ISSN 2219-2808 (online)

World Journal of *Clinical Pediatrics*

World J Clin Pediatr 2017 August 8; 6(3): 132-160

Published by Baishideng Publishing Group Inc

WJCP

World Journal of Clinical Pediatrics

Contents

Quarterly Volume 6 Number 3 August 8, 2017

Contents

World Journal of Clinical Pediatrics
Volume 6 Number 3 August 8, 2017

NAME OF JOURNAL
World Journal of Clinical Pediatrics

ISSN
ISSN 2219-2808 (online)

LAUNCH DATE
June 8, 2012

FREQUENCY
Quarterly

EDITORIAL OFFICE
Xiu-Xia Song, Director
World Journal of Clinical Pediatrics
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
7901 Stoneridge Drive,
Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLICATION DATE
August 8, 2017

INSTRUCTIONS TO AUTHORS
http://www.wjgnet.com/bpg/gerinfo/204

ONLINE SUBMISSION
http://www.f6publishing.com

World Journal of Clinical Pediatrics

Submit a Manuscript: http://www.f6publishing.com

World J Clin Pediatr 2017 August 8; 6(3): 132-142

DOI: 10.5409/wjcp.v6.i3.132

ISSN 2219-2808 (online)

REVIEW

Role of vitamin D in cystic fibrosis and non-cystic fibrosis bronchiectasis

Maria Moustaki, Ioanna Loukou, Kostas N Priftis, Konstantinos Douros

Maria Moustaki, Ioanna Loukou, Cystic Fibrosis Unit, "Aghia Sophia" Children's Hospital, 11527 Athens, Greece

Kostas N Priftis, Konstantinos Douros, Pediatric Allergy and Respiratory Unit, 3rd Department of Pediatrics, "Attikon" Hospital, University of Athens School of Medicine, 12462 Athens, Greece

Author contributions: Moustaki M and Loukou I wrote the first draft of the manuscript; Priftis KN and Douros K reviewed the draft, made changes, and completed the final version; all authors approved the submitted version.

Conflict-of-interest statement: The authors declare no conflict of interest.

Manuscript source: Invited manuscript

Correspondence to: Dr. Kostas N Priftis, Assistant Professor, Pediatric Allergy and Respiratory Unit, 3rd Department of Pediatrics, "Attikon" Hospital, University of Athens School of Medicine, 1 Rimini Str, 12462 Chaidari, Greece. kpriftis@otenet.gr
Telephone: +30-210-5832228
Fax: +30-210-5832229

Received: January 11, 2017
Peer-review started: January 11, 2017
First decision: February 20, 2017
Revised: May 26, 2017
Accepted: June 12, 2017
Article in press: June 13, 2017
Published online: August 8, 2017

Abstract

Bronchiectasis is usually classified as cystic fibrosis (CF) related or CF unrelated (non-CF); the latter is not considered an orphan disease any more, even in developed countries. Irrespective of the underlying etiology, bronchiectasis is the result of interaction between host, pathogens, and environment. Vitamin D is known to be involved in a wide spectrum of significant immunomodulatory effects such as down-regulation of pro-inflammatory cytokines and chemokines. Respiratory epithelial cells constitutively express 1α-hydroxylase leading to the local transformation of the inactive 25(OH)-vitamin D to the active 1,25$(OH)_2$-vitamin D. The latter through its autocrine and paracrine functions up-regulates vitamin D dependent genes with important consequences in the local immunity of lungs. Despite the scarcity of direct evidence on the involvement of vitamin D deficiency states in the development of bronchiectasis in either CF or non-CF patients, it is reasonable to postulate that vitamin D may play some role in the pathogenesis of lung diseases and especially bronchiectasis. The potential contribution of vitamin D deficiency in the process of bronchiectasis is of particular clinical importance, taking into consideration the increasing prevalence of vitamin D deficiency worldwide and the significant morbidity of bronchiectasis. Given the well-established association of vitamin D deficiency with increased inflammation, and the indicative evidence for harmful consequences in lungs, it is intriguing to speculate that the administration of vitamin D supplementation could be a reasonable and cost effective supplementary therapeutic approach for children with non-CF bronchiectasis. Regarding CF patients, maybe in the future as more data become available, we have to re-evaluate our policy on the most appropriate dosage scheme for vitamin D.

Key words: Vitamin D; Bronchiectasis; Cystic fibrosis; Vitamin D supplementation

Core tip: Vitamin D deficiency seems to be associated with respiratory health. Herein, we present the experimental and epidemiological data that imply a role of vitamin D

deficiency in the development of cystic fibrosis (CF) and non-CF bronchiectasis. Numerous experimental data provide insight to the mechanism by which vitamin D modulates immunity, and therefore its deficiency may enhance the susceptibility to infectious diseases and affect the control of inflammation process. Epidemiological data provide evidence for the association of vitamin D deficiency and bronchiectasis, either directly or indirectly, through its relation with the risk for respiratory tract infections. This knowledge is of interest for the pediatrician as vitamin D supplementation may be a future candidate therapeutic option for bronchiectasis.

Moustaki M, Loukou I, Priftis KN, Douros K. Role of vitamin D in cystic fibrosis and non-cystic fibrosis bronchiectasis. *World J Clin Pediatr* 2017; 6(3): 132-142 Available from: URL: http://www.wjgnet.com/2219-2808/full/v6/i3/132.htm DOI: http://dx.doi.org/10.5409/wjcp.v6.i3.132

INTRODUCTION

In 1922, vitamin D was identified as a nutrient, derived from cod, shark and burbot liver oil, which promoted calcium deposition in the bones of rachitic rats[1]. In 1925, it was found that vitamin D is mainly synthesized in the skin by the transformation of 7-dehydrocholesterol upon exposure to sunlight[2,3]. Nowadays, it is well known that the main source of vitamin D is the skin through the transformation of its precursor, 7-dehydrocholesterol by ultraviolet B radiation. Only tiny amounts are ingested from the usual diet, with the exception of fish oil and dairy products fortified with vitamin D.

Vitamin D is hydroxylated in the liver by mitochondrial 25-hydroxylase enzyme to 25(OH) vitamin D [25(OH)D, calcidiol], and then an amount of this compound undergoes a further conversion to 1,25(OH)$_2$ vitamin D [1,25(OH)$_2$D, calcitriol] by the kidney enzyme 25-hydroxyvitamin D-1-α hydroxylase (1α-hydroxylase). The latter is encoded by the gene *CYP27B1*[4]. Additionally, the mitochondrial enzyme 25-hydroxyvitamin D-24 hydroxylase produces the inactive forms 24,25(OH)$_2$D and 1,24,25(OH)$_3$D using as substrates the 25(OH)D and 1,25(OH)$_2$D, respectively[5,6].

1,25(OH)$_2$D and 25(OH)D are the most biologically active and the major circulating forms of vitamin D, respectively[7,8]. The relatively stable metabolite 25(OH)D and, to some extent, 1,25(OH)$_2$D are bound to the vitamin D binding protein (VDBP)[9]. In total, 99% of circulating vitamin D compounds are bound either to the VDBP or, to a lesser degree, to albumin and lipoproteins[10].

The serum levels of the 25(OH)D reflect the vitamin's body stores are used to determine its status[11]. Calcitriol is not an adequate status indicator as it has short half life and its synthesis depends mainly on homeostatic regulation mechanisms and not on 25(OH)D levels[12,13]. The deficiency and insufficiency status of vitamin D are generally defined by 25(OH)D serum levels < 20 ng/mL and 20-30 ng/mL, respectively[14]. Using these definitions it has been estimated that about 1 billion people worldwide have either vitamin D deficiency or insufficiency, with children and adolescents being at high risk for vitamin D deficiency[15]. However, the definition of the different states of vitamin D status is not unambiguous and it remains a matter of debate among scientists.

To date, calcitriol is considered a hormone with endocrine actions that are not limited to calcium and phosphorus homeostasis and bone turnover, as it was initially thought. For the exertion of most of its biological actions calcitriol, interacts with the nuclear vitamin D receptor (VDR) which belongs to the superfamily of nuclear receptors for steroid hormones[10]. As early as 1979, it was shown in a rat model that receptors of calcitriol exist in target tissues that were not known to participate in vitamin D metabolism until then[16]. The first time the extra-skeletal effects of vitamin D were observed was in early 80's, with the reports of differentiation-inducing effect of 1,25(OH)$_2$D$_3$ in mouse leukemia and human myeloid leukemia cells[17,18]. Thus far, it is recognized that VDRs are present in several (but not in all) tissues throughout the body such as skin, placenta, pancreas, breast, prostate, and immunity cells[7,19]. Additionally, it was shown that 1,25(OH)$_2$D can also be produced extrarenally as 1α-hydroxylase has been isolated in different tissues and cells such as prostate, breast, colon, lung, skin, pancreatic β cells, immune cells (including alveolar macrophages, dentritic cells and lymphocytes), and airway epithelia[10,20]. Extrarenally produced 1,25(OH)$_2$D has autocrine and paracrine functions inhibiting cell proliferation, promoting cell differentiation, regulating apoptosis and modulating immune responses[10].

