ml, should be strongly encouraged in all patients with COPD. Even though causality and therapeutic benefits remain to be established for pulmonary inflammation and other comorbidities, prevention of vertebral fractures will positively affect pulmonary function (46).

Antimicrobial effects. Along with a progressive loss of pulmonary function, patients with COPD become more prone to acute exacerbations, which are an important cause of hospitalization and in turn lead to a faster decline in FEV₁ (47). Exacerbations are most often triggered by viruses, bacteria, atypical strains, or a combination of these (48–50). In approximately 50% of exacerbations potential bacterial pathogens are detected in cultures of sputa. The same pathogens may also be detected in stable COPD (~30–40%) but the significance of this bacterial colonization is not entirely understood (50–52). Treatment with antibiotics decreases inflammation not only when

a total and persistent eradication is achieved but also in subjects with colonized airways for whom decreased inflammation correlates with a lower bacterial load (53). Therefore, appropriate antimicrobial treatment is considered as a mainstay in the treatment of acute exacerbations, whereas, in case of colonization, repetitive and long-term antibiotic treatments are still avoided as they unequivocally contribute to the multiresistance of colonizing strains. A potent alternative approach would be the up-regulation of the innate immune defense system, especially with regard to native antimicrobial polypeptides (AMP) (54). Wang and colleagues demonstrated that in distinct cell types, such as epithelial cells and white blood cells, the genes encoding for antimicrobial polypeptides such as cathelicidin (LL-37) are driven by VDRE-containing promoters (55). In monocytes, a local increase of the 1,25-(OH)₂D-VDR complex (via TLR-2) stimulates the production of LL-37, resulting in an improved intracellular eradication of mycobacterium tuberculosis (56). LL-37 was also found to be very effective in killing a number of antibiotic-resistant strains such as *Pseudomonas aeruginosa* and *Staphylococcus aureus*, different viruses, and chlamydia (57, 58). As LL-37 is also diffusely expressed in the surface epithelia of human airways, in the submucosal glands, and in secretory granules of macrophages and neutrophils (59), vitamin D insufficiency may contribute to chronic respiratory infections and airway colonization (60). Conversely, increasing 25-OHD concentrations to an optimal range in patients with COPD might reduce bacterial load and concomitant exacerbations.

Immune modulation. All cells of the adaptive immune system (dendritic cells, monocytes, T cells and B cells, NK cells) express VDR either constitutively or after appropriate immune stimulation and are sensitive to 1,25-(OH)₂D action. High levels of vitamin D are potent inhibitors of dendritic cell maturation with lower expression of major histocompatibility complex (MHC) class II molecules, down-regulation of costimulatory molecules and lower production of proinflammatory cytokines such as IL-2, IL-12, IFN- γ and IL-23 (15, 16). In several mouse models, 1,25-(OH)₂D tapers down the adaptive immune system from a Th1/Th17 response toward a Th2 and regulatory T-cell answer, indicating potential beneficial effects on the occurrence and progression of Th1-mediated autoimmune diseases in humans (6, 61–63). Unlike multiple sclerosis, type I diabetes, rheumatoid arthritis, and Crohn's disease, COPD is generally not considered an autoimmune disease. Still, an important role for the adaptive immune system in COPD might be suspected as the numbers of pulmonary CD4⁺ and CD8⁺ cells rise with increasing severity of the disease (64, 65). Elastin fragments that are liberated upon smoke-induced inflammation (66) may induce elastin fragment-specific Th1 cells that were recently detected in severe stages of human COPD (67). Similarly, Th17 cells that have been implicated in rheumatoid arthritis and several models of autoimmune disease, are likely to be involved in COPD, as IL-17 is a key cytokine for neutrophil recruitment and mucus production by goblet cells (68). Although the specific role of antigen-specific "autoimmune" lymphocyte subsets and Th17 cells in COPD deterioration remains to be elucidated (69, 70), we speculate that a down-regulation of both cell types by vitamin D would be beneficial. The peak in winter and early spring, when 25-OHD levels are lowest, of exacerbations of autoimmune diseases as well as exacerbations of COPD, may further strengthen the hypothesis that vitamin D, COPD, and adaptive immunity are linked (71).

