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An update on vitamin D and human immunity

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Abstract

In the last five years there has been a remarkable change in our understanding of the health benefits of vitamin D. The classical actions of vitamin D as a determinant of mineral metabolism and rachitic bone disease have been expanded to include a broader role in skeletal homeostasis and prevalent bone disorders such as osteoporosis. However, it is the non-skeletal functions of vitamin D that have attracted most attention. Although, pluripotent responses to vitamin D have been recognized for many years, our new perspective on non-classical vitamin D function stems from two more recent concepts. The first is that impaired, vitamin D status is common to many populations across the globe. This has prompted studies to explore the health impact of sub-optimal circulating levels of vitamin D, with association studies linking vitamin D 'insufficiency' to several chronic health problems including autoimmune and cardiovascular disease, hypertension and common cancers. In support of a broader role for vitamin D in human health, studies in vitro and using animal models have highlighted immunomodulatory and anti-cancer effects of vitamin D that appear to depend on localized activation of vitamin D. The conclusion from these reports is that many non-classical actions of vitamin D are independent of conventional vitamin D endocrinology and are therefore more sensitive to variations in vitamin D status. The current review summarizes these developments, with specific reference to the newly-identified effects of vitamin D on the immune system, but also highlights the challenges in translating these observations to clinical practice.

Introduction

At the end of 2010 the Institute of Medicine (IOM), an independent, non-profit, non-government organization, based in the USA published the findings of a lengthy study to define the references values that best represent the levels of vitamin D and calcium that are optimal for human health [1]. The select panel of scientists and clinicians that made up this IOM committee was faced with several challenges, not the least because the physiology and nutrition of vitamin D and calcium has for many years been intertwined. *An additional challenge to any appraisal of vitamin D nutrition is the terminology that defines the various metabolites contributing to vitamin D physiology. The term "vitamin D" specifically refers to the parental vitamin D produced endogenously by the action of sunlight on 7-dehydrocholesterol in skin (also known as vitamin* D_3*, or cholecalciferol), or obtained from dietary foodstuffs as either vitamin* D_3 *or vegetable vitamin* D_2 *(also known as ergocalciferol). Vitamin D derived from sunlight or diet undergoes metabolism, firstly to 25-hydroxyvitamin D (25OHD) which is the main circulating form of vitamin D used to define "vitamin D status". At physiological concentrations, 25OHD appears to be inactive as a signaling molecule. Consequently the target cell function of vitamin D is determined by conversion of 25OHD to active 1,25-dihydroxyvitamin D* ($1,25(OH)_2D$)*, which is catalyzed by the vitamin D-activating enzyme 25-hydroxyvitamin D-1*α*-hydroxylase (CYP27B1). The* $1,25(OH)_2D$ *produced in this manner then functions as a steroid hormone by binding to the nuclear vitamin D receptor (VDR) and acting as a regulator of gene transcription* [2].

In the section of the IOM report that focuses specifically on vitamin D, the committee addressed four principal issues: 1) *the health outcomes that are associated with vitamin D and its principal metabolites – pro-hormone 25OHD and active* $1,25(OH)_2D$; 2) the circulating level of vitamin D *(or more precisely the serum concentration of 25OHD)* that is optimal for these health outcomes; 3) the daily intake of vitamin D required to achieve and maintain optimal *vitamin D (25OHD) status*; 4) the likelihood of adverse side-effects from vitamin D supplementation. The report concluded that classical effects on skeletal homeostasis remained the most clinically robust health outcome associated with vitamin D [1]. Based on this the IOM suggested that a serum level of 50 nM (20 ng/ml) 25OHD was sufficient to optimize bone mineral density (BMD) as a marker of skeletal health *for most populations in the United States and Canada*. *However, the IOM did acknowledge that people with darker skin pigmentation (for whom UV-light induction of epidermal vitamin D production is less efficient), and those living at more Northerly latitudes may find it harder to meet this target level. This may be particularly relevant to populations in Northern Europe, where several countries are further North than many Canadian cities. To achieve the 50 nM target* level of circulating 25OHD, the IOM recommended a modest increase in the recommended daily allowance for supplemental vitamin D to 600 IU/day. They also stated that although no adverse side-effects had been reported for doses of supplemental vitamin D up to 10,000 IU/day, a safe upper limit of 4,000 IU/day was preferable. The IOM also pointed out that although clinical trials data did not currently support non-skeletal actions of vitamin D as a robust health outcome, there was nevertheless sufficient evidence to support more detailed studies in the future.

