

REVIEW

A review of the critical role of vitamin D in the functioning of the immune system and the clinical implications of vitamin D deficiency

Gerry K. Schwalfenberg

University of Alberta, Edmonton, Alberta, Canada

This review looks at the critical role of vitamin D in improving barrier function, production of antimicrobial peptides including cathelicidin and some defensins, and immune modulation. The function of vitamin D in the innate immune system and in the epithelial cells of the oral cavity, lung, gastrointestinal system, genito-urinary system, skin and surface of the eye is discussed. Clinical conditions are reviewed where vitamin D may play a role in the prevention of infections or where it may be used as primary or adjuvant treatment for viral, bacterial and fungal infections. Several conditions such as tuberculosis, psoriasis, eczema, Crohn's disease, chest infections, wound infections, influenza, urinary tract infections, eye infections and wound healing may benefit from adequate circulating 25(OH)D as substrate. Clinical diseases are presented in which optimization of 25(OH)D levels may benefit or cause harm according to present day knowledge. The safety of using larger doses of vitamin D in various clinical settings is discussed.

Received: April 14, 2010

Revised: July 7, 2010

Accepted: July 9, 2010

Keywords:

Cathelicidin / Defensins / Epithelial barrier / Innate immunity / Vitamin D

1 An overview of the role of vitamin D in immunity and barrier function

Vitamin D deficiency and insufficiency is a global issue [1] which has significant implications for health [2, 3]. It is well known that vitamin D is involved in the classical calcium homeostasis pathway with deficiency resulting in rickets, [4] a short latency disease, and osteoporosis, a long latency disease (Fig. 1-3B).

Less known is the role of vitamin D in the immune system and barrier function [5, 6] (Fig. 1-4B).

Vitamin D is a secosteroid hormone produced in the skin from 7-dehydrocholesterol after exposure to ultraviolet B light or available in some foods and supplements. It is then hydroxylated in the liver to hydroxyvitamin D (25(OH)D)

and further hydroxylated in the kidney to 1,25-dihydroxyvitamin D (1,25(OH)₂D) which is the active hormone involved in calcium absorption in the gut. Circulating 25(OH)D may also be used as substrate in many cells to locally produce 1,25(OH)₂D, the active hormone, via the CYP27B1 (25-hydroxylase) enzyme and is coactivated by the CYP24A1 (24-hydroxylase) enzyme [7]. There have been a number of excellent reviews of vitamin D and immune response and barrier function [8–10].

In understanding the role of vitamin D in the immune system, it is important to review the many levels of vitamin D action: its clinical relevance to the immune body and prevention of disease.

The first level of vitamin D action is the physical barrier of epithelial cells in the skin, gut, respiratory and urinary tract, which protect us from many common bacterial infections. The active hormone 1,25(OH)₂D is important in upregulating genes via the 1 α -hydroxylase enzyme, which then encode proteins required for tight junctions (e.g. occludin), gap junctions (e.g. connexin 43) and adherens junctions (e.g. E-cadherin) [11–13].

Second, vitamin D has a role as a potent stimulator of antimicrobial peptides in innate immunity [14]. The production of cathelicidin and some defensins (defensins

Correspondence: Dr. Gerry K. Schwalfenberg, University of Alberta, Suite 4301, 9628-156 Street, Edmonton, Alberta T6P 4J5, Canada

E-mail: schwalle@ualberta.ca

Fax: +1-780-489-1211

Abbreviations: BV, bacterial vaginosis; PAMP, pathogen-associated molecular pattern; TLR, toll-like receptor

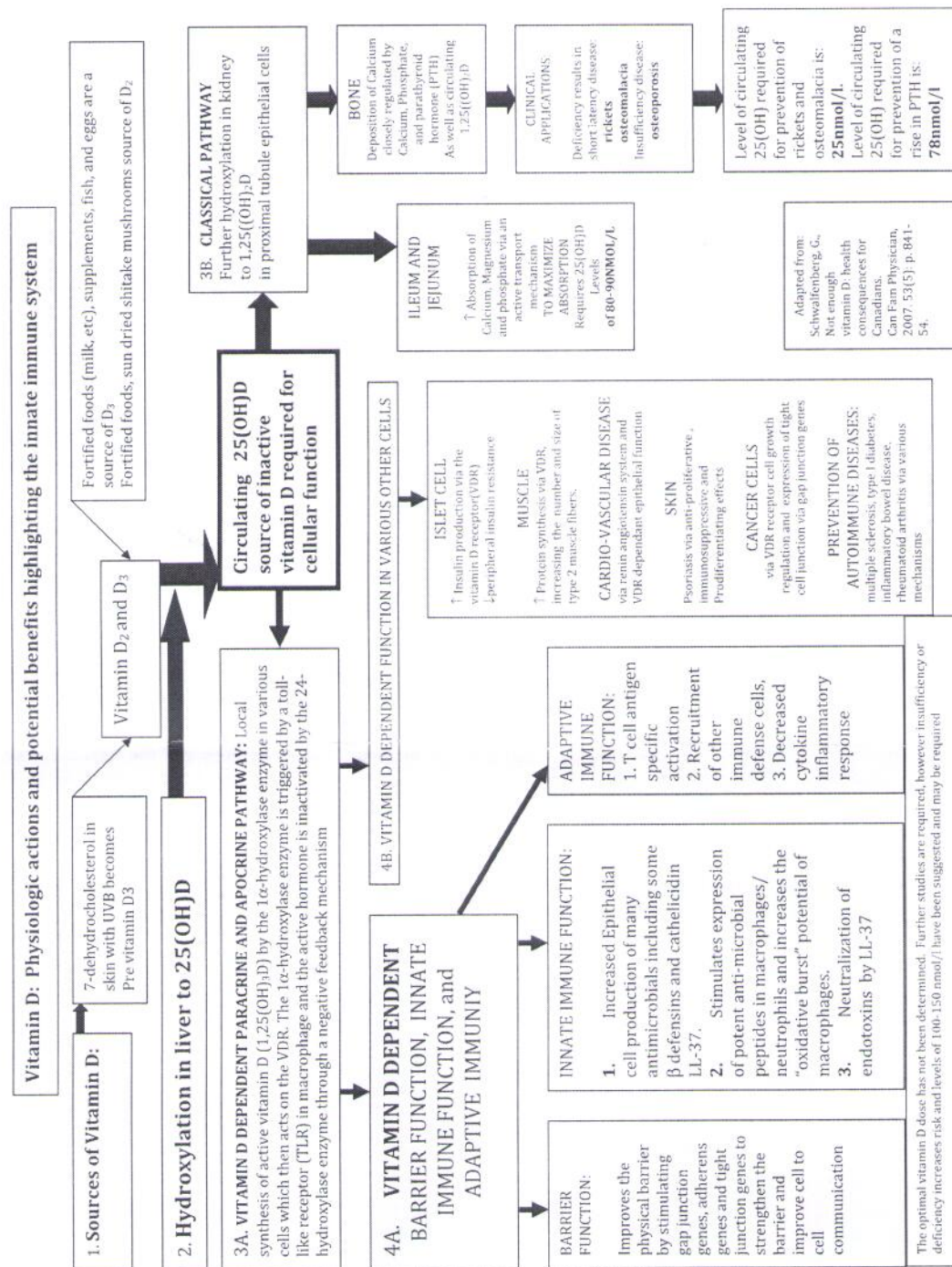


Figure 1. Vitamin D: physiologic actions and potential benefits highlighting the innate immune system.

hBD-2) in the human body is dependent on sufficient circulating 25(OH)D [15]. It is believed that local production of 1,25(OH)₂D, the active hormone in various tissues, may be the preferred mode of response to antigenic microbial challenges [16]. 1,25(OH)₂D has the ability to induce expression of cathelicidin in bronchial [17], urogenital epithelial cells, [18] keratinocytes [19] and myeloid cell lines

[20]. Local injury or infection in most epithelial sites results in expression of cathelicidin. It has been determined that innate immunity and the production of antimicrobial peptides can defend us against bacteria [21], viruses [22] and fungi [23]. Furthermore, these pathogens have pathogen-associated molecular patterns (PAMP's) that are relatively invariant and are shared by many organisms but not the