Lung tissue remodeling. 1,25-(OH)₂D is not only involved in the regulation of proliferation, differentiation, and apoptosis of different cell types. Indirectly or directly, 1,25-(OH)₂D also regulates extracellular matrix homeostasis in tissues other than bone, within particular lung and skin tissue via the control of

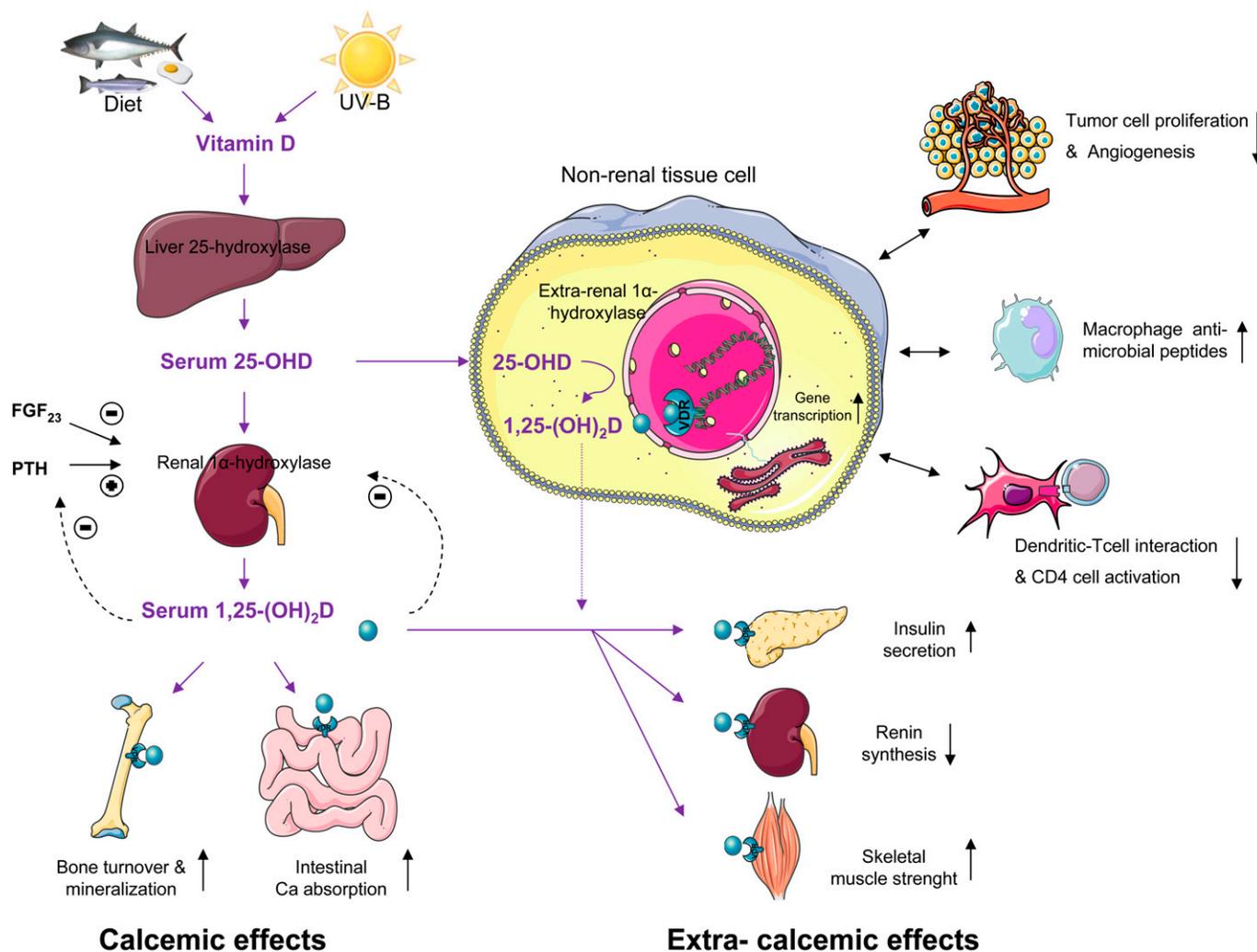


Figure 1. Schematic presentation of calcemic and extracalcemic effects of vitamin D that are potentially important in patients with COPD.

