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Review article

The relationship between Vitamin D status and exacerbation in COPD patients– a literature review

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ABSTRACT

Objective: To investigate the relationship between Vitamin D and exacerbation in COPD patients.
Methods: The PubMed database was searched for articles published from 2012 onwards using search terms related to Vitamin D and exacerbation in COPD patients. Meta-analysis, clinical trials, observational studies, and human studies were included. Non-English articles or articles with full text unavailable were excluded; a total of 15 articles were selected.
Results: The association between exacerbation frequency and Vitamin D levels in observational studies remains controversial, however, meta-analysis revealed a negative association between serum Vitamin D and exacerbation. Also, two clinical trials showed that Vitamin D3 supplementation in COPD patients reduced the risk of moderate and severe exacerbation. Vitamin D binding protein (VDBP) polymorphisms seem to affect patient exacerbation susceptibility.
Conclusions: Few studies in literature have data related to diet, 25-hydroxyVitamin D [25(OH)D] and polymorphism in COPD exacerbation. One clinical trial indicates Vitamin D supplementation plays a role in COPD patients with hypovitaminosis D in preventing exacerbations. Further studies are needed to elucidate the role of Vitamin D in this population and to establish the best marker for Vitamin D, which patient subgroups will benefit, and the best supplement dosage without leading to toxicity.

1. Introduction

Vitamin D is now recognized for more than just its importance in regulating calcium and phosphorus in the human body. In the last decade, great interest has been shown of its actions in other systems. These have been called non-classical actions and involve: cell growth, immune system activities, inflammation, modulation of the renin-angiotensin system, muscle function, nervous system, and maintenance of cardiac function and structure [1–3].

Vitamin D deficiency is a general widespread issue in adults and may be a risk factor for respiratory disease; it is associated with reduced lung function and emphysema [4,5]. Epidemiological and observational studies show a relationship between blood Vitamin D level and clinical parameters in patients with chronic obstructive pulmonary disease – COPD [6–9].

Studies have also shown an association between low plasma Vitamin D levels and COPD exacerbations [10]. Frequent exacerbations are associated with increased mortality risk, lower lung function and promote COPD progression [11–13]. As acute exacerbations in COPD are often triggered by viral or bacterial infections, the ability of Vitamin D to enhance cathelicidin expression might reduce pathogen load and the frequency of these exacerbations [14,15]. Furthermore, the discovery of nuclear Vitamin D receptor (VDR) and hydroxylase enzyme expression by immune cells has led to a surge into research on the potential role of Vitamin D in maintaining immune homeostasis and preventing the development of autoimmune processes [15]. It is unclear whether Vitamin D deficiency affects COPD development and progression or whether COPD patients develop a low Vitamin D status as a consequence of the disease [16].

This review summarizes the relationship between Vitamin D and exacerbation in COPD patients. We reviewed clinical trials and observational and human studies that investigated Vitamin D levels and

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Table 1
Studies on Vitamin D and exacerbation in COPD patients included in this review.