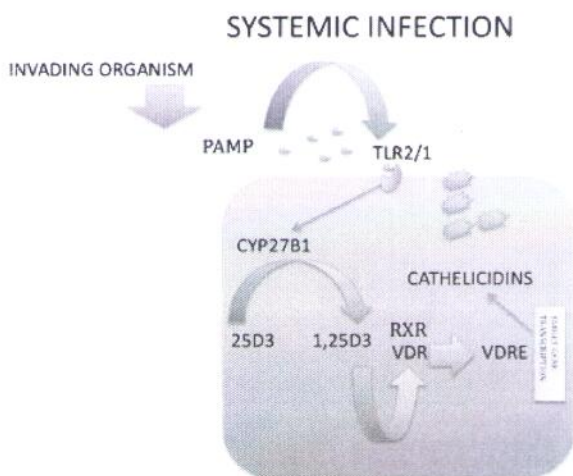


Figure 2. Cathelicidin induction via TLRs and vitamin D. PAMP on the invading organism triggers TLR2/1, toll-like receptor 1/2; inducing CYP27B1, (1 α -hydroxylase) enzyme; 25D3, 25 (OH)D; 1,25D3, 1,25(OH)₂D₃ (active vitamin D hormone); RXR, retinoid X receptor; VDR, vitamin D receptor; VDRE, vitamin D-response elements. Adapted from [8].

host. PAMP's trigger pathogen recognition receptors found on cell membranes [24]. There are at least 12 different pathogen recognition receptors's called toll-like receptors (TLR) in mammals. TLRs are found on many cells including macrophages, dendritic cells and epithelial cells. In humans, TLR2/1 and TLR4 when triggered result in the induction of the CYP27B1 (1 α -hydroxylase) enzyme. This in turn induces the production of active vitamin D (1,25(OH)₂D). The 1,25(OH)₂D binds to the vitamin D receptor along with retinoid X receptors which then bind to vitamin D-response elements unlocking the DNA, targeting genes that encode proteins [9] (Fig. 2). TLR2/1 binds to peptidoglycans found on Gram-positive bacteria such as streptococci and staphylococci. TLR4 is activated by LPS found on gram-negative bacteria, salmonella and *Escherichia coli*.

The human antimicrobial peptides include: 6 human α -defensins (HNP1-4 and HD-5,6), 4 human β -defensins (hBD-1 to 4), and cathelicidin (LL-37). Aside from antibacterial, antiviral and antifungal properties, these antimicrobial peptides also have other immune regulatory properties. Cathelicidin has many other functions including chemotaxis, cytokine and chemokine production, cell proliferation, increasing vascular permeability, wound healing, *etc.*, which has been reviewed in the literature [25, 26] The response time for production of these antimicrobial peptides is very rapid and time from recognition to the production of specific defense proteins is within minutes. However, the innate immune system does not retain memory of prior exposure. The interaction with the micro flora and synergy of these antimicrobials is just beginning to be understood [27–30].

Third, hydrogen peroxide secretion in human monocytes is also activated by 1,25(OH)₂D resulting in increased oxidative burst potential [31].

Fourth, vitamin D has a role in the attraction of other immune cells to promote wound healing or fight infection [32, 33]. Vitamin D is essential in activating antigen specific T-cell division should be the innate immune system fail to control infection [34] (Fig. 1; 4A).

Finally, vitamin D may prevent an over reaction of the inflammatory response in the adaptive immune system preventing further cell or tissue damage by inflammation [35]. Inflammation is suppressed by vitamin D by limiting excessive production of TNF α and IL-12 which are pro-inflammatory cytokines [36].

The following is a summary of some important areas in medicine where strengthening barrier function or inducing antimicrobial peptides via optimal vitamin D levels may improve clinical outcomes. Described also are some areas in medicine where the opposite may be true as well.

2 Oral health: dental caries and periodontal disease

Much of what is known about vitamin D and bone and dental health dates back as far as the 1930's. At that time, it was found that there was a direct correlation of the incidence of dental caries in 12- to 14-year-old white boys and the total available number of hours of sunlight *per year* [37]. As well, an analysis of more than 500 000 US rural children showed that there was a significant relationship between dental caries and the amount of sunshine and latitude [38]. With the introduction of fluoride treatment, this aspect of vitamin D has been largely forgotten which is unfortunate since dental fluorosis is now on the rise [39, 40]. More recently, a study of the use of full spectrum lighting (includes UVB) which induces vitamin D in the skin showed a significant reduction of the number of caries as compared with the control group [41]. It has been known since 1938 that dental caries are significantly reduced with the use of 800 IU of vitamin D or more. The use of 250 and 400 IU of vitamin D did not reduce cavities significantly [42]. There is evidence to suggest that tooth retention in both elderly men and women correlates with maintenance of normal bone density [43]. Even in the elderly, tooth loss was almost reduced by half in a 3-year followup with the use of calcium and vitamin D [44]. Much of this may be as a result of healthier bones and less periodontal infection. Periodontal disease is one of the main causes of tooth loss in the elderly. Low-serum 25(OH)D levels correlate with periodontal attachment loss [45]. Antimicrobial peptides may have antibacterial and LPS neutralizing activity against periodontopathogens [46]. Cathelicidin LL-37, hBD3 and hBD2 having the strongest antimicrobial activity. Some oral organisms such as *Streptococcus salivarius* may have probiotic effects, do not promote a proinflammatory response, may modulate over 500 genes and downregulate LL-37 responses. This then ensures that the organism is

tolerated by the host on the epithelial surface, to actively protect the host from inflammation from other pathogens [47]. Edentulous individuals have a near absence of α defensins which may make them more prone to oral pathogen infections [48]. In normal individuals, hBD-2 inhibits intracellular HIV replication and may prevent oral HIV transmission [49]. There are a multitude of factors involved in oral health which include pH [50], sugar intake [51], oral hygiene, etc. The effect of vitamin D inducing defensins and cathelicidin and strengthening the physical barrier in the oral cavity may contribute significantly to the improvement of oral health.

3 The gastrointestinal tract

Antimicrobial peptides such as α defensins, β defensins and human cathelicidin play a major role in the gastrointestinal tract controlling the endogenous bacterial flora and preventing an attack by pathogens [52]. It appears that this mixture of polypeptides works in synergy to protect against bacterial invasion [53]. The human cathelicidin LL-37 has been shown to be important in maintaining and re-establishing intestinal barrier integrity [26].

3.1 *Helicobacter pylori*

One of the most common infections is *Helicobacter pylori* with a prevalence ranging from 11 to 69% of the population [54]. Cathelicidin is significantly upregulated in the presence of *H. pylori* infection and may be expressed as a potential host defense mechanism [55]. β Defensins are also increased as the epithelium responds against potential pathogens [56]. Vitamin D may be important to control the inflammatory status in this disease [57]. A long term study using a vitamin D analogue 1 α -hydroxyvitamin D₃ resulted in a marked (greater than 50%) reduction of *H. pylori* infection over 20 years [58]. Further studies are warranted in this disease.

3.2 Crohn's disease

Vitamin D deficiency may contribute to the pathogenesis of inflammatory bowel disease as has been shown in preclinical studies [59] 1,25(OH)₂D has been shown to synergistically induce the genes encoding for hBD-2 and cathelicidin when exposed to bacterial lysosomal breakdown products. The breakdown product Muramyl dipeptide induces the gene-encoding pattern recognition receptor NOD2/CARD15/IBD1 in epithelial and monocytic cells [60]. NOD2 insufficiency contributes to the development of Crohn's disease [61]. There appears to be a strong molecular basis for the pathogenesis of Crohn's disease and vitamin D deficiency. The role of vitamin D insufficiency in the pathogenesis of inflammatory bowel disease is reasonably strong [60, 62].

3.3 Viral hepatitis

Recent evidence in the literature has shown that patients with low 25(OH)D do not respond well to interferon-based therapy and may have more severe fibrosis if they have genotype 1 chronic hepatitis C [63]. Standard of care treatment with peginterferon and ribavirin results in a 40–50% sustained virologic response. With the addition of vitamin D (1000–4000 IU) to achieve levels >80 nmol/L, 96% in the vitamin D group were HCV RNA-negative compared with 48% in the control group receiving standard of care therapy [64].

4 The respiratory tract and the innate immune system

Vitamin D deficiency is associated with severe acute lower respiratory infections in Indian children under 5 years [65]. Vitamin D levels are low in COPD patients [66]. It is also known that tobacco smoking is associated with increased susceptibility to infection, emphysema and lung cancer. Smoking (current or past history) is associated with lower levels of hBD-2 in sputum and pharyngeal washes in patients with acute pneumonia [67]. In severe pneumonia, vitamin D deficiency (rachitic levels) has been associated with poor outcomes and insufficient levels of vitamin D resulted in decreased circulating neutrophils and hypoxemia at day 5 of treatment [68]. Vitamin D may also have an effect on the development and severity of asthma possibly by modulation of innate immunity and its effect on viral infections [69–71].