transforming growth factor- β , matrix metalloproteinase, and plasminogen activator systems (72, 73). Its importance here might be illustrated by the $1,25(\text{OH})_2\text{D}$ -mediated toxicity of *Klotho*-null mice resulting in a phenotype of emphysema, skin atrophy, and osteoporosis (74). At present, we can only speculate if vitamin D-deficiency (or toxicity) negatively affects extracellular matrix formation in the lung and contributes to senescent or smoking-induced emphysema in humans (30).

Peripheral muscle function. Skeletal muscle weakness is a very common observation in moderate to severe COPD and is an independent predictor of respiratory failure and death (75). Although the underlying mechanism of skeletal muscle dysfunction in COPD is 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 are the main causes of deterioration (76, 77). Rehabilitation programs in COPD have been efficacious, but a large variability in training effects remains (78, 79). Different lines of evidence support a role of vitamin D in skeletal muscle health. Muscle weakness is a prominent feature in rickets and chronic renal failure, and epidemiological studies have found a positive association between 25-OHD levels and lower-extremity function in older persons (80). In the elderly, vitamin D status predicts physical performance and consequent decline during long-term follow-up (81). Moreover, several double-blind randomized control

trials demonstrated that vitamin D supplementation increased muscle strength and balance, and reduced the risk of falling in the elderly (17). Although the exact mechanism of action is currently unknown, it is tempting to extrapolate these general observations to a specific population of patients with COPD. We even speculate that muscle weakness and training effects in COPD might be related to serum 25-OHD levels and adequate substitution during rehabilitation. A recent publication on vitamin D receptor genotype polymorphism and quadriceps strength in COPD is supportive of this hypothesis (36). As the cross-sectional analysis from NHANES indicated that muscle strength continued to increase throughout the reference range of 9 to 37 ng/ml of 25-OHD, more rigorous oral supplementation might then become necessary (80).

Comorbid diseases. Although still defined using pulmonary criteria, COPD is considered a chronic disease state that is not confined to the lungs but is typically associated with systemic inflammation and different comorbidities (77, 82). The importance of such broader context has been indirectly confirmed by the Toward a Revolution in COPD Health (TORCH) study demonstrating that, in the prospective 3-year follow-up of a large cohort of patients with COPD, only one-third of deaths could be attributed to respiratory failure, whereas the majority died from lung cancer or cardiovascular events (1). Statins may slow down loss of pulmonary function in COPD (83) but their beneficial effects on COPD survival are likely to be explained

by a reduction of systemic inflammation, cardiovascular events (4), and eventually lung cancer (84). In line with the effects of statins, vitamin D deficiency has also been associated with arterial hypertension and congestive heart failure (27, 28), whereas survival from non-small cell lung cancer has been linked to 25-OHD levels and VDR genotypes (85, 86). It is beyond the scope of this perspective to further discuss the underlying mechanisms that are still far from being understood, but it is to be expected that vitamin D-mediated genetic control of proliferation, differentiation, and apoptosis of distinct cell types is involved. Whether sufficient vitamin D supplementation will finally reduce cardiovascular or lung cancer mortality in patients with COPD is currently unknown, but, given the potential beneficial effects of other antiinflammatory agents like statins in the treatment of COPD, we think it is worthwhile to further explore such hypothesis.