First Author [Ref.]	Study design	Sample size and gender (M/F)	Age (years)	FEV_1% predicted	Main result
Quint (Quint et al., 2012)	Prospective cohort	97 (61/36)	Mean (SD) 71.8 (± 8.8)	Mean (SD) 50.3 (± 19.7)	Low 25(OH)D levels in COPD are not associated with frequent exacerbations and do not increase susceptibility to HRV exacerbations. Independent of day length, patients who spend less time outdoors have lower 25-hydroxyVitamin D concentrations
Kunisaki (Kunisaki et al., 2012)	Prospective cohort	973 (585/388)	Mean (SD) 65.4 (± 8.6)	Mean (SD) 39.6 (± 15.6)	In patients with severe COPD, baseline 25(OH)D levels are not predictive of subsequent AECOPD
Ishii (Ishii et al., 2014)	Prospective cohort	361 (331/30)	Mean (SD) 68.9 (± 8.5)	Mean (SD) 60.3 (± 20.4)	GC variations of VDBP may affect exacerbation susceptibility, possibly leading to COPD worsening and its progression in the Japanese population
Persson (Persson et al., 2015)	Prospective cohort	426	Min-max 40–76	NA	VDBP polymorphisms showed no significant effect on exacerbation rate
Malinovschi (Malinovschi et al., 2014)	Retrospective cohort	97 (49/48)	Mean (SD) 67.5(± 10.5)	Mean (SD) 62.3 (± 18.0)	Severe Vitamin D deficiency was related to more frequent disease exacerbations and hospitalization during the year before Vitamin D measurement. This association was independent of patients' characteristics and comorbidities
Mekov (Mekov et al., 2015)	Cross-sectional	152 (108/44)	Mean (SD) 65.1 (± 9.9)	Mean (SD) 55.34 (± 19.5)	COPD patients admitted for exacerbation are a risk group for Vitamin D deficiency and insufficiency, which are associated with worse disease characteristics
Puhan (Puhan et al., 2014)	Cross-sectional	356 (208/148)	Mean (SD) 67.2(± 10.0)	Mean (SD) 56.0 (± 15.9)	This longitudinal study in a real-world COPD population that carefully minimized misclassification of exacerbations and the influence of confounding did not show an association between 25-hydroxyVitamin D and exacerbations and mortality
Zendedel (Zendedel et al., 2015)	Clinical trial	88 (28/60)	NA	Mean (SD) 34.6 ± 8.5 ^{CA} 34.4 ± 9.2 ^{CT}	Vitamin D intake decreased COPD exacerbation in patients with severe and very severe COPD
Martineau (Martineau et al., 2015)	Clinical trial	122 (76/47)^{VDG} 118 (69/49) ^{PG}	Mean (SD) 64.8(± 7.9)^{VDG} 64.5(± 9.2)^{PG}	Mean (SD) 63.7(± 20.6)^{VDG} 64.5 (± 20.7) ^{PG}	Vitamin D3 supplementation protected against moderate or severe exacerbation, but not upper respiratory infection, in patients with COPD with baseline 25(OH)D levels < 50 nmol/L. Findings suggest that correction of Vitamin D deficiency in patients with COPD reduces the risk of moderate or severe exacerbation.
Lehouck (Lehouck et al., 2012)	Clinical trial	91 (72/19) ^{VDG} 91 (73/18) ^{PG}	Mean (SD) 68 (± 9) ^{VDG} 68 (± 8) ^{PG}	Mean (SD) 44 (± 16) ^{VDG} 42 (± 14) ^{PG}	High-dose Vitamin D supplementation in a sample of patients with COPD did not reduce the incidence of exacerbations. In participants with severe Vitamin D deficiency at baseline, supplementation may reduce exacerbations
Rafiq (Rafiq et al., 2015)	Study protocol Clinical Trial	240	NA	NA	There is a study protocol in progress, in which 240 COPD patients with Vitamin D deficiency (25(OH)D concentration < 50 nmol/L) will receive Vitamin D3 16800 IU or placebo orally once a week for 1 year.
Zhu (Zhu et al., 2016)	Meta-analysis	NA	NA	NA	Vitamin D deficiency is associated with increased risk of COPD and severe COPD but not with COPD exacerbation.
Jung (Jung et al., 2015)	Cohort	193	Mean (SD) 66.1 (± 7.3)	Mean (SD) 89.9 (± 17.9)	No association between exacerbation and plasma 25(OH)D3 level was found
Moberg (Moberg et al., 2014)	Cohort	423 (165/258)	Mean (SD) 68.9 (± 9.3)	Mean (SD) 37.7 (± 13.8)	Leukocytes and CRP add little information on prognosis and Vitamin D does not seem to be a useful biomarker in severe COPD in a clinical setting
Persson (Persson et al., 2012)	Cross-sectional	433 (260/173)	Mean (SD) 63.5 (± 6.9)	Mean (SD) 49 (± 14)	The authors did not find any association between total white blood count and 25(OH)

Abbreviations: M = Male; F = Female; FEV_1 = forced expiratory volume in 1 s; SD = standard deviation; IQR = inter-quartile range; 25(OH)D = 25-hydroxyVitamin D; PG = placebo group, VDG = Vitamin D group; NA = not available.

their effects in this population. We searched the PubMed database for articles from 2012 using the terms “COPD”, “exacerbation” and “Vitamin D”. Two authors (RF and LMOC) independently screened the resulting titles and abstracts and further reviewed the full text for potentially eligible studies showing an association between Vitamin D and COPD exacerbation. Non-English articles, articles where the full text was unavailable, and cell or animal models were excluded. We also manually searched the reference lists of the selected articles to identify additional qualifying studies. Based on these search strategies, a total of 15 articles were selected. Table 1 shows the included studies characteristics. Their study designs consisted of one meta-analysis, one protocol study for clinical trial, three randomized clinical trials, and ten observational studies. The articles included, Vitamin D measured by dietary intake, serum or plasma 25-hydroxyVitamin D [25(OH)D], Vitamin D-binding protein (VDBP) gene polymorphisms, and Vitamin D receptor (VDR) polymorphisms.

2. Vitamin D levels review

COPD patients are classified in subgroups or phenotypes based on specific features, which are associated with prognosis; the most notable feature being frequent exacerbations [17]. Lower Vitamin D levels were associated with hospitalization caused by exacerbation after adjustments for gender, age, body mass index, smoking, and lung function; this association persisted after further adjusting for comorbidities [18].