Since the discovery that VDRs, and 1α-hydroxylase are present in several tissues and in different types of cells, several research efforts, either experimental or epidemiological, have been performed aiming to understand the biological significance of these findings. There is now a growing body of evidence suggesting that vitamin D may have a role in the evolvement of different diseases such as malignant, autoimmune, infectious, cardiovascular, and lung disorders[21]. More specifically, it seems that vitamin D through the modulation of immune and inflammatory responses may be involved in the pathophysiology of several respiratory disorders such as asthma, cystic fibrosis (CF), chronic obstructive lung diseases, cancer, respiratory infections, interstitial lung diseases and bronchiectasis[12,22-26]. Respiratory epithelial cells constitutively express 1α-hydroxylase leading to the local transformation of the inactive 25(OH)D to the active 1,25(OH)$_2$D[27]. This active form of vitamin D exerts its autocrine/paracrine function upregulating vitamin D dependent genes with important consequences in the local immunity of lungs[27]. It is reasonable therefore to postulate that vitamin D may play some role in the pathogenesis of lung diseases and especially bronchiectasis.

The aim of the current review is to present the existing scientific information on the possible association of vitamin D with bronchiectasis, related or not to CF. The potential contribution of vitamin D deficiency in the process of bronchiectasis is of particular clinical importance, taking into consideration the increasing prevalence of vitamin D deficiency worldwide and the significant morbidity of bronchiectasis, especially among children of socially disadvantaged populations[28].

BRONCHIECTASIS

Non-CF bronchiectasis

Bronchiectasis is a word of Greek origin and means dilated bronchi. This condition was first described in pathological specimens in 1819 by Rene Laennec, who also invented the stethoscope[29]. The term was used to describe dilated and inflamed bronchi according to the pathological findings[30].

Thirty years ago, bronchiectasis in children was considered an orphan disease[31]. Since then, and especially after bronchography was superseded by high resolution computed tomographic scanning (HRCT) as the most commonly used technique for diagnosis, it has been recognized that the burden of bronchiectasis in childhood is low but not negligible[31]. However, the etiology is now different from that noted in the 50's when symptoms of bronchiectasis usually started after pertussis or measles[32]. Bronchiectasis nowadays is classified as either related or unrelated to CF, with the latter defined as non-CF bronchiectasis. The etiology of non-CF pediatric bronchiectasis is only remotely associated with vaccine preventable diseases such as measles or pertussis. There are several original studies and reviews in the literature that discuss the etiology of pediatric non-CF bronchiectasis. A recent systematic review of 989 affected subjects from twelve relevant studies summarized the available information of cases diagnosed by chest computed tomography. Infectious diseases, such as pneumonia, measles, tuberculosis, varicella, accounted for 19% of non-CF pediatric bronchiectasis followed by primary immunodeficiency (17%), aspiration/foreign body (10%), and primary ciliary dyskinesia (7%). No causal association was identified in about a third of cases[33].

In the guidelines published by the Thoracic Society of Australia and New Zealand, the prerequisites for clinical suspicion of the syndrome in children is: (1) persistent wet cough not responding to four weeks of antibiotics; (2) more than three episodes of wet cough per year responding to antibiotics and lasting more than four weeks; or (3) a persisting for more than six weeks chest radiograph abnormality despite the appropriate treatment[34].

As it has already been mentioned, HRCT is now the gold standard for the diagnosis of bronchiectasis[33,34]. As it was shown by Grenier *et al*[35] in an adult population, using as diagnostic standard the bronchographic findings, HRCTs with 1.5 mm section thickness at 10 mm intersection spacing, attained a sensitivity of 96% and specificity of 93% regarding the detection of bronchiectasis. Eastham *et al*[36] studied retrospectively 93 children with HRCT confirmed bronchiectasis and found that they constituted 9.6% of all new referrals to their tertiary pediatric respiratory center; this number represented a 10-fold higher rate of the respective diagnosis prior to the introduction of HRCT scanning[37]. It is therefore plausible to assume that the introduction of HRCT scanning has contributed significantly to the recognition of the true burden of bronchiectasis in childhood. Furthermore, Eastham *et al*[36] showed that HRCT diagnosed bronchiectasis in children is not always irreversible; it may progress to established bronchiectasis, but it may also return to a pre-bronchiectatic stage, or even resolve entirely. It is therefore conceivable that the early recognition of bronchiectasis and the prompt initiation of the appropriate treatment are of great importance in order to prevent the establishment of irreversible lesions.

CF bronchiectasis

Cystic fibrosis is the most common lethal, autosomal recessive disorder, among Caucasians. It is due to mutations in a gene called cystic fibrosis transmembrane conductance regulator (CFTR) that encodes chloride channels called CFTR proteins; bronchial epithelial cells, express CFTR proteins in their apical membranes[38]. Pathologic CFTR mutations impair the production of the corresponding protein and therefore, there is dysregulation of ion movement in the bronchial surface, excessive absorption of airway surface liquid, and dehydration and hyperviscosity of airway secretions. The latter remain stagnant, form mucus plugs and obstruct bronchial lumen. The ensuing defective mucociliary clearance favours the intraluminal survival and proliferation of bacteria, and leads in chronic endobronchial infection[39-41]. Chronic infection induces a persistent and intense inflammatory response in the airways characterized by abundance of neutrophils. The main proinflammatory mediators involved in the recruitment of neutrophils are interleukin (IL)-1β, tumour necrosis factor α, leukotriene β4, and especially some cytokines of the CXC chemokine family, particularly CXCL8 (also known as IL-8)[42]. Neutrophils generate cytokines, oxidants and proteases, such as neutrophilic elastase. The produced proteases are so abundant that overpower the antiprotease protection of the lung[40,43,44]. However, despite extensive mobilization of the lung's defensive mechanisms, infection cannot be eradicated from the airways. On the contrary, it persists and deteriorates progressively, leading to worsening of chronic inflammation, further impairment of mucociliary clearance, and permanent presence of bacteria growing in biofilm structures. Collectively, these events represent a vicious cycle that results in progressive destruction of the airways and will eventually lead to bronchiectasis and respiratory failure. In addition to the above described sequence of detrimental events there is also evidence

suggesting that mutations of the *CFTR* gene, can have a direct deleterious impact on airway immunity, through dysregulation of inflammatory mediators production, ineffective airway inflammation, and modification of responses to pathogens[40,45].

Common features between CF and non-CF bronchiectasis and a possible role for vitamin D in disease pathogenesis

Irrespective of its underlying etiology, bronchiectasis is the result of the interaction between host, pathogens and environment[31]. Dysregulated host immune responses, airway inflammation and the presence of pathogens contribute to the pathophysiology of bronchiectasis. The current concept on the pathogenesis of bronchiectasis in children is the "vicious circle hypothesis". The vicious circle may begin with any event that impairs mucociliary clearance and permits the establishment of bacterial "colonisation" in the lower airways, and hence predisposes to biofilm formation[46]. What it follows is a period of persistent bacterial bronchitis, which acts as the driving force for the chronic inflammation, and finally creates sufficient bronchial damage to appear as bronchiectasis on a CT scan. The initial impairment to mucociliary clearance may be due to various reasons, such as a viral lower respiratory tract infection that destroys cilia which may take many weeks before fully recover[47]; airway inflammation and mucus plugging as in asthma; dehydration of the peri-ciliary liquid and mucus as in CF; structural obstruction as in tracheomalacia and foreign body aspiration; microaspirations and impaired cough in children with serious neurological impairments; or is in itself secondary to bacterial infections in patients with significant immunodeficiencies[48].

Vitamin D, as it was aforementioned, may have anti-infective and anti-inflammatory properties and therefore may play some role in the pathogenesis of the disease. For this reason, the host immune and inflammatory responses in CF and non-CF bronchiectasis in relation to vitamin D status, as well as its potential link with respiratory tract infections, will be presented in the following sections.

VITAMIN D AND IMMUNITY

Innate immunity

The presence of VDR in cells of the innate immune system, such as dendritic cells, peripheral blood mononuclear cells, activated T lymphocytes, and even quiescent CD4 T cells[49,50] along with the presence in macrophages and dendritic cells of the enzymes responsible for activation and degradation of vitamin D (1a-hydroxylase, and 25-hydroxyvitamin D-24-hydroxylase, respectively)[51], implies that vitamin D has an active part in innate immunity. Indeed, several studies have shown that vitamin D possesses a modulatory function exerted in a number of ways, some of which will be discussed below. Antimicrobial activity of innate immunity is influenced by vitamin D through the induction in monocytes, skin, and lung, of cathelicidin[52,53] which is an antimicrobial peptide having a central role in host defense against bacterial infections[54,55]. It is most likely that vitamin D inhibits the growth of bacteria in the airways through cathelicidin. It is known that the ability of CF airway epithelia to kill bacteria is impaired[56]. The antibacterial activity of CF bronchial cells against *Pseudomonas aeruginosa* can be partially restored through cathelicidin induction after treatment with $1,25(OH)_2D$[57,58]. Besides, cathelicidin expression in the airways is associated with local - but not serum - levels of vitamin D[59,60], and bronchial cells with mutated CFTR have a decreased ability to activate vitamin D[61]. Collectively, the above results may suggest that vitamin D up-regulates activity of cathelicidin, and perhaps of other innate immunity components, in response to bronchial bacterial infections. This up-regulation seems to be impaired in CF airways due to inadequate local activation of vitamin D.

The immune stimulus per se can affect local 25(OH) D metabolism as it is suggested by the increase in 1a-hydroxylase mRNA expression and $1,25(OH)_2D$ synthesis of respiratory epithelial cells, after stimulation of Toll-like receptor-3 by viral RNA[27]. The above evidence strongly supports the hypothesis that a local pro-inflammatory microenvironment can influence vitamin's D metabolism. This fascinating phenomenon has been described in patients suffering from Crohn's disease[62]; however, up to now, there are no studies examining the effects of chronic endobronchial infection on the local metabolism of vitamin D.