CONCLUSIONS

Although vitamin D deficiency is associated with many major chronic diseases, the causality or therapeutic benefits of vitamin D supplementation beyond bone and calcium homeostasis still needs to be investigated. According to the National Institutes of Health clinical trial register, several well-controlled intervention studies are currently examining vitamin D supplementation in different autoimmune diseases and tuberculosis. Given the increased risk for osteopenia and osteoporosis in COPD, vitamin D supplementation should be considered for all patients with COPD. Yet, a potential benefit of improved vitamin D status on noncalcemic endpoints in patients with severe COPD, in which deficiency or relative insufficiency of vitamin D is often present, has not been explored. We postulate that COPD is an optimal candidate disease for such studies because it often integrates repetitive infections, persistent inflammation, muscular dysfunction, and different comorbidities in one, all domains that vitamin D may affect. As current treatments in COPD are lacking efficacy, randomized control trials with vitamin D supplementation should therefore be strongly encouraged. With recommendations for vitamin D treatment only based on bone maintenance, the challenge in such randomized controlled trials will be primarily to demonstrate efficacy and safety and secondarily to define optimal target serum levels for 25-OHD in this disease as a proof of concept for other than calcemic endpoints.

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References

- Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, Yates JC, Vestbo J. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007; 356:775–789.
- Tashkin DP, Celli B, Senn S, Burkhardt D, Kesten S, Menjoge S, Decramer M. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008;359:1543–1554.
- Cazzola M, Ciapri C, Page CP, Matera MG. Targeting systemic inflammation: novel therapies for the treatment of chronic obstructive pulmonary disease. *Expert Opin Ther Targets* 2007;11:1273–1286.
- Mancini GB, Etmnan M, Zhang B, Levesque LE, FitzGerald JM, Brophy JM. Reduction of morbidity and mortality by statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers in patients with chronic obstructive pulmonary disease. *J Am Coll Cardiol* 2006;47:2554–2560.
- Uitterlinden AG, Fang Y, Van Meurs JB, Pols HA, Van Leeuwen JP. Genetics and biology of vitamin D receptor polymorphisms. *Gene* 2004;338:143–156.
- Bouillon R, Bischoff-Ferrari H, Willett W. Vitamin D and health: perspectives from mice and man. *J Bone Miner Res* 2008;23:974–979.
- Holick MF. Vitamin D deficiency. *N Engl J Med* 2007;357:266–281.
- Lips P. Vitamin D physiology. *Prog Biophys Mol Biol* 2006;92:4–8.
- DeLuca HF. Overview of general physiologic features and functions of vitamin D. *Am J Clin Nutr* 2004;80:1689S–1696S.
- Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. *Am J Clin Nutr* 2006; 84:18–28.
- Boonen S, Lips P, Bouillon R, Bischoff-Ferrari HA, Vanderschueren D, Haentjens P. Need for additional calcium to reduce the risk of hip fracture with vitamin D supplementation: evidence from a comparative metaanalysis of randomized controlled trials. *J Clin Endocrinol Metab* 2007;92:1415–1423.
- Norman AW, Bouillon R, Whiting SJ, Vieth R, Lips P. 13th Workshop consensus for vitamin D nutritional guidelines. *J Steroid Biochem Mol Biol* 2007;103:204–205.
- Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. *Endocr Rev* 2001;22:477–501.
- Overbergh L, Decallonne B, Valckx D, Verstuyf A, Depovere J, Laureys J, Rutgeerts O, Saint-Arnaud R, Bouillon R, Mathieu C. Identification and immune regulation of 25-hydroxyvitamin D-1-alpha-hydroxylase in murine macrophages. *Clin Exp Immunol* 2000; 120:139–146.
- van Etten E, Mathieu C. Immunoregulation by 1,25-dihydroxyvitamin D3: basic concepts. *J Steroid Biochem Mol Biol* 2005;97:93–101.
- Baeke F, Etten EV, Gysemans C, Overbergh L, Mathieu C. Vitamin D signaling in immune-mediated disorders: Evolving insights and therapeutic opportunities. *Mol Aspects Med* 2008;29:376–387.
- Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, Staehelin HB, Bazemore MG, Zee RY, Wong JB. Effect of Vitamin D on falls: a meta-analysis. *JAMA* 2004;291:1999–2006.
- Giovannucci E, Liu Y, Rimm EB, Hollis BW, Fuchs CS, Stampfer MJ, Willett WC. Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. *J Natl Cancer Inst* 2006;98:451–459.
- Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. *Am J Clin Nutr* 2007;85:1586–1591.
- Munger KL, Zhang SM, O'Reilly E, Hernan MA, Olek MJ, Willett WC, Ascherio A. Vitamin D intake and incidence of multiple sclerosis. *Neurology* 2004;62:60–65.
- Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. *JAMA* 2006; 296:2832–2838.
- Merlino LA, Curtis J, Mikuls TR, Cerhan JR, Criswell LA, Saag KG. Vitamin D intake is inversely associated with rheumatoid arthritis: results from the Iowa Women's Health Study. *Arthritis Rheum* 2004;50:72–77.
- Scragg R, Sowers M, Bell C. Serum 25-hydroxyvitamin D, diabetes, and ethnicity in the Third National Health and Nutrition Examination Survey. *Diabetes Care* 2004;27:2813–2818.
- Mathieu C, Gysemans C, Giulietti A, Bouillon R. Vitamin D and diabetes. *Diabetologia* 2005;48:1247–1257.
- Pittas AG, Dawson-Hughes B, Li T, Van Dam RM, Willett WC, Manson JE, Hu FB. Vitamin D and calcium intake in relation to type 2 diabetes in women. *Diabetes Care* 2006;29:650–656.
- Chiu KC, Chu A, Go VL, Saad MF. Hypovitaminosis D is associated with insulin resistance and beta cell dysfunction. *Am J Clin Nutr* 2004; 79:820–825.
- Forman JP, Giovannucci E, Holmes MD, Bischoff-Ferrari HA, Tworoger SS, Willett WC, Curhan GC. Plasma 25-hydroxyvitamin D levels and risk of incident hypertension. *Hypertension* 2007;49:1063–1069.
- Wang TJ, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, Lanier K, Benjamin EJ, D'Agostino RB, Wolf M, Vasan RS. Vitamin D deficiency and risk of cardiovascular disease. *Circulation* 2008;117:503–511.
- Nnoaham KE, Clarke A. Low serum vitamin D levels and tuberculosis: a systematic review and meta-analysis. *Int J Epidemiol* 2008;37:113–119.