We identified one meta-analysis consisting of 21 observational studies from which five studies assessed Vitamin D levels and exacerbation in the blood; this study revealed that patients with exacerbation had lower 25(OH)D levels compared to stable patients [19]. In contrast, prospective and cohort studies did not show an association between exacerbation frequency and blood Vitamin D levels [20–24].

It is important to remember that observational studies may have difficulties in showing associations between Vitamin D concentration and outcomes such as respiratory picture exacerbation in COPD patients: 1) Studies based on a single serum Vitamin D measurement can lead to weak associations. In fact, a cohort study that included repeated Vitamin D measurements reported changes in numeric values during different seasons [24]. 2) The marker chosen to represent Vitamin D nutritional status may not be the most appropriate. 3) Another concern is to assume that the association between 25(OH)D and COPD outcomes is linear. Studies on Vitamin D and cardiovascular diseases have shown a non-linear association [25,26]. A linear association probably underestimates the true estimated effect. 4) Observational studies fail to show the existence of a causal relationship; this requires a randomized controlled trial.

3. Vitamin D binding protein (VDBP)

As mentioned above, 25(OH)D level may not represent real Vitamin D status and data suggest that assessing free Vitamin D may provide additional information and guide clinical practice. Free Vitamin D levels are dependent on VDBP - the higher the VDBP level, the lower the free Vitamin D level. The main role of VDBP is in transporting 25-hydroxyVitamin D, the main circulating form of Vitamin D, and 1,25-dihydroxyVitamin D, the most active Vitamin D metabolite. However, neither the level of 25(OH)D, VDBP, nor the ratio between them were significant predictors moderate or severe COPD exacerbations [27].

Analyzing VDBP gene polymorphisms can be another way of evaluating Vitamin D action. There are more than 120 polymorphism variations in the VDBP gene; for practical purposes GC1F, GC1S and GC2, the three major DBP polymorphic alleles in humans are the relevant ones yielding six allelic combinations and corresponding phenotypes [28]. Janssens and collaborators et al. [9] showed that GC polymorphism of the VDBP gene in COPD resulted in a 25% reduction of 25(OH)D serum concentration in homozygous carriers of the rs7041 at-risk T allele.

The association between VDBP gene polymorphisms and COPD exacerbation was studied by Ishii et al. [29]. The authors performed genotype analysis of COPD patients and controls to identify two coding single nucleotide polymorphisms of GC, rs4588 and rs7041. The authors found that subjects with a C allele at rs4588 had a higher exacerbation frequency [29]. In this way, the study of VDBP polymorphisms may help verify the causal relationship between Vitamin D and COPD. VDR gene polymorphisms, such as TaqI and BsmI have been identified [30]. Quint et al. investigated whether the frequency of VDR polymorphisms [*Fok*I (rs2228570), TaqIα (rs731236), *Bsm*I polymorphism (rs1544410)] differed between frequent and infrequent exacerbators in COPD patients, but no relationship was found between exacerbation frequency and any VDR polymorphism [20]. Thus, it seems that some VDBP polymorphisms, by decreasing the amount of free Vitamin D, lead to hypovitaminosis D facilitating exacerbations.

4. Vitamin D deficiency

In the last few years, studies have emphasized that Vitamin D deficiency levels in COPD patients contribute to respiratory system colonization and infections [4,31–35]; these show that the relationship between Vitamin D status and COPD exacerbation has been investigated. In observational studies, we found a retrospective cohort in which severe Vitamin D deficiency (< 25 nmol/L) was related to more frequent COPD exacerbations and patient hospitalization during the year prior to Vitamin D measurement [18]. In a longitudinal study, Persson et al. showed that COPD patients with hypovitaminosis D (< 50 nmol/L, n = 142) were more often current smokers, had more severe COPD, and were more likely to be frequent exacerbators [27].

Randomized controlled trials are known to be the “gold standard” design for establishing causal relationships between exposure and outcome [36]. We found three clinical trials where Vitamin D3 supplementation in COPD patients reduced the risk of moderate or severe exacerbation [33,37,38]. These trials offered 100,000 IU (2500 mcg) of oral Vitamin D3 or placebo every 4 weeks for 1 year [37], every month for 6 months [38] and every two months for one year [33]. In post-hoc subgroup analysis, Martineau and colleagues [37] found a significantly reduced exacerbation rate in patients with baseline 25(OH)D concentrations below 25 nmol/L. In a recent pilot trial [39] where exacerbation rate was assessed as a secondary outcome, no difference was found in exacerbation rate between the supplementation (1200 IU of oral of Vitamin D3 per day during 6 months) and placebo group. However, patients with an exacerbation in the preceding year were not included in contrast to the previous studies [33,37]. Also, patients with severe Vitamin D deficiency (< 15 nmol/L) were excluded, which may have led to the selection of COPD patients with a milder form of the disease, as suggested by the authors [39]. Thus, a group of patients with low Vitamin D levels may benefit from supplementation with this vitamin.