Dendritic cells have a critical role in innate immunity and can promote the differentiation of naïve $CD4^+$ T cells to either effector or regulatory T-cells (Treg). vitamin D can affect the stimulatory characteristics of DCs and change the balance towards the induction of $CD4^+CD25^+Foxp3^+$ Treg. It can also enhance recruitment of Treg cells at inflammatory sites[63]. This suppressive, anti-inflammatory function of vitamin D may contribute to the limitation of chronic bronchial inflammation and have a beneficial effect in the control of the disease.

Adaptive immunity

Vitamin D also plays a role in modifying adaptive immunity while it is not yet clear if it moves the balance towards Th1 or Th2 response. The literature has provided us with a surge of evidence, though sometimes the results are conflicting. Thus, it was demonstrated that the administration of vitamin D decreased Th1 cytokine secretion and inhibited T-cell proliferation[64,65]. Vitamin D was also shown to either inhibit or enhance Th2 cell differentiation and production of Th2 cytokines[66]. In another study on human cord naive CD4 and CD8 T cells it was demonstrated that vitamin D exhibits an inhibitory effect on IFN-γ production through IL-12, and it can also suppress IL-4, and IL-13 expression induced by IL-4[67]. Matheu *et al*[68] found that the administration of vitamin D in rodents could induce IL-4, IL-5, and IL-13. However, Jorde *et al*[69] study on the effects of vitamin

D administration in obese humans did not corroborated the previous result. Vitamin D supplementation did not induce Th2 responses *in vivo* whereas, on the other hand, proinflammatory TH17 responses were blocked by administration of vitamin D in mice and humans[70-72]. Regarding B cells, it is known that treatment with 1,25(OH)$_2$D hinders proliferation and differentiation to IgG secreting plasma cells[73]. Although there are enough data to recognize the impact of vitamin D in adaptive immunity, the picture becomes less clear when considering the direct consequences in CF and non-CF bronchiectasis. There are only some sparse data indirectly relating the immunological effects of vitamin D with bronchiectasis. Vitamin D reduces the expression in Th17 cells of IL-17, which is a cytokine found elevated in the sputum and the lungs of CF patients[74,75]. Aspergillus fumigatus, has been implicated as a common cause of both CF and non-CF bronchiectasis[76]. Recently, it was shown that CF patients with allergic bronchopulmonary aspergillosis (ABPA) had increased Th2 reactivity, and this was associated with lower serum vitamin D levels. When 1,25(OH)$_2$D was added to CD4$^+$ T cells isolated from these patients, the induction of IL-5 and IL-13 by Aspergillus decreased and Th2 responses of CD4$^+$ T cells were reduced[71]. Aspergillus-induced lung inflammation in CF was further studied by Coughlan *et al*[77] who demonstrated that Aspergillus bronchial colonization can increase Th2 cytokine production, through down-regulation of VDR expression. This down-regulation could be reversed with itraconazole treatment of Aspergillus[77]. The authors suggested that supplementation of vitamin D could probably have a useful therapeutic effect in preventing ABPA on condition that there would be concurrent elimination of Aspergillus to permit VDR expression.

INDIRECT EVIDENCE IMPLYING A ROLE OF VITAMIN D IN THE PATHOGENESIS OF BRONCHIECTASIS

Relation between vitamin D and lung disease: Experimental and epidemiological data

Despite the knowledge gained over the years on the role of vitamin D in musculoskeletal system, the existing evidence over its effects in the pathogenesis and outcome of CF and non-CF bronchiectasis is sparse. There are some interesting data however implying a pathogenetic role of vitamin D insufficiency in the induction of damage in lung tissue.

The main reasoning behind this hypothesis is that lung is deprived of the vitamin's anti-inflammatory capacity. Vitamin D down-regulates cytokines and chemokines that promote tissue destruction, and are found in abundance in CF and non-CF bronchiectatic lungs[22,78]. It was shown that CF respiratory epithelial cells and macrophages incubated with 1,25(OH)$_2$D displayed a significant down-regulation in the neutrophil-attracting chemokine, IL-8[79,80], and that high doses of cholecalciferol (250000 IU) in adults hospitalized with pulmonary exacerbation of CF resulted in a reduction in the serum levels of IL-6 and TNF-α[81].

The anti-inflammatory activity of vitamin D may originate from the promotion of anti-inflammatory/regulatory cytokines secretion, such as IL-10[82]. However, the mechanisms involved in up-regulation of anti-inflammatory and down-regulation of pro-inflammatory cytokines may not be simply due to the 1,25(OH)$_2$D binding to vitamin D Response Elements (VDRE), which are specific upstream sequences in gene promoters that activate gene transcription. They may also occur through other indirect modulatory routes acting through signaling proteins that control the expression of anti- and pro-inflammatory cytokines[78].

MAPK phosphatase 1 (MKP-1), is such an example; the enzyme is an inhibitor of pro-inflammatory signaling and contains VDRE within its gene promoter. It is known to be up-regulated by either 25(OH)D or 1,25(OH)$_2$D, in a dose-dependent manner. 1,25(OH)$_2$D induces the expression of MKP-1 in human monocytes[83]. In blood mononuclear cells isolated from asthmatic patients, baseline MKP-1 mRNA was associated with serum 25(OH)D levels. Also, in patients not treated with inhaled steroids, dexamethasone-induced MKP-1 expression increased with higher 25(OH)D levels. These results imply that local 1,25(OH)$_2$D production may increase MKP-1 expression[78,84].

Other likely mechanisms implicated in cytokine suppression may include VDRE-independent inhibition of a major pro-inflammatory factor, namely nuclear-factor kappa B (NF-κB). 1,25(OH)$_2$D has been associated with a significant decline in translocation of NF-κB into the nucleus, possibly through the stimulation of IκB-α (the inhibitor of NF-κB) by 1,25(OH)$_2$D[19,85]. 1,25(OH)$_2$D has been shown to modulate IκB-α through either transcriptional or transcription-independent mechanisms, resulting in an increase of mRNA expression of IκB-α and stabilization of IκB-α protein[86,87]. The above data are summarized in Table 1.

In two retrospective studies vitamin D insufficiency was found to be correlated with the severity of lung disease in CF children. Simoneau *et al*[88] observed that vitamin D insufficiency was associated with Pseudomonas bronchial infection, and McCauley *et al* observed that 25(OH)D levels were negatively associated with the rate of pulmonary exacerbations in children, and positively with FEV1 in adolescents. The results from some studies in CF patients indicate towards an association between low 25(OH)D levels and declining lung function. However, this finding was not universal, and has not been confirmed in children[81,89-93]. The effects of vitamin D in the lung function of adults, but not pediatric, CF patients may suggest that vitamin D deficiency exerts greater influence on CF lungs as the disease progresses[78]. A reduction in the strength of respiratory muscles has been proposed as a likely mechanism, though there is no evidence to prove it. Furthermore, the relation might not be causal since the severity of lung disease may result

Table 1 Potential immunological functions of vitamin D involved in the pathogenesis of lung disease

Function	Affected immune responses
Direct down-regulation of pro-inflammatory cytokines	IL-8, IL-6, and TNF-α
Direct up-regulation of regulatory cytokines	IL-10
Up-regulation of MKP-1	Inhibition of MAPKs pathways (critical for the mounting of innate immune responses)
Increase production and stabilization of IκB-α	Inhibition of NF-κB (regulates the expression of numerous inflammatory components)

MAPK: Mitogen-activated protein kinases; IL: Interleukin; TNF: Tumor necrosis factor; MKP-1: MAPK phosphatase-1; NF-κB: Nuclear-factor kappa B; IκB-α: Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (the inhibitor of NF-κB).

in the sequence of reduced physical activity, less sun exposure, and decrease in serum 25(OH)D levels.

Vitamin D and respiratory tract infection: Epidemiological studies

Bacterial bronchial infection constitutes an integral part in the pathogenesis of bronchiectasis, although it has also been suggested that resident microbiota as well as viral and other infections (mycobacteria) are among the pathogens of the vicious cycle of bronchiectasis pathophysiology[31]. It is has been well known since 1959 that the majority of children with bronchiectasis grew some pathogen in their sputum cultures. Recent bronchoalveolar lavage studies have shown that the most commonly isolated pathogens in children with non-CF bronchiectasis are non typeable *Haemophilus influenza, Streptococcus pneumonia, Moraxella catarrhalis,* and to a lesser extent *Staphylococcus aureus* and *Pseudomonas.aeruginosa*[31,36,94].

Vitamin D deficiency is related with the risk of lung infections[95] and may be implicated in the bronchiectasis development and progression through this pathway. The first example of a possible association between vitamin D deficiency and an infectious disease was tuberculosis. It was in 1848, prior to the discovery of vitamin D, when in a study held in a London hospital, 1000 patients with tuberculosis were given either the usual care for the disease, or care plus cod liver oil three times a day. About a third of patients in the control group deteriorated or died compared to only a fifth of those on cod-liver oil[96]. Since 1980, many studies investigated a possible association of tuberculosis and vitamin D deficiency. A meta-analysis conducted in 2008 by Nnoaham *et al*[97] showed that low serum vitamin D levels were associated with increased risk for active tuberculosis. Although this meta-analysis included studies with only adult subjects, it was also shown in two later studies that serum vitamin D levels were lower in children with latent or active tuberculosis compared to the non-infected controls[98,99].