4.1 Respiratory viral infections and innate immunity

In general, seasonal flu strikes in the northern hemisphere during the winter when vitamin D levels are lowest as a result of less UVB radiation. The seasonality of flu was first described by Hope-Simpson [72] and expanded later on in a review article [73]. Saliva may be an important barrier to Influenza A viral infection where human neutrophil defensins and many other inhibitory proteins are present in sufficient concentration [74]. Vitamin D has been shown to up regulate expression of cathelicidin in respiratory epithelial cells and plays a major role in host defense [75]. Viral RNA increases active vitamin D in respiratory epithelial cells and expression of cathelicidin, whereas bacterial wall components do not [75]. Vitamin D also activates secretion of hydrogen peroxide in monocytes [31]. Human neutrophil defensins, hBD-2 have activity against respiratory syncytial virus [76] and influenza A virus, para influenza virus and adenovirus. Exposure to rhinovirus may result in an indirect respiratory epithelial cell response as well as increasing hBD-2 [77]. In the second year of a trial, using 2000 IU daily of vitamin D the cold/influenza symptoms was nearly eliminated [78]. Despite this, a controlled trial using 2000 IU daily of vitamin D₃ for 3 months to prevent symptomatic

Table 1. Human studies with UV exposure or vitamin D supplementation relating to the Innate Immune Function

Study author and N	Type of study	Results	Discussion
Oral disease			
Kaiser, H., and East, B. R. N > 500 000 [38]	Observational study	Dental caries correlate with UV exposure	Number of sunlight hours and latitude correlate inversely with number of dental caries
Hargreaves, J. A., Thompson, G. W. N = 102 [41]	Randomized controlled study	Significant reduction of dental caries with full spectrum light exposure in school $p < 0.001$	Highly significant results despite a small sample size. Repeat studies warranted
Krall, E. A., <i>et al.</i> N = 145 [44]	Randomized control study with vitamin D and calcium	Tooth loss was 13% in patients taking supplements <i>versus</i> 27% not taking supplements over 3 years	Vitamin D was not independently related to risk of losing teeth
H. pylori			
Kwaura, A. N = 34 [58]	Observational study using 40IU daily for 20 years of 1 α -hydroxyvitamin D3	<i>H. pylori</i> infection With vitamin D 5/15 Without vitamin D 13/19	<i>H. pylori</i> infection was significantly lower in vitamin D treatment group
Hepatitis C			
Abu-Mouch N = 58 [64]	Randomized control study adding vitamin D 1000–4000IU to achieve 25(OH)D levels > 75 nmol/L	Response rate with usual antiviral treatment With vitamin D 26/27 Without vitamin D 15/31	96% responded with vitamin D treatment
Influenza			
Aloia, J. F. and Li-Ng, M. N = 204 [78]	3-year randomized placebo control using 2000IU of vitamin D3 in African American women	Number of flu or cold episodes in the treated group were 1/3 of the placebo group 8 <i>versus</i> 26	Significant reduction of reported flu. Small sample needs to be replicated
Li-Ng, M. <i>et al.</i> N = 162 [79]	12-wk randomized placebo control trial	No significant difference in incidence of flu or cold symptoms	Short trial with this dose may take more than 3 months to achieve adequate vitamin D levels
Urashima, M. <i>et al.</i> N = 334 [80]	4-month randomized placebo control trial using 1200IU vitamin D in school children	RR of 0.58 compared with control group $p = 0.04$ Asthma attacks significantly reduced in treatment group $p = 0.006$ (secondary outcome)	Significant reduction of influenza A but not B
Tuberculosis			
Nyrasyam, E. W. <i>et al.</i> N = 67 [89]	Randomized placebo controlled study using 10 000IU vitamin D daily	77.1% sputum conversion rate in antibiotic only group (placebo) compared with 100% in vitamin D group	Highly significant results. However, small sample size
Wejse, C. <i>et al.</i> N = 365 [90]	Double blind randomized control study	Use of 100 000 IU at 1, 5 and 8 months. No significant difference in groups	Dose may not be high enough to result in a difference
Postoperative complications			
Bishoff-Ferrari, H. <i>et al.</i> N = 173. [109]	Randomized factorial design study using 800 or 2000 IU daily cholecalciferol and intense	39% reduction in hospital readmission in the group using 2000 IU daily cholecalciferol	90% reduction in infection rate
Eczema			
Hata, T. R. <i>et al.</i> N = 20 [123]	Observational study	Supplementation for 3 wk of 4000IU vitamin D daily resulted in a 600% increase in cathelicidin levels	Highly significant result since this is the first clinical study showing induction of cathelicidins with oral vitamin D3

upper respiratory tract infections did not show any difference from placebo [79]. Most recently, a randomized control study in school children receiving 1200 IU of vitamin D for the winter months resulted in a significant reduction (RR of 0.58) in developing Influenza A during the flu season.

Asthma attacks were significantly reduced in the vitamin D supplementation group (RR of 0.36) which was a secondary outcome [80] (Table 1).

The role of LPS, which is one of the endotoxin products, produced by pathogenic microorganisms and its interaction

with LL-37 is just emerging. LL-37 is a potent LPS-neutralizing factor and may be beneficial in treatment in respiratory diseases such as COPD and hypersensitivity pneumonia [81]. At this time, there is evidence that lung function correlates with circulating vitamin D levels, justifying the need for randomized controlled trials with exploration of the appropriate dose of vitamin D required for successful prevention and treatment [82].

4.2 Tuberculosis and innate immunity

It is estimated that up to 30% of the world's population has been infected by *Mycobacterium tuberculosis*. This disease has significant morbidity and mortality estimated at 1.7 million people annually [83]. There are about 9 million new cases a year many of which have multiple drug resistance [84]. Treatment for mycobacterium infections included the use of UVB therapy in sanatoria in the late 1800's. Niels Ryberg Finsen was awarded the Nobel Prize in 1903 for the treatment of mycobacterium infections with UVB.

The innate immune system is activated by TLRs on macrophages which induce CYP27b1 [85]. This autocrine pathway requires adequate vitamin D in the form of 25(OH)D as a substrate for the formation of activated vitamin D(1,25(OH)₂D). This upregulates the production of cathelicidin, which increase antimicrobial activity against tuberculosis [86]. Vitamin D can also induce nitric oxide killing of bacteria [87].

There have been several studies looking at various doses of vitamin D in treatment of mycobacterium. Sun exposure can result in the production of 10–20 000 IU of vitamin D [88] in a relatively short period of time and sun or UVB exposure was always considered part of the treatment of TB many decades ago. A recent study showed that using 10 000 IU of vitamin D₃ daily in addition to the antibiotics resulted in 100% sputum conversion rates as compared 77% in those using the antibiotics alone at 1 year [89]. A randomized control trial using 100 000 IU in the first month, at 5 and 8 months (a dose that would result in less than 1000 IU daily) showed no difference in the control or treatment group [90] (Table 1).

5 The genito urinary tract and the innate immune system

5.1 Bacterial vaginosis

Bacterial vaginosis (BV) is a common condition in the child bearing years affecting up to 29% of women in some studies [91]. Low birth weight, premature delivery and clinical chorioamnionitis may result from BV when identified before 20 wk gestation during pregnancy [92]. In one study, BV was strongly associated with vitamin D deficiency 25(OH)D < 37.5 nmol/L with an odds ratio of 4.4 in preg-

nant African American adolescents [93]. An inverse dose–response relationship between 25(OH)D levels and BV was found in another study of low-income pregnant women. At 16 wk gestation, the prevalence of BV was 65% higher and 26% higher with 25(OH)D of 20 and 50 nmol/L, respectively, as compared with 25(OH)D levels of 75 nmol/L [94].

The vaginal epithelia is more than a simple physical barrier protecting against infection. The surface is replete with antimicrobial peptides that mediate innate host defenses against invading pathogens [95]. Even seminal fluid, which has high concentrations of cathelicidin that are activated by gastricsin (a prostate-derived protease) and the acidic pH of the vagina, synergistically interact to prevent infection following sexual intercourse [96].

5.2 Viral infections

Recent literature has drawn attention to the relationship between HIV infection and vitamin D. Studies suggest an increased prevalence of vitamin D deficiency in HIV-infected hosts especially in winter as well as those with dark skin color [97, 98]. Reduced HIV-1 replication in peripheral blood mononuclear cells has been demonstrated with the antimicrobial peptide LL-37 [99] and 1,25-dihydroxyvitamin D₃ [100]. This antimicrobial peptide may have a contributory role in the local protection against HIV-1 in epithelial cells; however, 1,25(OH)₂D may also increase HIV replication in other cell lines [101]. Thus more studies are required to determine the clinical relevance of vitamin D in this infection.