30. Black PN, Scragg R. Relationship between serum 25-hydroxyvitamin D and pulmonary function in the third national health and nutrition examination survey. *Chest* 2005;128:3792–3798.
31. Wright RJ. Make no bones about it: increasing epidemiologic evidence links vitamin D to pulmonary function and COPD. *Chest* 2005;128:3781–3783.
32. Chatila WM, Wynkoop WA, Vance G, Criner GJ. Smoking patterns in African Americans and whites with advanced COPD. *Chest* 2004;125:15–21.
33. Schellenberg D, Pare PD, Weir TD, Spinelli JJ, Walker BA, Sandford AJ. Vitamin D binding protein variants and the risk of COPD. *Am J Respir Crit Care Med* 1998;157:957–961.
34. Lauridsen AL, Vestergaard P, Hermann AP, Brot C, Heickendorff L, Mosekilde L, Nexø E. Plasma concentrations of 25-hydroxy-vitamin D and 1,25-dihydroxy-vitamin D are related to the phenotype of Gc (vitamin D-binding protein): a cross-sectional study on 595 early postmenopausal women. *Calcif Tissue Int* 2005;77:15–22.
35. TaesYE, Goemaere S, Huang G, Van Pottelbergh I, De Bacquer D, Verhasselt B, Van den Broeke C, Delanghe JR, Kaufman JM. Vitamin D binding protein, bone status and body composition in community-dwelling elderly men. *Bone* 2006;38:701–707.
36. Hopkinson NS, Li KW, Kehoe A, Humphries SE, Roughton M, Moxham J, Montgomery H, Polkey MI. Vitamin D receptor genotypes influence quadriceps strength in chronic obstructive pulmonary disease. *Am J Clin Nutr* 2008;87:385–390.
37. Sampsonas F, Karkoulas K, Kaparianos A, Spiropoulos K. Genetics of chronic obstructive pulmonary disease, beyond A1-antitrypsin deficiency. *Curr Med Chem* 2006;13:2857–2873.
38. Forli L, Halse J, Haug E, Bjortuft O, Vatn M, Kofstad J, Boe J. Vitamin D deficiency, bone mineral density and weight in patients with advanced pulmonary disease. *J Intern Med* 2004;256:56–62.
39. Jorgensen NR, Schwarz P, Holme I, Henriksen BM, Petersen LJ, Backer V. The prevalence of osteoporosis in patients with chronic obstructive pulmonary disease: a cross sectional study. *Respir Med* 2007;101:177–185.
40. Chapuy MC, Preziosi P, Maamer M, Arnaud S, Galan P, Hercberg S, Meunier PJ. Prevalence of vitamin D insufficiency in an adult normal population. *Osteoporos Int* 1997;7:439–443.
41. Dawson-Hughes B, Heaney RP, Holick MF, Lips P, Meunier PJ, Vieth R. Estimates of optimal vitamin D status. *Osteoporos Int* 2005;16:713–716.
42. Vieth R. Vitamin D toxicity, policy, and science. *J Bone Miner Res* 2007;22:V64–V68.
43. Sin DD, Man JP, Man SF. The risk of osteoporosis in Caucasian men and women with obstructive airways disease. *Am J Med* 2003;114:10–14.
44. Leech JA, Dulberg C, Kellie S, Pattee L, Gay J. Relationship of lung function to severity of osteoporosis in women. *Am Rev Respir Dis* 1990;141:68–71.
45. Schlaich C, Minne HW, Bruckner T, Wagner G, Gebest HJ, Grunze M, Ziegler R, Leidig-Bruckner G. Reduced pulmonary function in patients with spinal osteoporotic fractures. *Osteoporos Int* 1998;8:261–267.