Similarly, it has been demonstrated that vitamin D deficiency is related with the risk for acute respiratory tract infection. It was in 1975 when Salimpour[100] found that 43% of 200 rachitic children suffered from bronchopneumonia, a finding that he characterized as unexpected. Later, it was corroborated by other investigators that children with rickets were at increased risk for developing respiratory infectious disease[101,102]. Muher *et al* found that, after correcting for confounders, there was a 13-fold increased incidence of rickets among Ethiopian children hospitalized with pneumonia compared to controls[101]. The results of another study from Jordan pointed to the same direction[102]. More specifically, 85% of the rachitic infants were admitted due to lower respiratory tract infections compared to only 30% of the control non-rachitic group. In two other studies from the Indian subcontinent it was found that serum vitamin D levels in non-rachitic children with lower respiratory tract infection were significantly lower compared to healthy controls[103,104]. This finding, however, was not confirmed by other investigators[105]. It is of interest however, that McNally *et al*[106] who found no association between 25(OH) vitamin D levels and risk of hospitalization for acute lower tract infection (bronchiolitis or pneumonia), observed that vitamin D deficiency influenced disease severity. More specifically, the children with acute lower tract infection who were eventually admitted to the pediatric intensive care unit, had significantly lower serum vitamin D levels compared to either the rest of the group with milder respiratory infection or the control group with no respiratory infection.

A systematic review of observational studies that was conducted by Jolliffe *et al*[95] showed that there was a significant association between low vitamin D status and the risk for acute respiratory tract infections in subjects of all ages (children and adults). On the other hand, they found that the randomized controlled clinical trials, which investigated the protective role of vitamin D supplementation from respiratory tract infections, did not point to the same direction. They attributed this inconsistency to the heterogeneity of the included trials regarding both the dose of vitamin D supplementation and the baseline levels of vitamin D prior to the intervention. Bergman *et al*[107] conducted a similar meta-analysis and found that vitamin D supplementation had a protective effect against acute respiratory infection in subjects of all ages (6 mo-75 years). However, they recognized as limitations of their meta-analysis the heterogeneity of included studies and the high likelihood of publication bias. Another systematic review[108] that included only randomized controlled pediatric trials failed to show a significant association between vitamin D supplementation and

risk for acute respiratory infection. The researchers emphasized that their results should be interpreted with caution due to the small number and heterogeneity of included studies. It seems therefore that although many studies have revealed an association between vitamin D deficiency and risk for acute respiratory infection the data are not sufficient enough to support supplementation with vitamin D as a preventive measure to lower this risk.

As calcitriol exerts most of its biological actions *via* binding to the VDR, the possibility that VDR polymorphisms were associated with the risk of respiratory infections was also explored by a number of investigators[109-111]. The majority of studies were performed in children with RSV bronchiolitis and it was suggested that there was a positive association between the FokI minor allele (ff) and susceptibility to RSV bronchiolitis[112]. This association seems to be biologically plausible since f allele encodes a less active VDR that may affect the final activity of calcitriol[110]. More recently, a VDR polymorphism was found to be associated with the susceptibility to community acquired pneumonia as well as with the disease severity in Chinese children[113].

VITAMIN D AND BRONCHIECTASIS: CLINICAL STUDIES AND CHALLENGES

To the best of our knowledge, there are no clinical studies directly exploring the presumed link between vitamin D deficiency and CF or non-CF bronchiectasis, in children. However, there is a case control study in adults with non-CF bronchiectasis. More specifically, Chalmers *et al*[114] showed that 50% of patients with bronchiectasis were vitamin D deficient and 43% insufficient, and these percentages were significantly higher in comparison with the control group. They also found that vitamin D deficient patients were more commonly colonized with bacteria. Vitamin D deficient patients had lower FEV1, more frequent pulmonary exacerbations, higher sputum levels of inflammatory markers (myeloperoxidase, neutrophil elastase, IL-8) and demonstrated a more rapid decline in lung function over 3 years follow-up. However, the assessment of LL-37 levels in airways, and neutrophil phagocytosis either revealed a significant difference to the opposite direction of the initial hypothesis, or they failed to show any difference. Therefore, the authors were not able to provide an explanation on the hypothesized mechanism, namely, the implication of vitamin D deficiency in bronchiectasis severity.

Another small study in patients with primary cilia dyskinesia (PCD) showed that 79% of patients with bronchiectasis had vitamin D deficiency or insufficiency. However, 72% of the total population had also vitamin D deficiency or insufficiency, and there was no difference between PCD patients with and without bronchiectasis in vitamin D levels[115]. The study may have failed to provide clear results because of its small sample size.

The paucity of studies prevents firm conclusions on the association between vitamin D deficiency and CF or non-CF bronchiectasis. And what is more, some authors have even expressed doubts on the anti-inflammatory of vitamin D. Among other things, it has been argued that vitamin D is primarily synthesized in the skin through the exposure to UV radiation and therefore it may simply be a surrogate of sunlight exposure[116]. As it is well known, UV radiation has immunomodulatory properties in itself, irrespective of the UV-synthesized vitamin D[117]. It has also been speculated that the observed low vitamin D levels could be a direct consequence of reduced outdoor physical activity of patients with chronic lung diseases such as bronchiectasis[114,116]. This very important issue, to the best of our knowledge, has not been examined as a confounder in any of the relevant studies. Another issue that has been discussed in the literature is whether 25(OH)D could be a negative acute phase reactant and therefore its values may not be a reliable indicator of vitamin D status in inflammatory conditions[118,119].

VITAMIN D AS A THERAPEUTIC POTENTIAL IN BRONCHIECTATIC LUNG DISEASE

Given the well-established association of vitamin D deficiency with increased inflammation, and the indicative evidence for harmful consequences in lungs, it is intriguing to speculate that the administration of vitamin D supplementation could be a reasonable and cost effective supplementary therapeutic approach for children with non-CF bronchiectasis. Vitamin D (as well as the rest of lipid-soluble vitamins), in doses sufficient to achieve serum levels > 30 ng/mL, has been part of the standard treatment for CF since many decades ago.

Vitamin D desirable serum levels reflect our current knowledge on preserving bone health. However, the issue of dose will become much more complex if we consider administering vitamin D for lung diseases, since we have to take into account the - yet unknown - levels required for its extra-skeletal functions. To make matters more complicated, a given dose of vitamin D will not necessarily attain the same increase of 25(OH)D serum levels in all patients. The required daily doses to reach optimal levels for bone health, vary greatly in patients ranging from 400 to 5000 IU daily[120]. The dose needed in order to attain the vitamin's maximum immune-modulatory function is probably higher than the dose required for optimal bone health. Based on currently available data, $1,25(OH)_2D$ exerts its immune-modulatory functions at concentrations ranging from 10-100 nmol/L[78], which are much higher than the usually observed serum levels of 100 to 135 pmol/L[121]. This apparent paradox is due to the fact that vitamin D function in tissues is exerted mainly by the locally-produced $1,25(OH)_2D$[122]. Indeed, lung epithelial cells express high levels of 1a-hydroxylase and are able of producing locally high levels of $1,25(OH)_2D$. When these

cells were supplemented with 1 mmol/L of 25(OH)D, they produced 600 pmol/L of $1,25(OH)_2D$[27].

The above highlight briefly how complex still remains the tempting prospect of including vitamin D supplements to the armamentarium of remedies for non-CF bronchiectasis. Among the many issues that have to be sufficiently addressed before any recommendations can be made, is to show that vitamin D supplementation is associated with measurable disease outcomes, define which patients would be benefited by this treatment, the serum levels that have to be attained, and the optimal doses. Physicians' clinical decisions could be only assisted through carefully designed randomized controlled trials that will provide substantiated answers to above questions.

CONCLUSION

Vitamin D deficiency is associated with the risk for respiratory infectious diseases as it has been shown in epidemiological studies; additionally, vitamin D has a variety of immune-modulatory properties. Given the above, it is plausible to assume that there is an association between vitamin D deficiency and bronchiectasis. However, this association has been corroborated only in a single epidemiological study in adult population with non-CF bronchiectasis, and so it is premature to conclude causality. Nevertheless, the clarification of this issue is of great clinical importance. Maybe, in the light of new data, we have to reconsider the most appropriate doses and serum levels of vitamin D in CF. As for non-CF bronchiectasis, vitamin D supplementation could be an effective and safe option in the management of the disease, especially so because of the paucity of really effective treatment regimens.