Herpes simplex virus is inhibited by cervico-vaginal fluid in healthy subjects but protection was mainly from neutrophils, which contain β defensins and LL-37.

The defensins and LL-37 appear to play a role in the clearing of HPV infections [102, 103]. The role of vitamin D, which is required for hBD-2 and LL-37 production, has not been adequately explored in these infections.

5.3 The urinary tract

There are many host defense mechanisms in the urinary tract such as the Tamm-Horsfall protein, lactoferrin and lipocalin preventing infection. In the urinary tract, infection induces epithelial cells to respond rapidly to produce the cathelicidin LL-37, protecting against infection [18]. Ascending infections may be prevented by this response. As well, vitamin D downregulates the inflammatory response in the adaptive immune system by attenuating the production of INF- γ thus reducing inflammation which can result in irreversible damage [104]. With this new information on the role of vitamin D in the protection of the epithelium in this organ system, it would be prudent to have well-controlled studies using vitamin D in primary prevention or adjuvant therapy for the

treatment of urinary tract infections. Urinary tract infections are common in the nursing home environment where 25(OH)D levels are generally low [105]. As well studies need to be done to see if vitamin D would reduce *Candida albicans* skin infections and vaginal infections following treatment of urinary tract infections [23]. A lack of fungicidal killing of *C. albicans* has been demonstrated in hereditary resistance to active vitamin D [106].

6 The skin and the innate immune system

6.1 Wound healing

Cathelicidin antimicrobial proteins (hCAP18) and defensins are strongly upregulated by epithelium shortly after wounding and are highest during the first 48 h and then decline slowly to preinjury levels when the wound closes [32]. The C-terminal fragment of the cathelicidin LL-37 has broad antimicrobial activity and may be required for wound closure because of its role in inducing epithelial proliferation as well. LL-37 has been shown to improve re-epithelialization and has the potential therapeutically to promote wound healing [107]. Vitamin D is required for the production of cathelicidin [15]. It has been found that chronic ulcers have low levels of LL-37 which may be the reason for impaired re-epithelialization. In burns, the lack of defensins has been suggested as a mechanism for increased susceptibility to infection and subsequent sepsis [108]. In a study using 2000 IU versus using 800 IU of vitamin D (cholecalciferol) daily after hip fracture in elderly patients resulted in fewer hospital readmissions by 39% in the group using 2000 IU of vitamin D daily. This reduction of readmissions in the group that was using 2000 IU of vitamin D was as a result of a reduction of fall related injury by –60% and fewer infections by –90% [109]. Well-controlled studies should be done to determine the benefit of giving a one-time dose of 100 000 IU of vitamin D 1 wk preoperatively to enhance wound healing and for the prevention of postsurgical infectious complications.

6.2 Bacterial skin infections

With the increase in bacterial resistance to antibiotics and increase in life-threatening infections, it may be most prudent to strengthen the bodies natural first line of defenses [110]. Keratinocytes not only provide a physical barrier but are also able to produce cathelicidin which provide protection against bacterial skin pathogens [111]. Antimicrobial peptides are expressed in sweat which may be a unique delivery system for innate defenses on skin [112]. Unlike pharmacologic antibiotics, cathelicidin has maintained broad-spectrum antimicrobial activity and resistance to most antimicrobial strategies. Again, adequate vitamin D is essential for the production of cathelicidin. The antimicrobial activity is effective

against both gram-positive [113] and gram-negative bacteria [114]. Cathelicidin may prevent invasive group A streptococcus infection of the skin [115]. It would be wise to incorporate vitamin D optimization as a strategy for prevention and treatment of skin infections.

6.3 Psoriasis

Activated vitamin D (1,25(OH)₂D) in the skin plays an important role. It inhibits the proliferation of keratinocytes and augments their differentiation [116]. Psoriasis improves with sun exposure, and vitamin D analog creams are now mainstay therapy [117]. There are high levels of cathelicidin and inflammation in psoriatic plaques and despite significant inflammation the potential for infection is rare in early psoriasis [118].

6.4 Atopic eczema

In contrast to psoriasis, the epithelium in atopic dermatitis is known to have lower levels of cathelicidin and there is greater susceptibility to viral infections [119] and bacterial infections [120, 121]. Higher levels of cathelicidin may be protective. Vitamin D has been shown useful for treatment of hyperkeratotic palmoplantar eczema [122]. Oral vitamin D supplementation has also been shown to dramatically increase cathelicidin expression in atopic dermatitis lesions by about 600% [123]. The use of narrow bandwidth UVB which induces vitamin D production has shown significant benefit in young children for both psoriasis (63% clearing) and eczema (68% clearing) [124]. However, treatment courses for eczema were longer and long-term side effects may be a concern. Vitamin D may increase cathelicidin thus preventing infections in this disease.

6.5 Rosacea

Cathelicidin is found in abundance in rosacea and there is increased serine protease activity, which results in cathelicidin that is altered. These altered cathelicidin peptides in rosacea cause erythema and inflammatory cell infiltration [125]. Tetracyclines can inhibit serine proteases indirectly [126]. It is believed that targeting the vitamin D₃ pathway and blocking cathelicidin expression or blocking protease activity may improve this disease [127]. At least from our present knowledge, it would appear that vitamin D might not be helpful for this condition.

6.6 Acne

The common belief of the usefulness of ultraviolet radiation in acne has long been held. UVB radiation has been shown

in vitro to reduce the colony count of *Propionibacterium acnes* and *Staphylococcus aureus* which may result in improvement in response to other treatment modalities [128]. UVB radiation results in a modest improvement in acne; however, one must weigh this against damage to the skin and potential for skin cancer. There has been an association of prediagnostic vitamin D levels and the development of basal cell carcinoma [129]. The use of blue light and low-dose UVB at 312 nm (which is known to induce vitamin D production) significantly reduced inflammatory cytokines in keratinocyte cells more than blue light alone [130]. The use of isotretinoin may result in a significant fall in 1,25(OH)₂D but does not appear to change 25(OH)D levels [131]. The interaction between testosterone (which is involved in acne) and vitamin D also needs to be explored more since testosterone has been shown to increase 1,25(OH)₂D in target organs such as the gut and bone [132].

7 Ocular infections

The role of antimicrobial peptides in the ocular system has been reviewed in an excellent article [133]. *Pseudomonas aeruginosa* and *S. aureus* are common eye infections resulting in keratitis. Cathelicidin may prevent bacterial biofilm formation by *P. aeruginosa* [134]. Human β defensins 2 and 3 promote resistance to *P. aeruginosa* infection [135]. Briefly, 1,25(OH)₂D has been shown to increase the induction of genes encoding for human β defensin 2 [60]. Lipoproteins from *S. aureus* also trigger the innate response through TLR-2/1 which is vitamin D dependant [136]. Defensins and cathelicidin are produced by corneal and conjunctival epithelial cells and may act synergistically to protect the eye from infections and cathelicidin may also promote wound healing [133].

8 Discussion

Since there is a world-wide problem with inadequate levels of vitamin D(1), there may be room to improve the vitamin D status by supplementing vitamin D [3]. There is some evidence that this may result in significant healthcare savings along with decreased morbidity and mortality [137]. This estimate has not addressed the potential benefit that vitamin D may have on the innate immune system because information on this aspect is just emerging.

With increasing antibiotic-resistant bacteria, there is a need for the development of strategies for treatment of the infections and the systemic inflammation response syndrome. LL-37 has some direct antimicrobial activity and has potent antiendotoxin activity [138]. Low vitamin D levels correlate with low antimicrobial peptide levels (LL-37) in critically ill patients as compared with normal controls and there is evidence that LL-37 levels are regulated by vitamin D status [30, 139]. Cathelicidin is also known to be effective against Methicillin-resistant *S. aureus*, a major human pathogen that may cause

serious illness such as pneumonia, toxic shock syndrome, food poisoning or staphylococcal-scalded skin syndrome. Presently, no strains show complete resistance to these peptides [21]. Vitamin D insufficiency may contribute to the variable induction of antimicrobial peptide activity.

Exposure of skin to ultraviolet radiation (UVB) can easily result in the production in the skin of 10–20 000 IU of vitamin D [88]. A single dose of 100 000 IU of vitamin D has been shown to raise the 25(OH)D from 86.4 to 114.1 nmol/L within 1 wk [140]. Vitamin D supplementation can be addressed reasonably quickly with the use of 4000 IU daily resulting in raising the 25(OH)D levels from 56.25 to 88.75 nmol/L in only 3 wk [123]. All of these supplement strategies using significant doses bring 25(OH)D levels up to physiological levels without toxicity. There is little or no evidence that less than 10 000 IU of vitamin D₃ used on a daily basis causes toxicity [141]. However, the use of yearly dose of 500 000 IU of vitamin D₃ given orally to prevent fractures did not confer benefit [142]. Human studies using various doses of vitamin D in various conditions are summarized in Table 1.