The report was endorsed by many organizations such as the American Society for Bone and Mineral Research and the cautious recommendations of the IOM have been supported in other reports [3, 4]. However, support for the IOM proposals was not universal, and the report received a more hostile reception from many researchers in the world of vitamin D [5-8]. A key underlying cause of this dichotomy of opinion was the remarkable increase of data highlighting non-classical effects of 25OHD and 1,25(OH)$_2$D, and the health consequences this may have in humans with impaired vitamin D status. The remainder of this review will consider some of the reports that have contributed to this new perspective on vitamin D and physiology, how this relates to the IOM's report, and the future challenges that need to be addressed to better define the role of vitamin D in human health. *This now includes a role for vitamin D in prevention and* *treatment of common cancers [9, 10], hypertension and cardiovascular disease [11, 12], and brain development [13]. As the function of vitamin D in each of these areas of human health is a subject in its own right, the current review will focus specifically on another prominent non-classical action of vitamin D – namely its role as an immunomodulator.*

Vitamin D-sufficiency, -insufficiency and -deficiency

For many years the vitamin D status of individuals was defined simply by presence or absence of rachitic bone disease (osteomalacia in adults), a relatively rare clinical problem in the 21st Century. Under these parameters serum levels of 25OHD less than 20 nM (8 ng/ml) were considered an approximate marker of vitamin D-deficiency. However, a variety of studies carried out over the last ten years have suggested that sub-optimal vitamin D status can occur in the absence of rickets/osteomalacia. This new perspective on vitamin D status arose from reports indicating that serum levels of 25OHD continue to correlate inversely with serum parathyroid hormone (PTH) concentrations up to concentrations of approximately 75 nM (30 ng/ml) [14]. Similar observations were also made for intestinal calcium uptake [15, 16], leading to the conclusion that optimal vitamin D status occurred at serum concentrations >75 nM [17]. These data also endorsed broader use of the term, vitamin D 'insufficiency'*, first coined in the 1980s [18]*, to define subjects with sub-optimal vitamin D status (< 75 nM serum 25OHD) who did not have rachitic bone disease (< 20 nM 25OHD). *Whilst recognizing this new perspective on vitamin D, the IOM report highlighted other publications that contradicted the association studies defining 75 nM 25OHD as the optimal level of vitamin D for calciotropic function. In some studies a lower optimal serum concentration of 25OHD was defined [19, 20], and in some cases it was not possible to define an optimal plateau point [21]. Indeed, some studies have described U-shaped associations, with higher levels of serum 25OHD being apparently linked to poorer health outcomes such as rare cancers [22]. Thus for specific biological and clinical readouts, the optimal level of vitamin D status may vary considerably.*

Circulating levels of 25OHD are a direct reflection of vitamin D status, which for any given individual will depend on access to vitamin D either through exposure to U.V. light and epidermal synthesis of vitamin D or as a result of dietary intake. Consequently vitamin D status can vary significantly in populations depending on geographical, social or economic factors. The implication of the new parameters for vitamin D status was that a significant proportion of populations across the globe who were previously considered to be in the normal range for serum 25OHD levels, would now fall into the category of vitamin D-insufficiency [23]. This, in turn, raised the question of whether vitamin D-insufficiency is associated with health problems that are distinct from rachitic bone disease. Answers to this question began to arise from two entirely different sources: the first from in vitro analysis of the immunomodulatory actions of vitamin D, and the second from epidemiological association studies. These are detailed in the following sections.