REFERENCES

1 Vitamin D. *Science* 1927; **65**: x [PMID: 17758928 DOI: 10.1126/science.65.1683.0x-s]
2 **McCollum EV**, Pitz W, Simmonds N, Becker JE, Shipley PG, Bunting RW. The effect of additions of fluorine to the diet of the rat on the quality of the teeth. 1925. Studies on experimental rickets. XXI. An experimental demonstration of the existence of a vitamin which promotes calcium deposition. 1922. The effect of additions of fluorine to the diet of the rat on the quality of the teeth. 1925. *J Biol Chem* 2002; **277**: E8 [PMID: 11991957]
3 **Hume EM**, Lucas NS, Smith HH. On the Absorption of Vitamin D from the Skin. *Biochem J* 1927; **21**: 362-367 [PMID: 16743844 DOI: 10.1042/bj0210362]
4 **Holick MF**, Schnoes HK, DeLuca HF, Suda T, Cousins RJ. Isolation and identification of 1,25-dihydroxycholecalciferol. A metabolite of vitamin D active in intestine. *Biochemistry* 1971; **10**: 2799-2804 [PMID: 4326883 DOI: 10.1021/bi00790a023]
5 **DeLuca HF**. Evolution of our understanding of vitamin D. *Nutr Rev* 2008; **66**: S73-S87 [PMID: 18844850 DOI: 10.1111/j.1753-4887.2008.00105.x]
6 **Holick MF**, Schnoes HK, DeLuca HF, Gray RW, Boyle IT, Suda T. Isolation and identification of 24,25-dihydroxycholecalciferol, a metabolite of vitamin D made in the kidney. *Biochemistry* 1972; **11**: 4251-4255 [PMID: 4342902 DOI: 10.1021/bi00773a009]
7 **Christakos S**, DeLuca HF. Minireview: Vitamin D: is there a role in extraskeletal health? *Endocrinology* 2011; **152**: 2930-2936 [PMID: 21673104 DOI: 10.1210/en.2011-0243]
8 **Christakos S**, Dhawan P, Verstuyf A, Verlinden L, Carmeliet G. Vitamin D: Metabolism, Molecular Mechanism of Action, and Pleiotropic Effects. *Physiol Rev* 2015; **96**: 365-408 [PMID: 26681795 DOI: 10.1152/physrev.00014.2015]
9 **Daiger SP**, Schanfield MS, Cavalli-Sforza LL. Group-specific component (Gc) proteins bind vitamin D and 25-hydroxyvitamin D. *Proc Natl Acad Sci USA* 1975; **72**: 2076-2080 [PMID: 49052 DOI: 10.1073/pnas.72.6.2076]
10 **Dusso AS**, Brown AJ, Slatopolsky EA. Vitamin D and renal failure. In: FeldmanD, PikeJW, GlorieuxFH (eds). Vitamin D, 2nd ed. Amsterdam, The Netherlands: Elsevier, 2005: 1313-1338
11 **Holick MF**. The cutaneous photosynthesis of previtamin D3: a unique photoendocrine system. *J Invest Dermatol* 1981; **77**: 51-58 [PMID: 6265564 DOI: 10.1111/1523-1747.ep12479237]
12 **Herr C**, Greulich T, Koczulla RA, Meyer S, Zakharkina T, Branscheidt M, Eschmann R, Bals R. The role of vitamin D in pulmonary disease: COPD, asthma, infection, and cancer. *Respir Res* 2011; **12**: 31 [PMID: 21418564 DOI: 10.1186/1465-9921-12-31]
13 **Mailhot G**. Vitamin D bioavailability in cystic fibrosis: a cause for concern? *Nutr Rev* 2012; **70**: 280-293 [PMID: 22537214 DOI: 10.1111/j.1753-4887.2012.00471.x]
14 **Holick MF**, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM; Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2011; **96**: 1911-1930 [PMID: 21646368 DOI: 10.1210/jc.2011-0385]
15 **Holick MF**. Vitamin D deficiency. *N Engl J Med* 2007; **357**: 266-281 [PMID: 17634462 DOI: 10.1056/nejmra070553]
16 **Stumpf WE**, Sar M, Reid FA, Tanaka Y, DeLuca HF. Target cells for 1,25-dihydroxyvitamin D3 in intestinal tract, stomach, kidney, skin, pituitary, and parathyroid. *Science* 1979; **206**: 1188-1190 [PMID: 505004 DOI: 10.1126/science.505004]
17 **Miyaura C**, Abe E, Kuribayashi T, Tanaka H, Konno K, Nishii Y, Suda T. 1 alpha,25-Dihydroxyvitamin D3 induces differentiation of human myeloid leukemia cells. *Biochem Biophys Res Commun* 1981; **102**: 937-943 [PMID: 6946774 DOI: 10.1016/0006-291X(81)91628-4]
18 **Abe E**, Miyaura C, Sakagami H, Takeda M, Konno K, Yamazaki T, Yoshiki S, Suda T. Differentiation of mouse myeloid leukemia cells induced by 1 alpha,25-dihydroxyvitamin D3. *Proc Natl Acad Sci USA* 1981; **78**: 4990-4994 [PMID: 6946446 DOI: 10.1073/pnas.78.8.4990]
19 **Chen Y**, Liu W, Sun T, Huang Y, Wang Y, Deb DK, Yoon D, Kong J, Thadhani R, Li YC. 1,25-Dihydroxyvitamin D promotes negative feedback regulation of TLR signaling via targeting microRNA-155-SOCS1 in macrophages. *J Immunol* 2013; **190**: 3687-3695 [PMID: 23436936 DOI: 10.4049/jimmunol.1203273]
20 **Hansdottir S**, Monick MM. Vitamin D effects on lung immunity and respiratory diseases. *Vitam Horm*2011; **86**: 217-237 [PMID: 21419273 DOI: 10.1016/B978-0-12-386960-9.00009-5]
21 **Holick MF**. Vitamin D: extraskeletal health. *Rheum Dis Clin North Am* 2012; **38**: 141-160 [PMID: 22525849 DOI: 10.1016/j.rdc.2012.03.013]
22 **Bartley J**, Garrett J, Grant CC, Camargo CA Jr. Could vitamin d have a potential anti-inflammatory and anti-infective role in bronchiectasis? *Curr Infect Dis Rep* 2013; **15**: 148-157 [PMID: 23371406 DOI: 10.1007/s11908-013-0321-9]
23 **Douros K**. Cystic fibrosis and vitamin D: the quest for more pieces of the puzzle. *Acta Paediatr* 2016; **105**: 854 [PMID: 27059820 DOI: 10.1111/apa.13424]
24 **Douros K**, Loukou I, Boutopoulou B, Fouzas S. Does Vitamin D Deficiency Epidemic Parallel with Allergy and Asthma Epidemic? *Mini Rev Med Chem* 2015; **15**: 967-973 [PMID: 26242700 DOI: 10.2174/1389557515121507311108027]
25 **Finklea JD**, Grossmann RE, Tangpricha V. Vitamin D and chronic lung disease: a review of molecular mechanisms and clinical studies. *Adv Nutr* 2011; **2**: 244-253 [PMID: 22332056 DOI: 10.3945/an.111.000398]
26 **Loukou I**, Boutopoulou B, Fouzas S, Douros K. Vitamin D and Cystic Fibrosis Lung Disease. *Mini Rev Med Chem* 2015; **15**: 974-983 [PMID:

26242701 DOI: 10.2174/1389557515121507311115291]
27 **Hansdottir S**, Monick MM, Hinde SL, Lovan N, Look DC, Hunninghake GW. Respiratory epithelial cells convert inactive vitamin D to its active form: potential effects on host defense. *J Immunol* 2008; **181**: 7090-7099 [PMID: 18981129 DOI: 10.4049/jimmunol.181.10.7090]
28 **Chang AB**, Brown N, Toombs M, Marsh RL, Redding GJ. Lung disease in indigenous children. *Paediatr Respir Rev* 2014; **15**: 325-332 [PMID: 24958089 DOI: 10.1016/j.prrv.2014.04.016]
29 **Stafler P**, Carr SB. Non-cystic fibrosis bronchiectasis: its diagnosis and management. *Arch Dis Child Educ Pract Ed* 2010; **95**: 73-82 [PMID: 20501530 DOI: 10.1136/adc.2007.130054]
30 **Barker AF**, Bardana EJ Jr. Bronchiectasis: update of an orphan disease. *Am Rev Respir Dis* 1988; **137**: 969-978 [PMID: 3281531 DOI: 10.1164/ajrccm/137.4.969]
31 **Goyal V**, Grimwood K, Marchant J, Masters IB, Chang AB. Pediatric bronchiectasis: No longer an orphan disease. *Pediatr Pulmonol* 2016; **51**: 450-469 [PMID: 26840008 DOI: 10.1002/ppul.23380]
32 **Clark NS**. Bronchiectasis in childhood. *Br Med J* 1963; **1**: 80-88 [PMID: 14021533 DOI: 10.1136/bmj.1.5323.80]
33 **Brower KS**, Del Vecchio MT, Aronoff SC. The etiologies of non-CF bronchiectasis in childhood: a systematic review of 989 subjects. *BMC Pediatr* 2014; **14**: 4 [PMID: 25492164 DOI: 10.1186/s12887-014-0299-y]
34 **Chang AB**, Bell SC, Torzillo PJ, King PT, Maguire GP, Byrnes CA, Holland AE, O'Mara P, Grimwood K; extended voting group. Chronic suppurative lung disease and bronchiectasis in children and adults in Australia and New Zealand Thoracic Society of Australia and New Zealand guidelines. *Med J Aust* 2015; **202**: 130 [PMID: 25669469 DOI: 10.5694/mjac14.00287]
35 **Grenier P**, Maurice F, Musset D, Menu Y, Nahum H. Bronchiectasis: assessment by thin-section CT.*Radiology* 1986; **161**: 95-99 [PMID: 3763889 DOI: 10.1148/radiology.161.1.3763889]
36 **Eastham KM**, Fall AJ, Mitchell L, Spencer DA. The need to redefine non-cystic fibrosis bronchiectasis in childhood. *Thorax* 2004; **59**: 324-327 [PMID: 15047953 DOI: 10.1136/thx.2003.011577]
37 **Nikolaizik WH**, Warner JO. Aetiology of chronic suppurative lung disease. *Arch Dis Child* 1994; **70**: 141-142 [PMID: 8129439 DOI: 10.1136/adc.70.2.141]
38 **Kerem B**, Rommens JM, Buchanan JA, Markiewicz D, Cox TK, Chakravarti A, Buchwald M, Tsui LC. Identification of the cystic fibrosis gene: genetic analysis. *Science* 1989; **245**: 1073-1080 [PMID: 2570460 DOI: 10.1126/science.2570460]
39 **Ciofu O**, Tolker-Nielsen T, Jensen PØ, Wang H, Høiby N. Antimicrobial resistance, respiratory tract infections and role of biofilms in lung infections in cystic fibrosis patients. *Adv Drug Deliv Rev* 2015; **85**: 7-23 [PMID: 25477303 DOI: 10.1016/j.addr.2014. 11.017]
40 **Cohen-Cymberknoh M**, Kerem E, Ferkol T, Elizur A. Airway inflammation in cystic fibrosis: molecular mechanisms and clinical implications. *Thorax* 2013; **68**: 1157-1162 [PMID: 23704228 DOI: 10.1136/thoraxjnl-2013-203204]
41 **Filkins LM**, O'Toole GA. Cystic Fibrosis Lung Infections: Polymicrobial, Complex, and Hard to Treat. *PLoS Pathog* 2015; **11**: e1005258 [PMID: 26719892 DOI: 10.1371/journal.ppat.1005258]
42 **Poghosyan A**, Patel JK, Clifford RL, Knox AJ. Epigenetic dysregulation of interleukin 8 (CXCL8) hypersecretion in cystic fibrosis airway epithelial cells. *Biochem Biophys Res Commun* 2016; **476**: 431-437 [PMID: 27240956 DOI: 10.1016/j.bbrc.2016.05.140]
43 **Elizur A**, Cannon CL, Ferkol TW. Airway inflammation in cystic fibrosis. *Chest* 2008; **133**: 489-495 [PMID: 18252915 DOI: 10.1378/chest.07-1631]
44 **Sly PD**, Gangell CL, Chen L, Ware RS, Ranganathan S, Mott LS, Murray CP, Stick SM; AREST CF Investigators. Risk factors for bronchiectasis in children with cystic fibrosis. *N Engl J Med* 2013; **368**: 1963-1970 [PMID: 23692169 DOI: 10.1056/nejmoa1301725]
45 **Heijerman H**. Infection and inflammation in cystic fibrosis: a short review. *J Cyst Fibros* 2005; **4** Suppl 2: 3-5 [PMID: 15970469 DOI: 10.1016/j.jcf.2005.05.005]
46 **Marsh RL**, Thornton RB, Smith-Vaughan HC, Richmond P, Pizzutto SJ, Chang AB. Detection of biofilm in bronchoalveolar lavage from children with non-cystic fibrosis bronchiectasis. *Pediatr Pulmonol* 2014; Epub ahead of print [PMID: 24644254 DOI: 10.1002/ppul.23031]
47 **Pittet LA**, Hall-Stoodley L, Rutkowski MR, Harmsen AG. Influenza virus infection decreases tracheal mucociliary velocity and clearance of Streptococcus pneumoniae. *Am J Respir Cell Mol Biol* 2010; **42**: 450-460 [PMID: 19520922 DOI: 10.1165/rcmb.2007-0417oc]
48 **Everard ML**. 'Recurrent lower respiratory tract infections' - going around in circles, respiratory medicine style. *Paediatr Respir Rev* 2012; **13**: 139-143 [PMID: 22726868 DOI: 10.1016/j.prrv.2012.03.003]
49 **Mahon BD**, Wittke A, Weaver V, Cantorna MT. The targets of vitamin D depend on the differentiation and activation status of CD4 positive T cells. *J Cell Biochem* 2003; **89**: 922-932 [PMID: 12874827 DOI: 10.1002/jcb.10580]
50 **Searing DA**, Leung DY. Vitamin D in atopic dermatitis, asthma and allergic diseases. *Immunol Allergy Clin North Am* 2010; **30**: 397-409 [PMID: 20670821 DOI: 10.1016/j.iac.2010.05.005]
51 **Adorini L**, Penna G, Giarratana N, Roncari A, Amuchastegui S, Daniel KC, Uskokovic M. Dendritic cells as key targets for immunomodulation by Vitamin D receptor ligands. *J Steroid Biochem Mol Biol* 2004; **89-90**: 437-441 [PMID: 15225816 DOI: 10.1016/j.jsbmb.2004.03.013]
52 **Gorman S**, Judge MA, Hart PH. Immune-modifying properties of topical vitamin D: Focus on dendritic cells and T cells. *J Steroid Biochem Mol Biol* 2010; **121**: 247-249 [PMID: 20211255 DOI: 10.1016/j.jsbmb.2010.02.034]
53 **Schauber J**, Dorschner RA, Yamasaki K, Brouha B, Gallo RL. Control of the innate epithelial antimicrobial response is cell-type specific and dependent on relevant microenvironmental stimuli. *Immunology* 2006; **118**: 509-519 [PMID: 16895558 DOI: 10.1111/j.1365-2567.2006.02399.x]
54 **Gallo RL**, Hooper LV. Epithelial antimicrobial defence of the skin and intestine. *Nat Rev Immunol* 2012; **12**: 503-516 [PMID: 22728527 DOI: 10.1038/nri3228]
55 **Nizet V**, Ohtake T, Lauth X, Trowbridge J, Rudisill J, Dorschner RA, Pestonjamasp V, Piraino J, Huttner K, Gallo RL. Innate antimicrobial peptide protects the skin from invasive bacterial infection. *Nature* 2001; **414**: 454-457 [PMID: 11719807 DOI: 10.1038/35106587]
56 **Smith JJ**, Travis SM, Greenberg EP, Welsh MJ. Cystic fibrosis airway epithelia fail to kill bacteria because of abnormal airway surface fluid. *Cell* 1996; **85**: 229-236 [PMID: 8612275 DOI: 10.1016/s0092-8674(00)81099-5]
57 **Wang TT**, Nestel FP, Bourdeau V, Nagai Y, Wang Q, Liao J, Tavera-Mendoza L, Lin R, Hanrahan JW, Mader S, White JH. Cutting edge: 1,25-dihydroxyvitamin D3 is a direct inducer of antimicrobial peptide gene expression. *J Immunol* 2004; **173**: 2909-2912 [PMID: 15322146 DOI: 10.4049/jimmunol.173.5.2909]
58 **Yim S**, Dhawan P, Ragunath C, Christakos S, Diamond G. Induction of cathelicidin in normal and CF bronchial epithelial cells by 1,25-dihydroxyvitamin D(3). *J Cyst Fibros* 2007; **6**: 403-410 [PMID: 17467345 DOI: 10.1016/j.jcf.2007.03.003]
59 **Adams JS**, Ren S, Liu PT, Chun RF, Lagishetty V, Gombart AF, Borregaard N, Modlin RL, Hewison M. Vitamin d-directed rheostatic regulation of monocyte antibacterial responses. *J Immunol* 2009; **182**: 4289-4295 [PMID: 19299728 DOI: 10.4049/jimmunol.0803736]
60 **Liu MC**, Xiao HQ, Brown AJ, Ritter CS, Schroeder J. Association of vitamin D and antimicrobial peptide production during late-phase allergic responses in the lung. *Clin Exp Allergy* 2012; **42**: 383-391 [PMID: 22092530 DOI: 10.1111/j.1365-2222.2011.03879.x]
61 **Pincikova T**, Svedin E, Domsgen E, Flodström-Tullberg M, Hjelte L. Cystic fibrosis bronchial epithelial cells have impaired ability to activate vitamin D. *Acta Paediatr* 2016; **105**: 851-853 [PMID: 26865115 DOI: 10.1111/apa.13361]
62 **Abreu MT**, Kantorovich V, Vasiliauskas EA, Gruntmanis U, Matuk R, Daigle K, Chen S, Zehnder D, Lin YC, Yang H, Hewison M, Adams JS. Measurement of vitamin D levels in inflammatory bowel disease patients reveals a subset of Crohn's disease patients with elevated 1,25-dihydroxyvitamin D and low bone mineral density. *Gut* 2004; **53**: 1129-1136 [PMID: 15247180 DOI: 10.1136/gut.2003.036657]
63 **Adorini L**, Penna G. Dendritic cell tolerogenicity: a key mechanism