From the previous discussion in this article, vitamin D appears to show promise in aiding the body's own natural defenses against viruses, bacteria and fungi. There is also evidence that vitamin D may strengthen the physical epithelial barrier *via* stimulating junction genes. Several conditions as outlined above may benefit from adequate 25(OH)D as substrate for the induction of cathelicidin and defensins to produce antimicrobial peptides. Conditions that may not improve or worsen with vitamin D may be rosacea and possibly acne.

Many studies need to be done to confirm the benefit of optimizing vitamin D levels. This in turn may reduce the significant morbidity and mortality associated with vitamin D deficiency.

9 Concluding remarks

The proper functioning of the body's defense system requires the presence of adequate levels of Vitamin D for barrier integrity, the production of antimicrobials, chemotaxis of other immune cells and regulation of inflammation in the innate and adaptive immune system. The level of 25(OH)D that is needed for maximal performance in each disorder has not been determined but may be considerably higher than previously believed for diseases such as *M. tuberculosis* and other infections. From a public health point of view, the improved outcomes in treatment and prevention of devastating diseases as summarized in Table 1 may result in considerable cost savings to health care. Diseases such as rosacea may require lower levels of vitamin D or even locally active serine proteases inhibitors and vitamin D antagonists to prevent harm. Local application may be required not to interfere with other benefits of vitamin D. The use of sanatoriums, which can easily provide

10 000 IU of vitamin D daily, may need to be revisited, as well as the use of short-term high-dose vitamin D for the prevention of wound infections.

Much still needs to be learned in this whole area. It appears appropriate to call for new and innovative studies using appropriate doses of vitamin D, which may greatly reduce morbidity and mortality worldwide.

Ethics approval not required. No funding has been provided for any part of this work.

The author has declared no conflict of interest.

10 References

- [1] Holick, M. F., Chen, T. C., Vitamin D deficiency: a worldwide problem with health consequences. *Am. J. Clin. Nutr.* 2008, *87*, 1080S–1086S.
- [2] Schwalfenberg, G., Not enough vitamin D: health consequences for Canadians. *Can. Fam. Physician* 2007, *53*, 841–854.
- [3] Genuis, S. J., Schwalfenberg, G. K., Hiltz, M. N., Vaselenak, S. A., Vitamin D status of clinical practice populations at higher latitudes: analysis and applications. *Int. J. Environ. Res. Public Health* 2009, *6*, 151–173.
- [4] Holick, M. F., Resurrection of vitamin D deficiency and rickets. *J. Clin. Invest.* 2006, *116*, 2062–2072.
- [5] Holick, M. F., High prevalence of vitamin D inadequacy and implications for health. *Mayo Clin. Proc.* 2006, *81*, 353–373.
- [6] Hewison, M., Zehnder, D., Chakraverty, R., Adams, J. S., Vitamin D and barrier function: a novel role for extra-renal 1 alpha-hydroxylase. *Mol. Cell. Endocrinol.* 2004, *215*, 31–38.
- [7] Norman, A. W., From vitamin D to hormone D: fundamentals of the vitamin D endocrine system essential for good health. *Am. J. Clin. Nutr.* 2008, *88*, 491S–499S.
- [8] Hewison, M., Vitamin D and innate immunity. *Curr. Opin. Investig. Drugs* 2008, *9*, 485–490.
- [9] Adams, J. S., Hewison, M., Unexpected actions of vitamin D: new perspectives on the regulation of innate and adaptive immunity. *Nat. Clin. Pract. Endocrinol. Metab.* 2008, *4*, 80–90.
- [10] White, J. H., Vitamin D signaling, infectious diseases, and regulation of innate immunity. *Infect. Immun.* 2008, *76*, 3837–3843.
- [11] Clairmont, A., Tessman, D., Stock, A., Nicolai, S. *et al.*, Induction of gap junctional intercellular communication by vitamin D in human skin fibroblasts is dependent on the nuclear vitamin D receptor. *Carcinogenesis* 1996, *17*, 1389–1391.
- [12] Gniadecki, R., Gajkowska, B., Hansen, M., 1,25-dihydroxyvitamin D3 stimulates the assembly of adherens junctions in keratinocytes: involvement of protein kinase C. *Endocrinology* 1997, *138*, 2241–2248.
- [13] Palmer, H. G., Gonzalez-Sancho, J. M., Espada, J., Berciano, M. T. *et al.*, Vitamin D(3) promotes the differentiation of colon carcinoma cells by the induction of E-cadherin and the inhibition of beta-catenin signaling. *J. Cell. Biol.* 2001, *154*, 369–387.
- [14] Chun, R. F., Adams, J. S., Hewison, M., Back to the future: a new look at 'old' vitamin D. *J. Endocrinol.* 2008, *198*, 261–269.
- [15] Wang, T. T., Nestel, F. P., Bourdeau, V., Nagai, Y. *et al.*, Cutting edge: 1,25-dihydroxyvitamin D3 is a direct inducer of antimicrobial peptide gene expression. *J. Immunol.* 2004, *173*, 2909–2912.
- [16] Hewison, M., Burke, F., Evans, K. N., Lammas, D. A. *et al.*, Extra-renal 25-hydroxyvitamin D3-1alpha-hydroxylase in human health and disease. *J. Steroid Biochem. Mol. Biol.* 2007, *103*, 316–321.
- [17] 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.
- [18] Chromek, M., Slamova, Z., Bergman, P., Kovacs, L. *et al.*, The antimicrobial peptide cathelicidin protects the urinary tract against invasive bacterial infection. *Nat. Med.* 2006, *12*, 636–641.
- [19] Weber, G., Heilborn, J. D., Chamorro Jimenez, C. I., Hammarsjo, A. *et al.*, Vitamin D induces the antimicrobial protein hCAP18 in human skin. *J. Invest. Dermatol.* 2005, *124*, 1080–1082.
- [20] Gombart, A. F., Borregaard, N., Koeffler, H. P., Human cathelicidin antimicrobial peptide (CAMP) gene is a direct target of the vitamin D receptor and is strongly up-regulated in myeloid cells by 1,25-dihydroxyvitamin D3. *FASEB J.* 2005, *19*, 1067–1077.
- [21] Komatsuzawa, H., Ouhara, K., Yamada, S., Fujiwara, T. *et al.*, Innate defences against methicillin-resistant *Staphylococcus aureus* (MRSA) infection. *J. Pathol.* 2006, *208*, 249–260.
- [22] Klotman, M. E., Chang, T. L., Defensins in innate antiviral immunity. *Nat. Rev. Immunol.* 2006, *6*, 447–456.
- [23] Lopez-Garcia, B., Lee, P. H., Yamasaki, K., Gallo, R. L., Antifungal activity of cathelicidins and their potential role in *Candida albicans* skin infection. *J. Invest. Dermatol.* 2005, *125*, 108–115.
- [24] Medzhitov, R., Toll-like receptors and innate immunity. *Nat. Rev. Immunol.* 2001, *1*, 135–145.
- [25] Niyonsaba, F., Nagaoka, I., Ogawa, H., Human defensins and cathelicidins in the skin: beyond direct antimicrobial properties. *Crit. Rev. Immunol.* 2006, *26*, 545–576.
- [26] Otte, J. M., Zdebik, A. E., Brand, S., Chromik, A. M. *et al.*, Effects of the cathelicidin LL-37 on intestinal epithelial barrier integrity. *Regul. Pept.* 2009, *156*, 104–117.
- [27] Niyonsaba, F., Ogawa, H., Protective roles of the skin against infection: implication of naturally occurring human antimicrobial agents beta-defensins, cathelicidin LL-37 and lysozyme. *J. Dermatol. Sci.* 2005, *40*, 157–168.