Vitamin D and innate immunity: a new paradigm for intracrine activation of 25OHD

The historical link between vitamin D and innate immune function stemmed initially from the use of cod liver oil as treatment for tuberculosis (TB) [24]. More recent work has focused on the cellular and molecular machinery that underpins the actions of vitamin D on the pathogen that causes TB, *Mycobacterium tuberculosis* (*M. tb).* In the first of these studies, carried out twenty five years ago, active $1,25(OH)_2D$ was shown to reduce the proliferation of *M. tb* in macrophages with this effect being enhanced by the cytokine interferon γ (IFNγ) [25], a known stimulator of macrophage CYP27B1 [26]. However, the major advance in our understanding of how vitamin D directs antibacterial responses in TB arose from much more recent studies aimed at defining the way in which monocytes and macrophages, key cells in directing bacterial killing, respond to an encounter with *M. tb*.

Monocytes and macrophages are able to phagocytose pathogens such as *M. tb*, but they can also sense pathogen-associated molecular patterns (PAMPs) by utilizing pattern-recognition receptors (PRR), such as toll-like receptors (TLRs) [27]. In 2006, studies to identify monocyte genes regulated in response to *M. tb* revealed that induction of CYP27B1 and VDR occurred following PAMP-sensing by TLR2/1[28]. These data suggested that monocytes promote localized activation of vitamin D in response to *M. tb*, with the resulting 1,25$(OH)_2$D binding to endogenous VDR. In this way vitamin D can act to modulate gene expression in response to an *M. tb* immune challenge – a classical intracrine mechanism (see Figure 1). Potential targets for this intracrine response include the antibiotic protein cathelicidin which is a direct transcriptional target for the 1,25$(OH)_2$D-VDR complex [29, 30]. Functional analyses showed that 25OHD-mediated induction of of cathelcidin is coincident with enhanced killing of *M. tb* in monocytes [28]. Thus, although TLR2/1 responses to *M. tb* initially involve activation of monocyte CYP27B1 and VDR, the efficacy of subsequent antibacterial activity may ultimately depend on the concentration of available 25OHD to support the intracrine conversion to 1,25$(OH)_2$D. Naturally-occurring variations in serum 25OHD have been shown to correlate with induction of monocyte cathelicidin expression [28]. The conclusion from these studies was that individuals with low serum 25OHD will be less able to support monocyte induction of antibacterial activity, and may therefore be at greater risk of infection. Conversely, supplementation of vitamin D-insufficient individuals in vivo has been shown to improve TLR-mediated induction of monocyte cathelicidin [31], and may therefore help to protect against infection.

The ability of a host to combat infection by pathogens such as *M. tb* is not solely dependent on innate antibacterial mechanisms. Studies from our group have shown that T-cell cytokines play a pivotal role in both amplifying and attenuating vitamin D-mediated cathelicidin production [32]. Indeed cytokine production by monocytes themselves may be central to the intracrine metabolism of vitamin D in this cell type [33, 34]. Thus, it seems likely that the ability to mount an appropriate response to infection will be highly dependent on the availability of vitamin D, with additional tuning of this response by other components of the normal human immune response. Vitamin D can also influence innate immune responses to pathogens via effects on antigen presentation by macrophages or dendritic cells (DCs). These cells are known to express VDR[35], and treatment with 1,25$(OH)_2D$ inhibits DC maturation, suppressing antigen presentation and promoting a tolerogenic T-cell response [36, 37] (see Figure 1). Like monocytes, DCs also express CYP27B1 so that both 1,25$(OH)_2D$ and 25OHD are able to modulate antigen presentation by DCs [38]. These data are supported by studies of VDR and CYP27B1 knockout mice which present with lymphatic abnormalities consistent with increased numbers of mature DCs [39, 40] and aberrant DC trafficking [41].