46. Nuti R, Siviero P, Maggi S, Guglielmi G, Caffarelli C, Crepaldi G, Gonnelli S. Vertebral fractures in patients with chronic obstructive pulmonary disease: the EOLO Study. *Osteoporos Int* 2008;Epub 2008 Oct 1.
47. Niewoehner DE. The impact of severe exacerbations on quality of life and the clinical course of chronic obstructive pulmonary disease. *Am J Med* 2006;119:38–45.
48. Lieberman D, Lieberman D, Ben-Yaakov M, Shmarkov O, Gelfer Y, Varshavsky R, Ohana B, Lazarovich Z, Boldur I. Serological evidence of *Mycoplasma pneumoniae* infection in acute exacerbation of COPD. *Diagn Microbiol Infect Dis* 2002;44:1–6.
49. Mogulkoc N, Karakurt S, Isalska B, Bayindir U, Celikel T, Korten V, Colpan N. Acute purulent exacerbation of chronic obstructive pulmonary disease and *Chlamydia pneumoniae* infection. *Am J Respir Crit Care Med* 1999;160:349–353.
50. Papi A, Bellettato CM, Braccioni F, Romagnoli M, Casolari P, Caramori G, Fabbri LM, Johnston SL. Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations. *Am J Respir Crit Care Med* 2006;173:1114–1121.
51. Sethi S, Evans N, Grant BJ, Murphy TF. New strains of bacteria and exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 2002;347:465–471.
52. Sethi S, Sethi R, Eschberger K, Lobbins P, Cai X, Grant BJ, Murphy TF. Airway bacterial concentrations and exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007;176:356–361.
53. White AJ, Gompertz S, Bayley DL, Hill SL, O'Brien C, Unsal I, Stockley RA. Resolution of bronchial inflammation is related to bacterial eradication following treatment of exacerbations of chronic bronchitis. *Thorax* 2003;58:680–685.
54. Zasloff M. Antimicrobial peptides of multicellular organisms. *Nature* 2002;415:389–395.
55. Wang TT, Nestel FP, Bourdeau V, Nagai Y, Wang Q, Liao J, Tavera-Mendoza L, Lin R, Hanrahan JW, Mader S, et al. Cutting edge: 1,25-dihydroxyvitamin D3 is a direct inducer of antimicrobial peptide gene expression. *J Immunol* 2004;173:2909–2912.
56. Liu PT, Stenger S, Li H, Wenzel L, Tan BH, Krutzyk SR, Ochoa MT, Schaubert J, Wu K, Meinken C, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science* 2006;311:1770–1773.
57. Gordon YJ, Huang LC, Romanowski EG, Yates KA, Proske RJ, McDermott AM. Human cathelicidin (LL-37), a multifunctional peptide, is expressed by ocular surface epithelia and has potent antibacterial and antiviral activity. *Curr Eye Res* 2005;30:385–394.
58. Turner J, Cho Y, Dinh NN, Waring AJ, Lehrer RI. Activities of LL-37, a cathelin-associated antimicrobial peptide of human neutrophils. *Antimicrob Agents Chemother* 1998;42:2206–2214.
59. Bals R, Wang X, Zasloff M, Wilson JM. The peptide antibiotic LL-37/hCAP-18 is expressed in epithelia of the human lung where it has broad antimicrobial activity at the airway surface. *Proc Natl Acad Sci USA* 1998;95:9541–9546.
