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

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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.

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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 in 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 (1α-hydroxylase) enzyme and is inactivated by the CYP24A (24-hydroxylase) enzyme [7]. There have been a number of excellent reviews of vitamin D and innate immunity and barrier function [8–10].

In understanding the role of vitamin D in this area, it is important to review the many levels of defense that may be clinically relevant in the human body and prevention of disease.

The first level of defense is the physical barrier of epithelial cells in the skin, gut, respiratory and urinary tract, which protect us from injury or invasion by infection. The active hormone $1,25(OH)_2D$ is important in upregulating genes *via* the 1α-hydroxylase enzyme, which then encode proteins required for tight junctions (*e.g.* occludin), gap junctions (*e.g.* connexion 43) and adherens junctions (*e.g.* E-cadherin) [11–13].

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

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

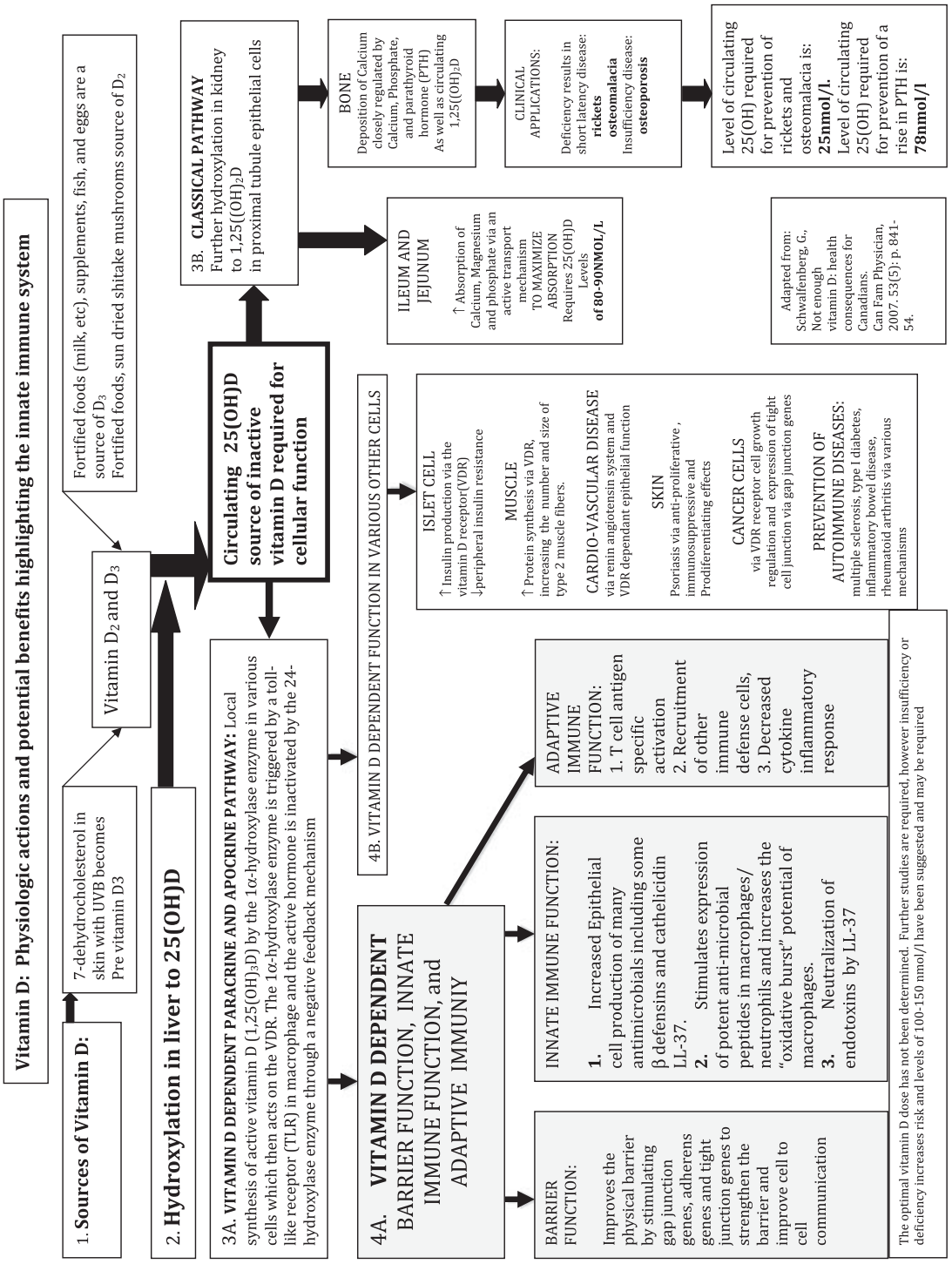

Figure 1. Vitamin D: physiologic actions and potential benefits highlighting the innate immune system.

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

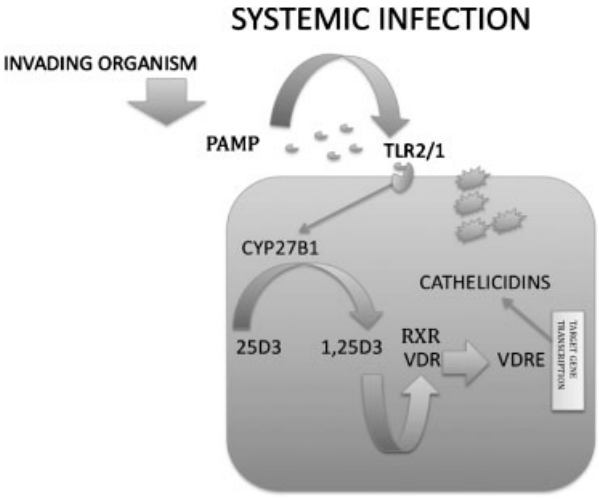

Figure 2. Cathelicidin induction *via* TLRs and vitamin D. PAMP on the invading organism triggers TLR2/1, toll-like receptor 1/2; inducing CYP27B1, (1α-hydroxylase) enzyme; 25D3, 25 (OH)D; 1,25D3, 1,25$(OH)_2D_3$ (active vitamin D hormone); RXR, retinoid X receptor; VDR, vitamin D receptor; VDRE, vitamin 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 (1α-hydroxylase) enzyme. This in turn induces the production of active vitamin D (1,25$(OH)_2$D). The 1,25$(OH)_2$D 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-1to 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$(OH)_2$D 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 TNFα 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 periodontapathogens [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 1α-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 D_3 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., *et al.