5. Final considerations

Fig. 1 illustrates the relationship between Vitamin D and COPD exacerbation.

Association between exacerbation frequency and Vitamin D in observational studies is still controversial, however, meta-analysis, which included some of the studies showing no association, revealed a negative association between serum Vitamin D and exacerbation [19]. This meta-analysis also showed that Vitamin D deficiency (< 50 nmol/L) was not associated with COPD exacerbation. This cutoff point is calculated for bone health and the best cut-off point for outcomes in COPD is still unknown; it is important to consider assay methods in the sources of heterogeneity when analyzing the association between Vitamin D deficiency and COPD. Furthermore, using only serum 25(OH)D measurements is not a good marker of Vitamin D nutritional status. Besides the routine 25(OH)D and 1,25(OH)2 Vitamin D testing, other

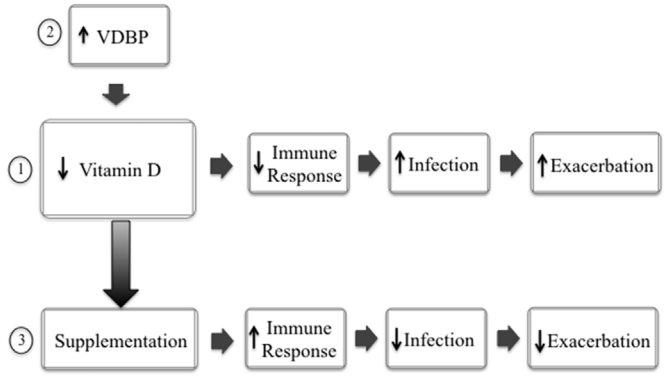

Fig. 1. Relationship between Vitamin D and COPD exacerbation. 1 – Low levels of Vitamin D are associated with decreased immune response and consequently lead to increased infections. COPD exacerbations are often triggered by viral or bacterial infections; therefore the risk exacerbation increases. 2 - Free Vitamin D levels are dependent on Vitamin D binding protein (VDBP) and therefore higher VDBP concentrations mean lower levels of free Vitamin D with a consequent increase in COPD exacerbation. 3 - Clinical trials have shown that supplementation reduces the risk of exacerbation in COPD patients with low Vitamin D levels enhancing innate immunity by upregulating antimicrobial peptides.

research assays have been developed for measuring 24,25(OH)2 Vitamin D, and free and bioavailable 25(OH)D, which are thought to be superior Vitamin D action markers in cases of low or high VDBP concentrations. Existing assays must be optimized and new assays developed to give researchers a better understand of the complex nature of Vitamin D physiology and metabolism, and to define the future of Vitamin D testing in clinical laboratories [40].

Data from literature suggest that GC polymorphisms affect susceptibility to exacerbations [29]. The action of Vitamin D in target cells occurs predominantly through its interaction with the Vitamin D receptor (VDR). VDR gene polymorphisms can also have a relationship with exacerbation. In order to determine 25(OH)D as a blood biomarker in COPD, the role of this genotype must be considered. Since GC polymorphisms seem to be associated with exacerbation frequency in COPD patients, more studies with more polymorphisms, including the VDR gene, are necessary.

Clinical trials, which are the gold standard, have shown that supplementation seems to reduce the risk of moderate or severe exacerbation, however, since the results are from subgroup analyses in individuals with 25(OH)D levels lower than 50 nmol/L [33] and lower than 25 nmol/L [37], other randomized controlled trials must be performed which include only patients with baseline 25(OH)D concentrations below 50 nmol/L for the benefits of supplementation to be confirmed. There is a study protocol in progress, in which 240 COPD patients with hypovitaminosis D (25(OH)D concentration $<$ 50 nmol/L) will receive Vitamin D3 16,800 IU (420mcg) or placebo orally once a week for 1 year. The results of this clinical trial will offer new insight into the effects of Vitamin D supplementation on exacerbation rate [41].

6. Conclusions

Literature has little data regarding studies on diet, 25(OH)D and polymorphism in COPD exacerbation. Clinical trials have indicated that Vitamin D supplementation in COPD patients with hypovitaminosis D prevents exacerbations. Further studies are needed to elucidate the role of Vitamin D in this population and to establish the best marker for Vitamin D, which subgroup of patients will benefit from supplementation, and what is the best dose to supplement without leading to toxicity.

Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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