- [28] Zheng, Y., Niyonsaba, F., Ushio, H., Nagaoka, I. *et al.*, Cathelicidin LL-37 induces the generation of reactive oxygen species and release of human alpha-defensins from neutrophils. *Br. J. Dermatol.* 2007, 157, 1124–1131.
- [29] Chen, X., Niyonsaba, F., Ushio, H., Okuda, D. *et al.*, Synergistic effect of antibacterial agents human beta-defensins, cathelicidin LL-37 and lysozyme against *Staphylococcus aureus* and *Escherichia coli*. *J. Dermatol. Sci.* 2005, 40, 123–132.
- [30] Nijnik, A., Hancock, R. E., The roles of cathelicidin LL-37 in immune defences and novel clinical applications. *Curr. Opin. Hematol.* 2009, 16, 41–47.
- [31] Cohen, M. S., Mesler, D. E., Snipes, R. G., Gray, T. K., 1,25-Dihydroxyvitamin D3 activates secretion of hydrogen peroxide by human monocytes. *J. Immunol.* 1986, 136, 1049–1053.
- [32] Heilborn, J. D., Nilsson, M. F., Kratz, G., Weber, G. *et al.*, The cathelicidin anti-microbial peptide LL-37 is involved in re-epithelialization of human skin wounds and is lacking in chronic ulcer epithelium. *J. Invest. Dermatol.* 2003, 120, 379–389.
- [33] Heilborn, J. D., Weber, G., Gronberg, A., Dieterich, C., Stahle, M., Topical treatment with the vitamin D analogue calcipotriol enhances the upregulation of the antimicrobial protein hCAP18/LL-37 during wounding in human skin *in vivo*. *Exp. Dermatol.* 2010, 19, 332–338.
- [34] von Essen, M. R., Kongsback, M., Schjerling, P., Olgaard, K. *et al.*, Vitamin D controls T cell antigen receptor signaling and activation of human T cells. *Nat. Immunol.* 2010, 11, 344–349.
- [35] Hewison, M., Freeman, L., Hughes, S. V., Evans, K. N. *et al.*, Differential regulation of vitamin D receptor and its ligand in human monocyte-derived dendritic cells. *J. Immunol.* 2003, 170, 5382–5390.
- [36] Cantorna, M. T., Yu, S., Bruce, D., The paradoxical effects of vitamin D on type 1 mediated immunity. *Mol. Aspects Med.* 2008, 29, 369–375.
- [37] Bion, E. R., Mean annual hours of sunshine and the incidence of dental caries. *Am. J. Public Health* 1939, 29, 777–780.
- [38] Kaiser, H., East, B. R., Relation of dental caries in rural children to sex, age and environment. *Am. J. Dis. Child.* 1940, 60, 1289–1303.
- [39] Rozier, R. G., The prevalence and severity of enamel fluorosis in North American children. *J. Public Health Dent.* 1999, 59, 239–246.
- [40] Clark, D. C., Trends in prevalence of dental fluorosis in North America. *Community Dent. Oral Epidemiol.* 1994, 22, 148–152.
- [41] Hargreaves, J. A., Thompson, G. W., Ultraviolet light and dental caries in children. *Caries Res.* 1989, 23, 389–392.
- [42] McBeath, E. C., Zucker, T. F., The role of vitamin D in the control dental caries. *Am. J. Public Health* 1938, 15, 547–564.
- [43] Krall, E. A., Osteoporosis and the risk of tooth loss. *Clin. Calcium* 2006, 16, 287–290.
- [44] Krall, E. A., Wehler, C., Garcia, R. I., Harris, S. S., Dawson-Hughes, B., Calcium and vitamin D supplements reduce tooth loss in the elderly. *Am. J. Med.* 2001, 111, 452–456.
- [45] Dietrich, T., Joshipura, K. J., Dawson-Hughes, B., Bischoff-Ferrari, H. A., Association between serum concentrations of 25-hydroxyvitamin D3 and periodontal disease in the US population. *Am. J. Clin. Nutr.* 2004, 80, 108–113.
- [46] Lee, S. H., Jun, H. K., Lee, H. R., Chung, C. P., Choi, B. K., Antibacterial and lipopolysaccharide (LPS)-neutralising activity of human cationic antimicrobial peptides against periodontopathogens. *Int. J. Antimicrob. Agents* 2010, 35, 138–145.
- [47] Cosseau, C., Devine, D. A., Dullaghan, E., Gardy, J. L. *et al.*, The commensal *Streptococcus salivarius* K12 down-regulates the innate immune responses of human epithelial cells and promotes host-microbe homeostasis. *Infect. Immun.* 2008, 76, 4163–4175.
- [48] Fanali, C., Inzitari, R., Cabras, T., Pisano, E. *et al.*, Alpha-defensin levels in whole saliva of totally edentulous subjects. *Int. J. Immunopathol. Pharmacol.* 2008, 21, 845–849.
- [49] Sun, L., Finnegan, C. M., Kish-Catalone, T., Blumenthal, R. *et al.*, Human beta-defensins suppress human immunodeficiency virus infection: potential role in mucosal protection. *J. Virol.* 2005, 79, 14318–14329.
- [50] Robyn, R. L., Robert, J. M., John, D. R., Pucker up: the effects of sour candy on your patients' oral health. A review of the dental erosion literature and pH values for popular candies. *Northwest Dent.* 2008, 87, 20–21, 4–5, 8–9 *passim*.
- [51] Falco, M. A., The lifetime impact of sugar excess and nutrient depletion on oral health. *Gen. Dent.* 2001, 49, 591–595.
- [52] Wehkamp, J., Schaubert, J., Stange, E. F., Defensins and cathelicidins in gastrointestinal infections. *Curr. Opin. Gastroenterol.* 2007, 23, 32–38.
- [53] Tollin, M., Bergman, P., Svenberg, T., Jornvall, H. *et al.*, Antimicrobial peptides in the first line defence of human colon mucosa. *Peptides* 2003, 24, 523–530.
- [54] Bruce, M. G., Maaroos, H. I., Epidemiology of *Helicobacter pylori* infection. *Helicobacter* 2008, 13, 1–6.
- [55] Hase, K., Murakami, M., Imura, M., Cole, S. P. *et al.*, Expression of LL-37 by human gastric epithelial cells as a potential host defense mechanism against *Helicobacter pylori*. *Gastroenterology* 2003, 125, 1613–1625.
- [56] George, J. T., Boughan, P. K., Karageorgiou, H., Bajaj-Elliott, M., Host anti-microbial response to *Helicobacter pylori* infection. *Mol. Immunol.* 2003, 40, 451–456.
- [57] Nasri, H., Baradaran, A., The influence of serum 25-hydroxy vitamin D levels on *Helicobacter pylori* infections in patients with end-stage renal failure on regular hemodialysis. *Saudi J. Kidney Dis. Transpl.* 2007, 18, 215–219.
- [58] Kawaura, A., Inhibitory effect of long term 1 α -hydroxyvitamin D3 administration on *Helicobacter pylori* infection. *J. Clin. Biochem. Nutr.* 2006, 38, 103–106.
- [59] Liu, N., Nguyen, L., Chun, R. F., Lagishetty, V. *et al.*, Altered endocrine and autocrine metabolism of vitamin D in a mouse model of gastrointestinal inflammation. *Endocrinology* 2008, 149, 4799–4808.
- [60] Wang, T. T., Dabbas, B., Laperriere, D., Bitton, A. J. *et al.*, Direct and indirect induction by 1,25-dihydroxyvitamin D3 of