in immunomodulation by vitamin D receptor agonists. *Hum Immunol* 2009; **70**: 345-352 [PMID: 19405173 DOI: 10.1016/j.humimm.2009.01.016]
64 **Jirapongsananuruk O**, Melamed I, Leung DY. Additive immunosuppressive effects of 1,25-dihydroxyvitamin D3 and corticosteroids on TH1, but not TH2, responses. *J Allergy Clin Immunol* 2000; **106**: 981-985 [PMID: 11080724 DOI: 10.1067/mai.2000.110101]
65 **Muthian G**, Raikwar HP, Rajasingh J, Bright JJ. 1,25 Dihydroxyvitamin-D3 modulates JAK-STAT pathway in IL-12/IFNgamma axis leading to Th1 response in experimental allergic encephalomyelitis. *J Neurosci Res* 2006; **83**: 1299-1309 [PMID: 16547967 DOI: 10.1002/jnr.20826]
66 **Dimeloe S**, Nanzer A, Ryanna K, Hawrylowicz C. Regulatory T cells, inflammation and the allergic response-The role of glucocorticoids and Vitamin D. *J Steroid Biochem Mol Biol* 2010; **120**: 86-95 [PMID: 20227496 DOI: 10.1016/j.jsbmb.2010.02.029]
67 **Pichler J**, Gerstmayr M, Szépfalusi Z, Urbanek R, Peterlik M, Willheim M. 1 alpha,25(OH)2D3 inhibits not only Th1 but also Th2 differentiation in human cord blood T cells. *Pediatr Res* 2002; **52**: 12-18 [PMID: 12084841 DOI: 10.1203/00006450-200207000-00005]
68 **Matheu V**, Bäck O, Mondoc E, Issazadeh-Navikas S. Dual effects of vitamin D-induced alteration of TH1/TH2 cytokine expression: enhancing IgE production and decreasing airway eosinophilia in murine allergic airway disease. *J Allergy Clin Immunol* 2003; **112**: 585-592 [PMID: 13679819 DOI: 10.1016/s0091-6749(03)00020-4]
69 **Jorde R**, Sneve M, Torjesen PA, Figenschau Y, Gøransson LG, Omdal R. No effect of supplementation with cholecalciferol on cytokines and markers of inflammation in overweight and obese subjects. *Cytokine* 2010; **50**: 175-180 [PMID: 20122848 DOI: 10.1016/j.cyto.2009.12.006]
70 **Chang JH**, Cha HR, Lee DS, Seo KY, Kweon MN. 1,25-Dihydroxyvitamin D3 inhibits the differentiation and migration of T(H)17 cells to protect against experimental autoimmune encephalomyelitis. *PLoS One* 2010; **5**: e12925 [PMID: 20886077 DOI: 10.1371/journal.pone.0012925]
71 **Kreindler JL**, Steele C, Nguyen N, Chan YR, Pilewski JM, Alcorn JF, Vyas YM, Aujla SJ, Finelli P, Blanchard M, Zeigler SF, Logar A, Hartigan E, Kurs-Lasky M, Rockette H, Ray A, Kolls JK. Vitamin D3 attenuates Th2 responses to Aspergillus fumigatus mounted by CD4+ T cells from cystic fibrosis patients with allergic bronchopulmonary aspergillosis. *J Clin Invest* 2010; **120**: 3242-3254 [PMID: 20714107 DOI: 10.1172/jci42388]
72 **Majak P**, Olszowiec-Chlebna M, Smejda K, Stelmach I. Vitamin D supplementation in children may prevent asthma exacerbation triggered by acute respiratory infection. *J Allergy Clin Immunol* 2011; **127**: 1294-1296 [PMID: 21315433 DOI: 10.1016/j.jaci.2010.12.016]
73 **Chen S**, Sims GP, Chen XX, Gu YY, Chen S, Lipsky PE. Modulatory effects of 1,25-dihydroxyvitamin D3 on human B cell differentiation. *J Immunol* 2007; **179**: 1634-1647 [PMID: 17641030 DOI: 10.4049/jimmunol.179.3.1634]
74 **Dubin PJ**, McAllister F, Kolls JK. Is cystic fibrosis a TH17 disease? *Inflamm Res* 2007; **56**: 221-227 [PMID: 17607545 DOI: 10.1007/s00011-007-6187-2]
75 **Ikeda U**, Wakita D, Ohkuri T, Chamoto K, Kitamura H, Iwakura Y, Nishimura T. 1α,25-Dihydroxyvitamin D3 and all-trans retinoic acid synergistically inhibit the differentiation and expansion of Th17 cells. *Immunol Lett* 2010; **134**: 7-16 [PMID: 20655952 DOI: 10.1016/j.imlet.2010.07.002]
76 **Moss RB**. Fungi in cystic fibrosis and non-cystic fibrosis bronchiectasis. *Semin Respir Crit Care Med* 2015; **36**: 207-216 [PMID: 25826588 DOI: 10.1055/s-0035-1546750]
77 **Coughlan CA**, Chotirmall SH, Renwick J, Hassan T, Low TB, Bergsson G, Eshwika A, Bennett K, Dunne K, Greene CM, Gunaratnam C, Kavanagh K, Logan PM, Murphy P, Reeves EP, McElvaney NG. The effect of Aspergillus fumigatus infection on vitamin D receptor expression in cystic fibrosis. *Am J Respir Crit Care Med* 2012; **186**: 999-1007 [PMID: 22904183 DOI: 10.1164/rccm.201203-0478oc]
78 **Herscovitch K**, Dauletbaev N, Lands LC. Vitamin D as an antimicrobial and anti-inflammatory therapy for Cystic Fibrosis. *Paediatr Respir Rev* 2014; **15**: 154-162 [PMID: 24332502 DOI: 10.1016/j.prrv.2013.11.002]
79 **McNally P**, Coughlan C, Bergsson G, Doyle M, Taggart C, Adorini L, Uskokovic MR, El-Nazir B, Murphy P, Greally P, Greene CM, McElvaney NG. Vitamin D receptor agonists inhibit pro-inflammatory cytokine production from the respiratory epithelium in cystic fibrosis. *J Cyst Fibros* 2011; **10**: 428-434 [PMID: 21784717 DOI: 10.1016/j.jcf.2011.06.013]
80 **Herscovitch K**, Dauletbaev N, Berube J, Rousseau S, Lands L. Supplementation With 25-Hydroxyvitamin D3 Down-Regulates Pathogen-Stimulated Interleukin-8 Production In Cystic Fibrosis Macrophages And Airway Epithelial Cells. *Am J Respir Crit Care Med* 2012; **185**: A2803 [DOI: 10.1164/ajrccm-conference.2012.185.1]
81 **Grossmann RE**, Zughaier SM, Liu S, Lyles RH, Tangpricha V. Impact of vitamin D supplementation on markers of inflammation in adults with cystic fibrosis hospitalized for a pulmonary exacerbation. *Eur J Clin Nutr* 2012; **66**: 1072-1074 [PMID: 22805498 DOI: 10.1038/ejcn.2012.82]
82 **Majak P**, Jerzyńska J, Smejda K, Stelmach I, Timler D, Stelmach W. Correlation of vitamin D with Foxp3 induction and steroid-sparing effect of immunotherapy in asthmatic children. *Ann Allergy Asthma Immunol* 2012; **109**: 329-335 [PMID: 23062388 DOI: 10.1016/j.anai.2012.08.002]
83 **Zhang Y**, Leung DY, Richers BN, Liu Y, Remigio LK, Riches DW, Goleva E. Vitamin D inhibits monocyte/macrophage proinflammatory cytokine production by targeting MAPK phosphatase-1. *J Immunol* 2012; **188**: 2127-2135 [PMID: 22301548 DOI: 10.4049/jimmunol.1102412]
84 **Sutherland ER**, Goleva E, Jackson LP, Stevens AD, Leung DY. Vitamin D levels, lung function, and steroid response in adult asthma. *Am J Respir Crit Care Med* 2010; **181**: 699-704 [PMID: 20075384 DOI: 10.1164/rccm.200911-1710oc]
85 **Sadeghi K**, Wessner B, Laggner U, Ploder M, Tamandl D, Friedl J, Zügel U, Steinmeyer A, Pollak A, Roth E, Boltz-Nitulescu G, Spittler A. Vitamin D3 down-regulates monocyte TLR expression and triggers hyporesponsiveness to pathogen-associated molecular patterns. *Eur J Immunol* 2006; **36**: 361-370 [PMID: 16402404 DOI: 10.1002/eji.200425995]
86 **Riis JL**, Johansen C, Gesser B, Møller K, Larsen CG, Kragballe K, Iversen L. 1alpha,25(OH)(2)D(3) regulates NF-kappaB DNA binding activity in cultured normal human keratinocytes through an increase in IkappaBalpha expression. *Arch Dermatol Res* 2004; **296**: 195-202 [PMID: 15372276 DOI: 10.1007/s00403-004-0509-9]
87 **Stio M**, Martinesi M, Bruni S, Treves C, Mathieu C, Verstuyf A, d' Albasio G, Bagnoli S, Bonanomi AG. The Vitamin D analogue TX 527 blocks NF-kappaB activation in peripheral blood mononuclear cells of patients with Crohn's disease. *J Steroid Biochem Mol Biol* 2007; **103**: 51-60 [PMID: 17049230 DOI: 10.1016/j.jsbmb.2006.07.008]
88 **Simoneau T**, Bazzaz O, Sawicki GS, Gordon C. Vitamin D status in children with cystic fibrosis. Associations with inflammation and bacterial colonization. *Ann Am Thorac Soc* 2014; **11**: 205-210 [PMID: 24423241 DOI: 10.1513/annalsats.201306-171bc]
89 **Stephenson A**, Brotherwood M, Robert R, Atenafu E, Corey M, Tullis E. Cholecalciferol significantly increases 25-hydroxyvitamin D concentrations in adults with cystic fibrosis. *Am J Clin Nutr* 2007; **85**: 1307-1311 [PMID: 17490967]
90 **Rovner AJ**, Stallings VA, Schall JI, Leonard MB, Zemel BS. Vitamin D insufficiency in children, adolescents, and young adults with cystic fibrosis despite routine oral supplementation. *Am J Clin Nutr* 2007; **86**: 1694-1699 [PMID: 18065588]
91 **Pincikova T**, Nilsson K, Moen IE, Karpati F, Fluge G, Hollsing A, Knudsen PK, Lindblad A, Mared L, Pressler T, Hjelte L; Scandinavian Cystic Fibrosis Study Consortium. Inverse relation between vitamin D and serum total immunoglobulin G in the Scandinavian Cystic Fibrosis Nutritional Study. *Eur J Clin Nutr* 2011; **65**: 102-109 [PMID: 20859300 DOI: 10.1038/ejcn.2010.194]
92 **Chavasse RJ**, Francis J, Balfour-Lynn I, Rosenthal M, Bush A. Serum vitamin D levels in children with cystic fibrosis. *Pediatr Pulmonol* 2004; **38**: 119-122 [PMID: 15211694 DOI: 10.1002/ppul.20047]
93 **Sermet-Gaudelus I**, Souberbielle JC, Ruiz JC, Vrielynck S, Heuillon B, Azhar I, Cazenave A, Lawson-Body E, Chedevergne F, Lenoir G.