60. Zasloff M. Fighting infections with vitamin D. *Nat Med* 2006;12:388–390.
61. Daniel C, Sartory NA, Zahn N, Radeke HH, Stein JM. Immune modulatory treatment of trinitrobenzene sulfonic acid colitis with calcitriol is associated with a change of a T helper (Th) 1/Th17 to a Th2 and regulatory T cell profile. *J Pharmacol Exp Ther* 2008;324:23–33.
62. Mathieu C, Waer M, Laureys J, Rutgeerts O, Bouillon R. Prevention of autoimmune diabetes in NOD mice by 1,25 dihydroxyvitamin D3. *Diabetologia* 1994;37:552–558.
63. Mathieu C, Adorini L. The coming of age of 1,25-dihydroxyvitamin D(3) analogs as immunomodulatory agents. *Trends Mol Med* 2002;8:174–179.
64. Hogg JC, Chu F, Utokaparch S, Woods R, Elliott WM, Buzatu L, Cherniack RM, Rogers RM, Sciurba FC, Coxson HO, et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med* 2004;350:2645–2653.
65. Cosio MG, Majo J, Cosio MG. Inflammation of the airways and lung parenchyma in COPD: role of T cells. *Chest* 2002;121:160S–165S.
66. Houghton AM, Quintero PA, Perkins DL, Kobayashi DK, Kelley DG, Marconcini LA, Mecham RP, Senior RM, Shapiro SD. Elastin fragments drive disease progression in a murine model of emphysema. *J Clin Invest* 2006;116:753–759.
67. Lee SH, Goswami S, Grudo A, Song LZ, Bandi V, Goodnight-White S, Green L, Hacken-Bitar J, Huh J, Bakaeen F, et al. Anti-elastin autoimmunity in tobacco smoking-induced emphysema. *Nat Med* 2007;13:567–569.
68. Linden A, Adachi M. Neutrophilic airway inflammation and IL-17. *Allergy* 2002;57:769–775.
69. Curtis JL, Freeman CM, Hogg JC. The immunopathogenesis of chronic obstructive pulmonary disease: insights from recent research. *Proc Am Thorac Soc* 2007;4:512–521.
70. Barnes PJ. Immunology of asthma and chronic obstructive pulmonary disease. *Nat Rev Immunol* 2008;8:183–192.
71. Iikuni N, Nakajima A, Inoue E, Tanaka E, Okamoto H, Hara M, Tomatsu T, Kamatani N, Yamanaka H. What's in season for rheumatoid arthritis patients? Seasonal fluctuations in disease activity. *Rheumatology (Oxford)* 2007;46:846–848.
72. Boyan BD, Wong KL, Fang M, Schwartz Z. 1[alpha],25(OH)2D3 is an autocrine regulator of extracellular matrix turnover and growth factor release via ERp60 activated matrix vesicle metalloproteinases. *J Steroid Biochem Mol Biol* 2007;103:467–472.
73. Koli K, Keski-Oja J. Vitamin D3 regulation of transforming growth factor-beta system in epithelial and fibroblastic cells—relationships to plasminogen activation. *J Invest Dermatol Symp Proc* 1996;1:33–38.
74. Razaque MS, Sitara D, Taguchi T, St-Arnaud R, Lanske B. Premature aging-like phenotype in fibroblast growth factor 23 null mice is a vitamin D-mediated process. *FASEB J* 2006;20:720–722.
75. Gosselink R, Troosters T, Decramer M. Peripheral muscle weakness contributes to exercise limitation in COPD. *Am J Respir Crit Care Med* 1996;153:976–980.

