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.

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 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 stimulator of antimicrobial peptides in innate immunity [14]. The production of cathelicidin and some defensins (defensins
1. Sources of Vitamin D: 7-dehydrocholesterol in skin with UVB becomes pre-vitamin D3. Fortified foods (milk, etc.), supplements, fish, and eggs are a source of D3. Fortified foods, sun dried shitake mushrooms source of D2.

2. Hydroxylation in liver to 25(OH)D

3A. VITAMIN D DEPENDENT PARACrine AND APOcrINE PATHWAY: Local synthesis of active vitamin D (1,25(OH)2D) by the 1α-hydroxylase enzyme in various cells which then act on the VDR. The 1α-hydroxylase enzyme is triggered by a toll-like receptor (TLR) in macrophages and the active hormone is inactivated by the 24-hydroxylase enzyme through a negative feedback mechanism.

3B. CLASSICAL PATHWAY: Further hydroxylation in kidney to 1,25(OH)2D in proximal tubule epithelial cells.

4A. VITAMIN D DEPENDENT BARRIER FUNCTION, INNATE IMMUNE FUNCTION, AND ADAPTIVE IMMUNITY

BARRIER FUNCTION: Improves the physical barrier by stimulating gap junction genes, adherens genes, and tight junction genes to strengthen the barrier and improve cell-to-cell communication.

INNATE IMMUNE FUNCTION:
1. Increased epithelial cell production of many antimicrobials including some β defensins and cathelicidin LL-37.
2. Stimulates expression of potent anti-microbial peptides in macrophages/neutrophils and increases the "oxidative burst" potential of macrophages.
3. Neutralization of endotoxins by LL-37

ADAPTIVE IMMUNE FUNCTION:
1. T cell antigen specific activation
2. Recruitment of other immune defense cells
3. Decreased cytokine inflammatory response

4B. VITAMIN D DEPENDENT FUNCTION IN VARIOUS OTHER CELLS

ISLET CELL: Insulin production via the vitamin D receptor (VDR) and peripheral insulin resistance

MUSCLE: Protein synthesis via VDR, increasing the number and size of type 2 muscle fibers

CARDIO-VASCULAR DISEASE: via renin angiotensin system and VDR dependent endothelial function

SKIN: Psoriasis via pro-inflammatory, immunosuppressive and Proinflammatory effects

CANCER CELLS: via VDR receptor cell growth regulation and expression of tight junction via gap junction genes

PREVENTION OF AUTOIMMUNE DISEASES:
multiple sclerosis, type 1 diabetes, inflammatory bowel disease, rheumatoid arthritis via various mechanisms

The optimal Vitamin D dose has not been determined. Further studies are required, however insufficiency or deficiency increases risk and levels of 100-150 nmol/L have been suggested and may be required.

Figure 1. Vitamin D: physiologic actions and potential benefits highlighting the innate immune system.
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 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 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 signifi-
cantly 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-establish-
ishing 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 mononuclear 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 epithel-
ial 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 D1 for 3 months to prevent symptomatic
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

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