Vitamin D and adaptive immunity

Early studies of vitamin D and the immune system demonstrated VDR expression in both T- and B-cells [42]. Notably, VDR expression by these cells was only immunologically functional in active, proliferating cells, suggesting an antiproliferative role for 1,25$(OH)_2D$ on these cells [43]. T helper (Th) cells appear to be the principal target for 1,25$(OH)_2D$ which can suppress Th cell proliferation as well as modulating cytokines production by these cells [44]. Activation of naïve Th cells by antigen in turn leads to the generation of Th sub-groups with distinct cytokine profiles: Th_1 (IL-2, IFNγ, tumor necrosis factor alpha) and Th_2 (IL-3, IL-4, IL-5, IL-10), that respectively support cell-mediated and humoral immunity [45, 46]. In vitro 1,25$(OH)_2D$ inhibits Th_1 cytokines [47], whilst promoting Th_2 cytokines [48]. A third group of Th cells know to be influenced by vitamin D are interleukin-17 (IL-17)-secreting T-cells (Th_{17} cells). Autoimmune disease-susceptible non-obese diabetic (NOD) mice treated with 1,25D exhibit lower levels of IL-17 [49], and 1,25$(OH)_2D$-mediated suppression of murine retinal autoimmunity appears to involve inhibition of Th_{17} activity [50]. *Indeed, recent studies have shown that 1,25$(OH)_2D$ suppresses IL-17 production via direct transcriptional suppression of IL-17 gene expression [51]. Another group* *of T-cells known to be potently induced by $1,25(OH)_2D$ are regulatory T-cells (Treg)* [52]. *Although part of the Th cell family, Treg act to suppress immune responses by other T-cells as part of the machinery to prevent over-exuberant or autoimmune responses [53].* Recent studies have underlined the importance of Tregs in mediating the immunoregulatory actions of vitamin D. Administration of $1,25(OH)_2D$ systemically to patients with renal disease has been shown to expand circulating Treg populations [54].

Studies of vitamin D and T-cell function have to date focused primarily on the response of these cells to active $1,25(OH)_2D$. What is less clear is the mechanism by which variations in vitamin D status can also influence T-cells, despite reports linking serum levels of 25OHD with specific T-cell populations. For example, circulating levels of 25OHD have been shown to correlate with *Treg activity in patients with multiple sclerosis (MS) [55, 56]. There are four potential mechanisms by which serum 25OHD can influence T-cell function (see Figure 1): 1) direct effects on T-cells mediated via systemic $1,25(OH)_2D$; 2) indirect effects on antigen presentation to T-cells mediated via localized DC expression of CYP27B1 and intracrine synthesis of $1,25(OH)_2D$; 3) direct effects of $1,25(OH)_2D$ on T-cells following synthesis of the active form of vitamin D by CYP27B1-expressing monocytes or DCs – a paracrine mechanism; 4) intracrine conversion of 25OHD to $1,25(OH)_2D$ by T-cells. As yet it is unclear whether one or more of these mechanisms will apply to the regulation of specific T-cell types. For example, the effects of $1,25(OH)_2D$ on Treg can occur indirectly via effects on DCs [57], but may also involve direct effects on T-cells [58]. However, as outlined above DCs also express CYP27B1 [38, 59] and may therefore act as the conduit for 25OHD effects on Treg. Interestingly, reports have also described expression of CYP27B1 by T-cells [60], suggesting that 25OHD may also influence the function of these cells via an intracrine mechanism, although the precise relevance of this to specific T-cell types remains unclear.*

Despite the fact that expression of VDR by B-cells has been recognized for many years [42], the ability of 1,25(OH)$_2$D to suppress B-cell proliferation and immunoglobulin (Ig) production was initially considered to be an indirect effect mediated via Th cells [43]. However, more recent studies have confirmed direct effects of 1,25(OH)$_2$D on B-cell homeostasis [61], with notable effects including inhibition of plasma cell and class switched memory cells differentiation. These effects lend further support for vitamin D's proposed role in B-cell-related autoimmune disorders such as systemic lupus erythamtosus (SLE). Other B-cell targets known to be modulated by for 1,25(OH)$_2$D include IL-10 [62] and CCR10 [63], suggesting that the repertoire of B-cell responses to vitamin D extends beyond its effects on B-cell proliferation and Ig synthesis.