76. Decramer M, De Benedetto F, Del Ponte A, Marinari S. Systemic effects of COPD. *Respir Med* 2005;99 Suppl B:S3–10.
77. Decramer M, Rennard S, Troosters T, Mapel DW, Giardino N, Mannino D, Wouters E, Sethi S, Cooper CB. COPD as a lung disease with systemic consequences—clinical impact, mechanisms, and potential for early intervention. *COPD* 2008;5:235–256.
78. Troosters T, Gosselink R, Decramer M. Exercise training in COPD: how to distinguish responders from nonresponders. *J Cardiopulm Rehabil* 2001;21:10–17.
79. Troosters T, Casaburi R, Gosselink R, Decramer M. Pulmonary rehabilitation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005;172:19–38.
80. Bischoff-Ferrari HA, Dietrich T, Orav EJ, Hu FB, Zhang Y, Karlson EW, Dawson-Hughes B. Higher 25-hydroxyvitamin D concentrations are associated with better lower-extremity function in both active and inactive persons aged ≥ 60 y. *Am J Clin Nutr* 2004;80:752–758.
81. Wicherts IS, van Schoor NM, Boeke AJ, Visser M, Deeg DJ, Smit J, Knol DL, Lips P. Vitamin D status predicts physical performance and its decline in older persons. *J Clin Endocrinol Metab* 2007;92:2058–2065.
82. Fabbri LM, Rabe KF. From COPD to chronic systemic inflammatory syndrome? *Lancet* 2007;370:797–799.
83. Keddissi JI, Younis WG, Chbeir EA, Daher NN, Dernaika TA, Kinasewitz GT. The use of statins and lung function in current and former smokers. *Chest* 2007;132:1764–1771.
84. Khurana V, Bejjanki HR, Caldito G, Owens MW. Statins reduce the risk of lung cancer in humans: a large case-control study of US veterans. *Chest* 2007;131:1282–1288.
85. Zhou W, Heist RS, Liu G, Neuberger DS, Asomaning K, Su L, Wain JC, Lynch TJ, Giovannucci E, Christiani DC. Polymorphisms of vitamin D receptor and survival in early-stage non-small cell lung cancer patients. *Cancer Epidemiol Biomarkers Prev* 2006;15:2239–2245.
86. Zhou W, Heist RS, Liu G, Asomaning K, Neuberger DS, Hollis BW, Wain JC, Lynch TJ, Giovannucci E, Su L, et al. Circulating 25-hydroxyvitamin D levels predict survival in early-stage non-small-cell lung cancer patients. *J Clin Oncol* 2007;25:479–485.