- the NOD2/CARD15-beta defensin 2 innate immune pathway defective in Crohn's disease. *J. Biol. Chem.* 2010, *285*, 2227–2231.
- [61] Hugot, J. P., Chamaillard, M., Zouali, H., Lesage, S. *et al.*, Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease. *Nature* 2001, *411*, 599–603.
- [62] Lim, W. C., Hanauer, S. B., Li, Y. C., Mechanisms of disease: vitamin D and inflammatory bowel disease. *Nat. Clin. Pract. Gastroenterol. Hepatol.* 2005, *2*, 308–315.
- [63] Petta, S., Camma, C., Scazzone, C., Tripodo, C. *et al.*, Low vitamin D serum level is related to severe fibrosis and low responsiveness to interferon-based therapy in genotype 1 chronic hepatitis C. *Hepatology* 2010, *51*, 1158–1167.
- [64] Abu-Mouch, S., Abstract LB20. 60th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD. 2009). The Liver Meeting 2009.
- [65] 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.
- [66] Janssens, W., Bouillon, R., Claes, B., Carremans, C. *et al.*, Vitamin D deficiency is highly prevalent in COPD and correlates with variants in the vitamin D binding gene. *Thorax* 2010, *65*, 215–220.
- [67] Herr, C., Beisswenger, C., Hess, C., Kandler, K. *et al.*, Suppression of pulmonary innate host defence in smokers. *Thorax* 2009, *64*, 144–149.
- [68] Banajeh, S. M., Nutritional rickets and vitamin D deficiency – association with the outcomes of childhood very severe pneumonia: a prospective cohort study. *Pediatr. Pulmonol.* 2009, *44*, 1207–1215.
- [69] Litonjua, A. A., Childhood asthma may be a consequence of vitamin D deficiency. *Curr. Opin. Allergy Clin. Immunol.* 2009, *9*, 202–207.
- [70] Sutherland, E. R., Goleva, E., Jackson, L. P., Stevens, A. D., Leung, D. Y., Vitamin D levels, lung function and steroid response in adult asthma. *Am. J. Respir. Crit. Care Med.* 2010, *181*, 699–704.
- [71] Grant, W. B., The roles of vitamin D, temperature, and viral infections in seasonal risk of acquiring asthma. *Am. J. Respir. Crit. Care Med.* 2009, *179*, 1072, author reply -3.
- [72] Hope-Simpson, R. E., The role of season in the epidemiology of influenza. *J. Hyg. (Lond)*. 1981, *86*, 35–47.
- [73] Cannell, J. J., Vieth, R., Umhau, J. C., Holick, M. F. *et al.*, Epidemic influenza and vitamin D. *Epidemiol. Infect.* 2006, *134*, 1129–1140.
- [74] White, M. R., Helmerhorst, E. J., Ligtenberg, A., Karpel, M. *et al.*, Multiple components contribute to ability of saliva to inhibit influenza viruses. *Oral Microbiol. Immunol.* 2009, *24*, 18–24.
- [75] Hansdottir, S., Monick, M. M., Hinde, S. L., Lovan, N. *et al.*, Respiratory epithelial cells convert inactive vitamin D to its active form: potential effects on host defense. *J. Immunol.* 2008, *181*, 7090–7099.
- [76] Kota, S., Sabbah, A., Chang, T. H., Harnack, R. *et al.*, Role of human beta-defensin-2 during tumor necrosis factor-alpha/NF-kappaB-mediated innate antiviral response against human respiratory syncytial virus. *J. Biol. Chem.* 2008, *283*, 22417–22429.
- [77] Proud, D., Sanders, S. P., Wiehler, S., Human rhinovirus infection induces airway epithelial cell production of human beta-defensin 2 both *in vitro* and *in vivo*. *J. Immunol.* 2004, *172*, 4637–4645.
- [78] Aloia, J. F., Li-Ng, M., Re: epidemic influenza and vitamin D. *Epidemiol. Infect.* 2007, *135*, 1095–1096, author reply 7–8.
- [79] Li-Ng, M., Aloia, J. F., Pollack, S., Cunha, B. A. *et al.*, A randomized controlled trial of vitamin D3 supplementation for the prevention of symptomatic upper respiratory tract infections. *Epidemiol. Infect.* 2009, *137*, 1396–1404.
- [80] Urashima, M., Segawa, T., Okazaki, M., Kurihara, M. *et al.*, Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren. *Am. J. Clin. Nutr.* 2010, *91*, 1255–1260.
- [81] Golec, M., Cathelicidin LL-37: LPS-neutralizing, pleiotropic peptide. *Ann. Agric. Environ. Med.* 2007, *14*, 1–4.
- [82] Hughes, D. A., Norton, R., Vitamin D and respiratory health. *Clin. Exp. Immunol.* 2009, *158*, 20–25.
- [83] Glaziou, P., Floyd, K., Raviglione, M., Global burden and epidemiology of tuberculosis. *Clin. Chest Med.* 2009, *30*, 621–636, vii.
- [84] Zager, E. M., McNerney, R., Multidrug-resistant tuberculosis. *Biomed. Chromatogr. Infect. Dis.* 2008, *8*, 10.
- [85] Fabri, M., Modlin, R. L., A vitamin for autophagy. *Cell. Host Microbe* 2009, *6*, 201–203.
- [86] Liu, P. T., Stenger, S., Tang, D. H., Modlin, R. L., Cutting edge: vitamin D-mediated human antimicrobial activity against *Mycobacterium tuberculosis* is dependent on the induction of cathelicidin. *J. Immunol.* 2007, *179*, 2060–2063.
- [87] Waters, W. R., Nonnecke, B. J., Rahner, T. E., Palmer, M. V. *et al.*, Modulation of *Mycobacterium bovis*-specific responses of bovine peripheral blood mononuclear cells by 1,25-dihydroxyvitamin D(3). *Clin. Diagn. Lab Immunol.* 2001, *8*, 1204–1212.
- [88] Holick, M. F., Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. *Am. J. Clin. Nutr.* 2004, *80*, 1678S–1688S.
- [89] Nursyam, E. W., Amin, Z., Rumende, C. M., The effect of vitamin D as supplementary treatment in patients with moderately advanced pulmonary tuberculous lesion. *Acta Med. Indones.* 2006, *38*, 3–5.
- [90] Wejse, C., Gomes, V. F., Rabna, P., Gustafson, P. *et al.*, Vitamin D as supplementary treatment for tuberculosis: a double-blind, randomized, placebo-controlled trial. *Am. J. Respir. Crit. Care Med.* 2009, *179*, 843–850.
- [91] Allsworth, J. E., Peipert, J. F., Prevalence of bacterial vaginosis: 2001–2004 National Health and Nutrition Examination Survey data. *Obstet. Gynecol.* 2007, *109*, 114–120.
- [92] Svare, J. A., Schmidt, H., Hansen, B. B., Lose, G., Bacterial vaginosis in a cohort of Danish pregnant women: prevalence and relationship with preterm delivery, low birth-weight and perinatal infections. *Br. J. Obstet. Gynecol.* 2006, *113*, 1419–1425.