Low bone mineral density in young children with cystic fibrosis. *Am J Respir Crit Care Med* 2007; **175**: 951-957 [PMID: 17272788 DOI: 10.1164/rccm.200606-776oc]
94 **Williams H**, O'Reilly RN. Bronchiectasis in children: its multiple clinical and pathological aspects. *Arch Dis Child* 1959; **34**: 192-201 [PMID: 13844859 DOI: 10.1136/adc.34.175.192]
95 **Jolliffe DA**, Griffiths CJ, Martineau AR. Vitamin D in the prevention of acute respiratory infection: systematic review of clinical studies. *J Steroid Biochem Mol Biol* 2013; **136**: 321-329 [PMID: 23220552 DOI: 10.1016/j.jsbmb.2012.11.017]
96 **Kupferschmidt K**. Uncertain verdict as vitamin D goes on trial. *Science* 2012; **337**: 1476-1478 [PMID: 22997323 DOI: 10.1126/science.337.6101.1476]
97 **Nnoaham KE**, Clarke A. Low serum vitamin D levels and tuberculosis: a systematic review and meta-analysis. *Int J Epidemiol* 2008; **37**: 113-119 [PMID: 18245055 DOI: 10.1093/ije/dym247]
98 **Venturini E**, Facchini L, Martinez-Alier N, Novelli V, Galli L, de Martino M, Chiappini E. Vitamin D and tuberculosis: a multicenter study in children. *BMC Infect Dis* 2014; **14**: 652 [PMID: 25494831 DOI: 10.1186/s12879-014-0652-7]
99 **Gray K**, Wood N, Gunasekera H, Sheikh M, Hazelton B, Barzi F, Isaacs D. Vitamin d and tuberculosis status in refugee children. *Pediatr Infect Dis J* 2012; **31**: 521-523 [PMID: 22189532 DOI: 10.1097/inf.0b013e3182456c55]
100 **Salimpour R**. Rickets in Tehran. Study of 200 cases. *Arch Dis Child* 1975; **50**: 63-66 [PMID: 1124945 DOI: 10.1136/adc.50.1.63]
101 **Muhe L**, Lulseged S, Mason KE, Simoes EA. Case-control study of the role of nutritional rickets in the risk of developing pneumonia in Ethiopian children. *Lancet* 1997; **349**: 1801-1804 [PMID: 9269215 DOI: 10.1016/s0140-6736(96)12098-5]
102 **Najada AS**, Habashneh MS, Khader M. The frequency of nutritional rickets among hospitalized infants and its relation to respiratory diseases. *J Trop Pediatr* 2004; **50**: 364-368 [PMID: 15537725 DOI: 10.1093/tropej/50.6.364]
103 **Roth DE**, Shah R, Black RE, Baqui AH. Vitamin D status and acute lower respiratory infection in early childhood in Sylhet, Bangladesh. *Acta Paediatr* 2010; **99**: 389-393 [PMID: 19900174 DOI: 10.1111/j.1651-2227.2009.01594.x]
104 **Wayse V**, Yousafzai A, Mogale K, Filteau S. Association of subclinical vitamin D deficiency with severe acute lower respiratory infection in Indian children under 5 y. *Eur J Clin Nutr* 2004; **58**: 563-567 [PMID: 15042122 DOI: 10.1038/sj.ejcn.1601845]
105 **Roth DE**, Jones AB, Prosser C, Robinson JL, Vohra S. Vitamin D status is not associated with the risk of hospitalization for acute bronchiolitis in early childhood. *Eur J Clin Nutr* 2009; **63**: 297-299 [PMID: 17971825 DOI: 10.1038/sj.ejcn.1602946]
106 **McNally JD**, Leis K, Matheson LA, Karuananyake C, Sankaran K, Rosenberg AM. Vitamin D deficiency in young children with severe acute lower respiratory infection. *Pediatr Pulmonol* 2009; **44**: 981-988 [PMID: 19746437 DOI: 10.1002/ppul.21089]
107 **Bergman P**, Lindh AU, Björkhem-Bergman L, Lindh JD. Vitamin D and Respiratory Tract Infections: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *PLoS One* 2013; **8**: e65835 [PMID: 23840373 DOI: 10.1371/journal.pone.0065835]
108 **Xiao L**, Xing C, Yang Z, Xu S, Wang M, Du H, Liu K, Huang Z. Vitamin D supplementation for the prevention of childhood acute respiratory infections: a systematic review of randomised controlled trials.*Br J Nutr* 2015; **114**: 1026-1034 [PMID: 26310436 DOI: 10.1017/s000711451500207x]
109 **Kresfelder TL**, Janssen R, Bont L, Pretorius M, Venter M. Confirmation of an association between single nucleotide polymorphisms in the VDR gene with respiratory syncytial virus related disease in South African children. *J Med Virol* 2011; **83**: 1834-1840 [PMID: 21837802 DOI: 10.1002/jmv.22179]
110 **Roth DE**, Jones AB, Prosser C, Robinson JL, Vohra S. Vitamin D receptor polymorphisms and the risk of acute lower respiratory tract infection in early childhood. *J Infect Dis* 2008; **197**: 676-680 [PMID: 18266602 DOI: 10.1086/527488]
111 **Janssen R**, Bont L, Siezen CL, Hodemaekers HM, Ermers MJ, Doornbos G, van 't Slot R, Wijmenga C, Goeman JJ, Kimpen JL, van Houwelingen HC, Kimman TG, Hoebee B. Genetic susceptibility to respiratory syncytial virus bronchiolitis is predominantly associated with innate immune genes. *J Infect Dis* 2007; **196**: 826-834 [PMID: 17703412 DOI: 10.1086/520886]
112 **McNally JD**, Sampson M, Matheson LA, Hutton B, Little J. Vitamin D receptor (VDR) polymorphisms and severe RSV bronchiolitis: a systematic review and meta-analysis. *Pediatr Pulmonol* 2014; **49**: 790-799 [PMID: 24019226 DOI: 10.1002/ppul.22877]
113 **Li W**, Guo L, Li H, Sun C, Cui X, Song G, Wang J, Zhang Q. Polymorphism rs2239185 in vitamin D receptor gene is associated with severe community-acquired pneumonia of children in Chinese Han population: a case-control study. *Eur J Pediatr* 2015; **174**: 621-629 [PMID: 25367052 DOI: 10.1007/s00431-014-2433-0]
114 **Chalmers JD**, McHugh BJ, Docherty C, Govan JR, Hill AT. Vitamin-D deficiency is associated with chronic bacterial colonisation and disease severity in bronchiectasis. *Thorax* 2013; **68**: 39-47 [PMID: 23076388 DOI: 10.1136/thoraxjnl-2012-202125]
115 **Mirra V**, Caffarelli C, Maglione M, Valentino R, Perruolo G, Mazzarella C, Di Micco LL, Montella S, Santamaria F. Hypovitaminosis D: a novel finding in primary ciliary dyskinesia. *Ital J Pediatr* 2015; **41**: 14 [PMID: 25887861 DOI: 10.1186/s13052-015-0119-5]
116 **Foong RE**, Zosky GR. Vitamin D deficiency and the lung: disease initiator or disease modifier? *Nutrients* 2013; **5**: 2880-2900 [PMID: 23896653 DOI: 10.3390/nu5082880]
117 **Hart PH**, Gorman S, Finlay-Jones JJ. Modulation of the immune system by UV radiation: more than just the effects of vitamin D? *Nat Rev Immunol* 2011; **11**: 584-596 [PMID: 21852793 DOI: 10.1038/nri3045]
118 **Shee C**. Is hypovitaminosis D a consequence rather than cause of disease? *Thorax* 2013; **68**: 679 [PMID: 23386697 DOI: 10.1136/thoraxjnl-2012-203189]
119 **Waldron JL**, Ashby HL, Cornes MP, Bechervaise J, Razavi C, Thomas OL, Chugh S, Deshpande S, Ford C, Gama R. Vitamin D: a negative acute phase reactant. *J Clin Pathol* 2013; **66**: 620-622 [PMID: 23454726 DOI: 10.1136/jclinpath-2012-201301]
120 **Hanley DA**, Cranney A, Jones G, Whiting SJ, Leslie WD, Cole DE, Atkinson SA, Josse RG, Feldman S, Kline GA, Rosen C; Guidelines Committee of the Scientific Advisory Council of Osteoporosis Canada. Vitamin D in adult health and disease: a review and guideline statement from Osteoporosis Canada. *CMAJ* 2010; **182**: E610-E618 [PMID: 20624868 DOI: 10.1503/cmaj.080663]
121 **Need AG**, Horowitz M, Morris HA, Nordin BC. Vitamin D status: effects on parathyroid hormone and 1, 25-dihydroxyvitamin D in postmenopausal women. *Am J Clin Nutr* 2000; **71**: 1577-1581 [PMID: 10837301]
122 **Hewison M**, Zehnder D, Chakraverty R, Adams JS. Vitamin D and barrier function: a novel role for extra-renal 1 alpha-hydroxylase. *Mol Cell Endocrinol* 2004; **215**: 31-38 [PMID: 15026172 DOI: 10.1016/j.mce.2003.11.017]

P- Reviewer: Jafari SA, Makishima M, Serban ED
S- Editor: Kong JX **L- Editor**: A **E- Editor**: Lu YJ

Published by **Baishideng Publishing Group Inc**
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com