Vitamin D status, immunomodulation and human disease

Given the nature of the initial in vitro studies describing a role for vitamin D in killing of *M. tb*, it is not surprising that clinical extrapolation has focused on the effects of vitamin D on TB infection [64]. Epidemiology has shown that serum levels of 25OHD less than 75 nM are associated with higher incidence of TB [65-68], and reviews of prior studies have supported the protective effects of vitamin D against TB [69, 70]. *Although these studies do not necessarily indicate causation, they support further studies to assess clinical responses to vitamin supplementation. In one such report*, a single oral dose of 100,000 IU 2.5 mg (2.5 mg) vitamin D$_2$ prior to testing, suppressed the growth of *M. tb* in samples of whole blood *in vitro* [71]. Other studies of TB patients used vitamin D supplementation (10,000 IU/0.25 mg vitamin D$_3$/day) as an adjunct to conventional TB therapy. In this case vitamin D reduced the time for sputum smear conversion from acid fast bacteria (AFB) positive to AFB-negative status [72]. Two recent double blind randomized control studies have assessed vitamin D administration and TB. One study from TB clinics in Guinea-Bissau using 3 x 100,000 IU (3 x 2.5 mg) vitamin D$_3$ did not improve clinical outcomes [68]. However, it is difficult to interpret these data because the supplementation group did not show increased serum 25OHD levels when compared to the placebo group [68]. A similar study from the UK using 4 x 100,000 IU (4 x 2.5 mg) vitamin D_3 was successful in elevating serum 25OHD in TB patients, but also showed no overall difference in sputum conversion time between treatment and placebo groups [73]. In this case, the authors carried out additional analyses based on genetic variations in the TB patients. Specifically, a significant improvement in sputum conversion was observed in TB patients with the *Taq1* tt single nucleotide polymorphism (SNP) within the VDR gene [73]. Thus inherited factors may influence responses to vitamin D supplementation and this facet of vitamin D physiology is discussed in more detail in later sections of the review. *It is also important to recognize that all of the studies published to data have involved very specific end points, such as time from initiation of antibacterial therapy to sputum smear conversion, that do not necessarily define the impact of vitamin D supplementation on the management and clinical outcomes of patients with TB. Moreover, a further complication is provided by the fact that for most of these studies vitamin D supplementation occurred against the backdrop of conventional antibiotic therapy for TB. Future studies will need to address these issues and it is possible that a more effective use of supplemental vitamin D will be for the prevention rather than treatment of TB.*

The link between vitamin D and infection is unlikely to be restricted to TB. *Differential induction of CYP27B1 and VDR has been described for leprosy, another mycobacterial disease. Specifically, lesions with the less aggressive tuberculoid form of Leprosy (T-lep) have been shown to express much higher levels of CYP27B1 and VDR than lesions with the lepromatous form of leprosy (L-lep)* [74]*. In view of the fact that T-lep is associated with lower levels of mycobacterial infection than L-lep, it is possible that intracrine 1,25(OH)$_2$D plays a role in this feature of the disease by promoting antibacterial activity in T-lep patients, relative to their L-lep counterparts*. *With these observations in mind, it is interesting to note early reports describing the benefits of light irradiation as a strategy for the treatment of leprosy* [75, 76]*, similar to that initially described for forms of TB* [77]*.* In other infectious diseases such a sepsis, serum 25OHD levels have been correlated with circulating levels of cathelicidin, and this in turn was associated with increased risk of critical illness [78]. *The precise cell type associated with the link between serum 25OHD and cathelicidin in patients with sepsis is not clear. Previous reports have suggested that neutrophils are the main source of circulating cathelcidin* [79]*. However, although these cells express VDR* [80]*, they do not appear to have appreciable CYP27B1 activity, indicating that they are most likely responsive to 1,25(OH)$_2$D rather than 25OHD (see Figure 1). This contrasts with monocyte-derived cathelicidin which correlates better with circulating levels of 25OHD* [28, 31]*, consistent with an intracrine response.* Low vitamin D status has also been linked to infection and mortality in end-stage renal disease patients [81], and to upper respiratory tract infections [82]. With respect to the latter, it is interesting to note that cathelicidin can exhibit antiviral as well as antibacterial properties [83], so that its induction by vitamin D may enhance protection against disease such as influenza. In a similar vein, it is also important to recognize that the induction of cathelicidin by 25OHD and 1,25(OH)$_2$D has been reported for several human cell types outside the classical immune system, including keratinocytes [84], bronchial epithelial cells [85], myeloid cell lines [30], and decidual [86], and trophoblastic cells of the placenta [87]. Thus, the innate, antibacterial effects of vitamin D may be common to many human tissues and are therefore likely to influence a wide range of disease scenarios.