- [93] Davis, L. M., Chang, S. C., Mancini, J., Nathanson, M. S. *et al.*, Vitamin D insufficiency is prevalent among pregnant African American adolescents. *J. Pediatr. Adolesc. Gynecol.* 2010, 23, 45–52.
- [94] Bodnar, L. M., Krohn, M. A., Simhan, H. N., Maternal vitamin D deficiency is associated with bacterial vaginosis in the first trimester of pregnancy. *J. Nutr.* 2009, 139, 1157–1161.
- [95] Venkataraman, N., Cole, A. L., Svoboda, P., Pohl, J., Cole, A. M., Cationic polypeptides are required for anti-HIV-1 activity of human vaginal fluid. *J. Immunol.* 2005, 175, 7560–7567.
- [96] Sorensen, O. E., Gram, L., Johnsen, A. H., Andersson, E. *et al.*, Processing of seminal plasma hCAP-18 to ALL-38 by gastricsin: a novel mechanism of generating antimicrobial peptides in vagina. *J. Biol. Chem.* 2003, 278, 28540–28546.
- [97] Mueller, N. J., Fux, C. A., Ledergerber, B., Elzi, L. *et al.*, High prevalence of severe vitamin D deficiency in combined antiretroviral therapy-naïve and successfully treated Swiss HIV patients. *AIDS* 2010, 24, 1127–1134.
- [98] Van Den Bout-Van Den Beukel, C. J., Fievez, L., Michels, M., Sweep, F. C. *et al.*, Vitamin D deficiency among HIV type 1-infected individuals in the Netherlands: effects of antiretroviral therapy. *AIDS Res. Hum. Retroviruses* 2008, 24, 1375–1382.
- [99] Bergman, P., Walter-Jallow, L., Broliden, K., Agerberth, B., Soderlund, J., The antimicrobial peptide LL-37 inhibits HIV-1 replication. *Curr. HIV Res.* 2007, 5, 410–415.
- [100] Conner, R. I., Rigby, W. F., 1 Alpha,25-dihydroxyvitamin D3 inhibits productive infection of human monocytes by HIV-1. *Biochem. Biophys. Res. Commun.* 1991, 176, 852–859.
- [101] Kizaki, M., Ikeda, Y., Simon, K. J., Nanjo, M., Koeffler, H. P., Effect of 1,25-dihydroxyvitamin D3 and its analogs on human immunodeficiency virus infection in monocytes/macrophages. *Leukemia* 1993, 7, 1525–1530.
- [102] Meyer-Hoffert, U., Schwarz, T., Schroder, J. M., Glaser, R., Expression of human beta-defensin-2 and -3 in verrucae vulgares and condylomata acuminata. *J. Eur. Acad. Dermatol. Venereol.* 2008, 22, 1050–1054.
- [103] Conner, K., Nern, K., Rudisill, J., O'Grady, T., Gallo, R. L., The antimicrobial peptide LL-37 is expressed by keratinocytes in condyloma acuminatum and verruca vulgaris. *J. Am. Acad. Dermatol.* 2002, 47, 347–350.
- [104] Jeevan, A., Ullrich, S. E., De Gracia, M., Shah, R., Sun, Y., Mechanism of UVB-induced suppression of the immune response to *Mycobacterium bovis* bacillus Calmette-Guerin: role of cytokines on macrophage function. *Photochem. Photobiol.* 1996, 64, 259–266.
- [105] Schwalfenberg, G., Genuis, S., Vitamin D supplementation in a nursing home population. *Mol. Nutr. Food Res.* 2010 (in press).
- [106] Etzioni, A., Hochberg, Z., Pollak, S., Meshulam, T. *et al.*, Defective leukocyte fungicidal activity in end-organ resistance to 1,25-dihydroxyvitamin D. *Pediatr Res.* 1989, 25, 276–279.
- [107] Carretero, M., Escamez, M. J., Garcia, M., Duarte, B. *et al.*, *In vitro* and *in vivo* wound healing-promoting activities of human cathelicidin LL-37. *J. Invest. Dermatol.* 2008, 128, 223–236.
- [108] Bhat, S., Milner, S., Antimicrobial peptides in burns and wounds. *Curr. Protein Pept. Sci.* 2007, 8, 506–520.
- [109] Bischoff-Ferrari, H. A., Dawson-Hughes, B., Platz, A., Orav, E. J. *et al.*, Effect of high-dosage cholecalciferol and extended physiotherapy on complications after hip fracture: a randomized controlled trial. *Arch. Intern. Med.* 2010, 170, 813–820.
- [110] Frohm, M., Agerberth, B., Ahangari, G., Stahle-Backdahl, M. *et al.*, The expression of the gene coding for the antibacterial peptide LL-37 is induced in human keratinocytes during inflammatory disorders. *J. Biol. Chem.* 1997, 272, 15258–15263.
- [111] Braff, M. H., Zaiou, M., Fierer, J., Nizet, V., Gallo, R. L., Keratinocyte production of cathelicidin provides direct activity against bacterial skin pathogens. *Infect. Immun.* 2005, 73, 6771–6781.
- [112] Murakami, M., Ohtake, T., Dorschner, R. A., Schitteck, B. *et al.*, Cathelicidin anti-microbial peptide expression in sweat, an innate defense system for the skin. *J. Invest. Dermatol.* 2002, 119, 1090–1095.
- [113] Dorschner, R. A., Pestonjamas, V. K., Tamakuwala, S., Ohtake, T. *et al.*, Cutaneous injury induces the release of cathelicidin anti-microbial peptides active against group A Streptococcus. *J. Invest. Dermatol.* 2001, 117, 91–97.
- [114] Johansson, J., Gudmundsson, G. H., Rottenberg, M. E., Berndt, K. D., Agerberth, B., Conformation-dependent antibacterial activity of the naturally occurring human peptide LL-37. *J. Biol. Chem.* 1998, 273, 3718–3724.
- [115] Di Nardo, A., Yamasaki, K., Dorschner, R. A., Lai, Y., Gallo, R. L., Mast cell cathelicidin antimicrobial peptide prevents invasive group A Streptococcus infection of the skin. *J. Immunol.* 2008, 180, 7565–7573.
- [116] Gibbs, S., Backendorf, C., Ponc, M., Regulation of keratinocyte proliferation and differentiation by all-trans-retinoic acid, 9-cis-retinoic acid and 1,25-dihydroxy vitamin D3. *Arch. Dermatol. Res.* 1996, 288, 729–738.
- [117] Kaur, I., Saraswat, A., Kumar, B., Comparison of calcipotriol and coal tar in conjunction with sun exposure in chronic plaque psoriasis: a pilot study. *J. Dermatol.* 2001, 28, 448–450.
- [118] Henseler, T., Christophers E. Disease concomitance in psoriasis. *J. Am. Acad. Dermatol.* 1995, 32, 982–986.
- [119] Howell, M. D., Jones, J. F., Kisich, K. O., Streib, J. E. *et al.*, Selective killing of vaccinia virus by LL-37: implications for eczema vaccinatum. *J. Immunol.* 2004, 172, 1763–1767.
- [120] Leung, D. Y., Infection in atopic dermatitis. *Curr. Opin. Pediatr.* 2003, 15, 399–404.
- [121] Ong, P. Y., Ohtake, T., Brandt, C., Strickland, I. *et al.*, Endogenous antimicrobial peptides and skin infections in atopic dermatitis. *N. Engl. J. Med.* 2002, 347, 1151–1160.

- [122] Egawa, K., Topical vitamin D3 derivatives in treating hyperkeratotic palmoplantar eczema: a report of five patients. *J. Dermatol.* 2005, 32, 381–386.
- [123] Hata, T. R., Kotol, P., Jackson, M., Nguyen, M. *et al.*, Administration of oral vitamin D induces cathelicidin production in atopic individuals. *J. Allergy Clin. Immunol.* 2008, 122, 829–831.
- [124] Jury, C. S., McHenry, P., Burden, A. D., Lever, R., Bilsland, D., Narrowband ultraviolet B (UVB) phototherapy in children. *Clin. Exp. Dermatol.* 2006, 31, 196–199.
- [125] Yamasaki, K., Di Nardo, A., Bardan, A., Murakami, M. *et al.*, Increased serine protease activity and cathelicidin promotes skin inflammation in rosacea. *Nat. Med.* 2007, 13, 975–980.
- [126] Acharya, M. R., Venitz, J., Figg, W. D., Sparreboom, A., Chemically modified tetracyclines as inhibitors of matrix metalloproteinases. *Drug Resist. Updat.* 2004, 7, 195–208.
- [127] Schaubert, J., Gallo, R. L., Antimicrobial peptides and the skin immune defense system. *J. Allergy Clin. Immunol.* 2009, 124, R13–R18.
- [128] Kalayciyan, A., Oguz, O., Bahar, H., Torun, M. M., Aydemir, E. H., *In vitro* bactericidal effect of low-dose ultraviolet B in patients with acne. *J. Eur. Acad. Dermatol. Venereol.* 2002, 16, 642–643.
- [129] Asgari, M. M., Tang, J., Warton, M. E., Chren, M. M. *et al.*, Association of prediagnostic serum vitamin D levels with the development of basal cell carcinoma. *J. Invest. Dermatol.* 2010, 130, 1438–1443.
- [130] Shnitkind, E., Yaping, E., Geeri, S., Shalita, A. R., Lee, W. L., Anti-inflammatory properties of narrow-band blue light. *J. Drugs Dermatol.* 2006, 5, 605–610.
- [131] Rodland, O., Aksnes, L., Nilsen, A., Morken, T., Serum levels of vitamin D metabolites in isotretinoin-treated acne patients. *Acta Derm. Venereol.* 1992, 72, 217–219.
- [132] Otremski, I., Lev-Ran, M., Salama, R., Edelstein, S., The metabolism of vitamin D3 in response to testosterone. *Calcif. Tissue Int.* 1997, 60, 485–487.
- [133] McDermott, A. M., The role of antimicrobial peptides at the ocular surface. *Ophthalmic Res.* 2009, 41, 60–75.
- [134] Overhage, J., Campisano, A., Bains, M., Torfs, E. C. *et al.*, Human host defense peptide LL-37 prevents bacterial biofilm formation. *Infect. Immun.* 2008, 76, 4176–4182.
- [135] Wu, M., McClellan, S. A., Barrett, R. P., Zhang, Y., Hazlett, L. D., Beta-defensins 2 and 3 together promote resistance to *Pseudomonas aeruginosa* keratitis. *J. Immunol.* 2009, 183, 8054–8060.
- [136] Li, Q., Kumar, A., Gui, J. F., Yu, F. S., *Staphylococcus aureus* lipoproteins trigger human corneal epithelial innate response through toll-like receptor-2. *Microb. Pathog.* 2008, 44, 426–434.
- [137] Grant, W. B., Cross, H. S., Garland, C. F., Gorham, E. D. *et al.*, Estimated benefit of increased vitamin D status in reducing the economic burden of disease in western Europe. *Prog. Biophys. Mol. Biol.* 2009, 99, 104–113.
- [138] Mookherjee, N., Rehaume, L. M., Hancock, R. E., Cathelicidins and functional analogues as antiseptic molecules. *Expert Opin. Ther. Targets* 2007, 11, 993–1004.
- [139] Jeng, L., Yamshchikov, A. V., Judd, S. E., Blumberg, H. M. *et al.*, Alterations in vitamin D status and anti-microbial peptide levels in patients in the intensive care unit with sepsis. *J. Transl. Med.* 2009, 7, 28.
- [140] Wigg, A. E., Prest, C., Slobodian, P., Need, A. G., Cleland, L. G., A system for improving vitamin D nutrition in residential care. *Med. J. Aust.* 2006, 185, 195–198.
- [141] Hathcock, J. N., Shao, A., Vieth, R., Heaney, R., Risk assessment for vitamin D. *Am. J. Clin. Nutr.* 2007, 85, 6–18.
- [142] Sanders, K. M., Stuart, A. L., Williamson, E. J., Simpson, J. A. *et al.*, Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. *J. Am. Med. Assoc.* 2010, 303, 1815–1822.