* *N* = 145 [44]	Randomized control study with vitamin D and calcium	Tooth loss was 13% in patients taking supplements *versus* 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 40 IU daily for 20 years of 1α-hydroxyvitamin D3	*H. pylori* infection With vitamin D 5/15 Without vitamin D 13/19	*H. pylori* infection was significantly lower in vitamin D treatment group
Hepatitis C			
Abu-Mouch *N* = 58 [64]	Randomized control study adding vitamin D 1000–4000 IU 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 2000 IU 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 *versus* 26	Significant reduction of reported flu. Small sample needs to be replicated
Li-Ng, M. *et al.* *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. *et al.* *N* = 334 [80]	4-month randomized placebo control trial using 1200 IU 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			
Nyrsyam, E. W. *et al.* *N* = 67 [89]	Randomized placebo controlled study using 10 000 IU 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. *et al.* *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. *et al.* *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. *et al.* *N* = 20 [123]	Observational study	Supplementation for 3 wk of 4000 IU 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 D_3 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 pregnant 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 α,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]. Tetracylines can inhibit serine proteases indirectly [126]. It is believed that targeting the vitamin D_3 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 *S*taphylococcus *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 D_3 used on a daily basis causes toxicity [141]. However, the use of yearly dose of 500 000 IU of vitamin D_3 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 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 of 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.

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