The diverse effects of vitamin D on antigen presentation and lymphocyte function indicate that the immunomodulatory actions of vitamin D are not limited to innate, antimicrobial responses. In particular, vitamin D has been proposed as a putative environmental contributor to autoimmunity, adding to the underlying genetic component of these disease [88]. Lower serum 25OHD has been described for patients with type 1 diabetes at the time of diagnosis [89], and vitamin D supplementation has been reported to protect against type 1 diabetes [90]. Similar data have also been reported for vitamin D and MS [91, 92], and this has been supported by animal models of MS [93, 94]. Interestingly, the latter showed that vitamin D was more effective in protecting against experimental MS in female mice [95], with this effect being due to estrogen-mediated regulation of VDR and CYP27B1 [96]. Other autoimmune diseases that have also been linked to low vitamin D status include Crohn's disease [97], SLE [98], and rheumatoid arthritis [88] and *Graves disease* [99].

Vitamin D status and human disease: beyond serum levels of 25OHD

A key consequence of the revived interest in vitamin D and human health has been the increased demand for methodology to define serum vitamin D status. Cheaper and more widely used ELISA and RIA assays for serum 25OHD are now being superseded by liquid chromatography-mass spectroscopy (LC-MS) protocols which have the benefit of reducing assay drift [100]. *However, this strategy is not without its own methodology problems, notably the resolution and quantification of serum* $25OHD_2$ *and* $25OHD_3$*, and reporting of relatively high LC-MS values compared to conventional RIA/ELISA assays [101]. Further improvements in the standardization of routine serum vitamin D assays by organizations such as the Vitamin D External Quality Assessment Scheme (DEQAS) [102] is central to the future of vitamin D research. However, w*hatever the method used to define the vitamin D status of an individual, it is clear from several clinical studies that other factors, notably genetic variations, will greatly influence the physiological and clinical impact of any given level of vitamin D.

A large number of SNPs have been identified for the VDR gene and these may have a significant impact on vitamin D activity. VDR genotype has been closely studied in relation to bone disease [103], but has also been linked to other facets of human health including immune function. For example studies of various populations have shown that the "ff" genotype is more commonly observed in TB patients [65, 104, 105], although other studies were unable to replicate this observation [106, 107]. In a similar fashion, the recent double blind randomized control trial with high dose vitamin D showed no effect on sputum conversion time when assessed in relation to

FokI genotype, despite the fact that other VDR SNPs did appear to influence response to vitamin D supplementation [73]. The *Fok I* polymorphism “F” yields a VDR that has three fewer amino acids than the “f” form but nevertheless appears to be more active [108]. Other common VDR SNPs are located in the 3’ untranslated region of the VDR gene and their effect on VDR expression and function has yet to be clearly defined. These include the *Apa I*, *Bsm I* and *Taq I* polymorphisms that are thought to influence VDR activity through effects on mRNA stability. Recent studies have reported that the “B” *Bsm I* allele is more common in TB patients compared to healthy controls [109], whilst other reports have described prevalence of the “BB” genotype in TB [104]. As outlined above, only one study so far has assessed the effects of VDR genotype with respect to effects of vitamin D supplementation on TB. In this instance, improved sputum conversion rates were observed in TB patients with the “tt” *Taq1* VDR genotype following patient supplementation with vitamin D [73].

The effects of gene VDR genotype are not restricted to infectious diseases. VDR SNPs have also been linked to autoimmune diseases such as type 1 diabetes [110], multiple sclerosis [111, 112], Graves disease [113], rheumatoid arthritis [114], and SLE [114]. However, it should be recognized that not all studies of VDR genotype have shown associations with autoimmune disease [115]. Likewise, genetic variations within the vitamin D system are not restricted to the VDR gene. SNPs within the CYP27B1 gene have also been shown to affect susceptibility to autoimmune disease [116-118]. However, perhaps the most well characterized inherited variations within the vitamin D system are provided by the gene for the vitamin D binding protein (DBP). For example, coding-region variations in the DBP gene produce proteins whose serum concentration and affinity for vitamin D metabolites varies significantly [119]. Studies by our group have shown that differences in serum concentration and genotype of DBP play a pivotal role in modulating the bioavailability of 25OHD to target cells such as monocytes [120]. Specifically, antibacterial responses to 25OHD appear to be more pronounced with low affinity forms of DBP encoded by the gene polymorphisms commonly referred to as Group-Specific (Gc)1S and Gc2, when compared to high affinity forms of DBP such Gc1F. This suggests that monocytes respond to 'free' rather than DBP-bound 25OHD (see Figure 2). The role of DBP as a determinant of bioavailable vitamin D has been further emphasized by recent studies showing that in healthy adults free rather than total 25OHD is the best correlate of bone mineral density [121]. It will be interesting in future studies to see if non-classical responses to vitamin D are also linked to DBP concentration and genotype. To date the link between DBP genotype and human immune function has only been assessed in one report, which described an association between the Gc2 allele and active TB [122]. However, this was only observed for a cohort of patients with low vitamin D status and so the contribution of DBP genotype to disease activity is difficult to interpret in this setting.

It is important to recognize that studies linking inherited variations in VDR, CYP27B1 and DBP genes and the immunomodulatory actions of vitamin D have involved substantial differences in population size, making it difficult to make firm conclusions about the relative impact of these variations compared to effects of vitamin D status alone. For example, the improved response of TB patients following treatment with vitamin D involved only 12 patients with the VDR tt genotype out of a total of 126 [73]*. However, other studies have involved much larger populations. Notably, a recent Genome-Wide Association Study of almost 34,000 individuals has shown that gene variants of DBP act as an inherited determinant of serum vitamin D status by influencing the serum concentrations of DBP* [123] *which are known to be linked to serum levels of 25OHD and* $1,25(OH)_2D$ [124, 125]. Thus, circulating levels of DBP and binding affinity for vitamin D metabolites as determined by DBP/Gc genotype may not only determine the bioavailability of 25OHD to target cells but may also influence the overall level of vitamin D in circulation (see Figure 2). To add another level of complexity to this particular facet of vitamin D physiology, it is important to recognize that DBP can also function as a macrophage-activation factor (MAF) when glycosylated [126]. Recent studies have shown that the MAF activity of DBP may be beneficial in protecting against lung diseases such as chronic obstructive pulmonary disease [127].

Conclusions and Future Prospects

Non-classical, extra-skeletal effects of vitamin D have been recognized for more than twenty five years. Initially, these observations were centered on either the over-production of $1,25(OH)_2D$ in diseases states such as sarcoidosis, or were viewed as secondary activities of the VDR that could provide potential targets for therapeutically administered $1,25(OH)_2D$. The latter fueled many studies of synthetic $1,25(OH)_2D$ analogs as treatment for common cancers and autoimmune disease [128]. These were aimed at reducing the known hypercalcaemic side-effects of hormonal $1,25(OH)_2D$ but studies were almost universally unsuccessful, at least at the in vivo level.

The new era of vitamin D that has become so high profile over the last few years has taken a completely different approach based on two key concepts. The first stems from increasing evidence for widespread tissue distribution of the vitamin D-activating enzyme CYP27B1, thus supporting a more localized, intracrine or paracrine function for vitamin D outside the skeleton. Unlike the renal CYP27B1 that supports circulating levels of $1,25(OH)_2D$, production of the active form of vitamin D at non-renal sites is less likely to be influenced by hormonal regulators such as PTH, and will instead be primarily dependent on the availability of substrate 25OHD. Serum levels of 25OHD – in other words the vitamin D status of any given individual – have provided the second, and most contentious, new concept for our changed perspective on vitamin D. Association studies have highlighted potential links between vitamin D status and common human diseases but it is still unclear whether this is causal or due to impaired extra-renal activation and function of vitamin D. Likewise, it is unclear whether the level of vitamin D-sufficiency (50 nM, 20 ng/ml serum 25OHD) recently recommended by the IOM is valid for both skeletal and non-skeletal actions of vitamin D. The IOM emphasized the need for more randomized control trials to assess the impact of increased serum 25OHD on extra-skeletal health. Many of these studies are currently underway and notably include several trials aimed at assessing the immunomodulatory impact of supplementary vitamin D, although anticancer effects are also prominent.

The IOM report report firmly endorsed the link between adequate vitamin D status and bone health but the authors also acknowledged the wealth of data linking vitamin D with other facets of human health and the IOM underlined the need for more research to better define these associations. Again, many studies to address this are currently underway and include in vitro, animal model and clinical trial approaches. However, as highlighted in this review, we postulate that a more fundamental issue may also need to be addressed – namely consideration of parameters that are ancillary to vitamin D status. It is possible that inherited factors will play a key role in defining activity of vitamin D for any give serum concentration of 25OHD. This has been demonstrated for VDR genotypes in TB patients supplemented with vitamin D [73], although the underlying basis for this remains unclear. As outlined in Figure 2, it is possible to propose a plausible mechanism by which genetic variants in the DBP gene are able to influence both endocrine and intracrine functions of vitamin D. This would endorse the 'free hormone hypothesis', with low affinity or low abundance DBP facilitating improved availability of 25OHD at target cells such as monocytes. Such a model would indicate that it is no longer sufficient to report total serum levels of vitamin D metabolites but levels of 'free' vitamin D metabolites should also be reported. This strategy has been successfully used in association studies for skeletal function, with free 25OHD being estimated based on established affinity constants and serum levels of DBP protein [121]. Extra-skeletal actions of vitamin D have yet to be studied but it is possible that such an approach will be central to future clinical trials and may help to clarify why some patients show better responses to vitamin D supplementation than others. This is a particular issue when comparing vitamin D responses in different racial/ethnic groups as DBP gene alleles show very clear patterns of distribution according to race [129].

Future studies to assess the broader health benefits of increased serum 25OHD status will also need to investigate the optimal mode of vitamin D supplementation needed to efficiently achieve this level. *Irrespective of the daily dose of supplementation, it is still unclear whether the different forms of vitamin D, vitamin* D_2 *and vitamin* D_3*, have particular advantages for specific responses to vitamin D. Several studies (although not all* [130]*) have reported greater supplementation efficacy with vitamin* D_3 [131-133]*. However, this was based on the simple criterion of ability to raise serum 25OHD levels and it is possible that* $25OHD_2$ *and* $25OHD_3$ *will have similar potencies in terms of conversion to their 1,25-dihydroxylated counterparts, and subsequent effects mediated via the VDR. At present little is known about variable immunomodulatory responses to vitamin* D_2 *and* D_3*. The synthetic analog of* $1,25(OH)_2D$*, 19-nor 1,25-dihydroxyvitamin* D_2 *(also known as Paracalcitol) has been reported to exhibit similar immunomodulatory effects to* $1,25(OH)_2D_3$ [134]*, but similar actions of* $1,25(OH)_2D_2$ *have yet to be studied. In particular, it will be interesting to investigate the potential differential binding of* $25OHD_2$ *and* $25OHD_3$ *to DBP and how this relates to their renal endocrinology and target cell bioavailability. Collectively these observations suggest that despite the major research advances that have been made over the last five years, our understanding of the non-classical actions of vitamin D is far from complete. The next five years may turn out to be even more eventful.*

Legend to Figures

Figure 1. Mechanisms for innate and adaptive immune responses to vitamin D. Vitamin D derived from the action of sunlight on the epidermis (vitamin D_3 only), or obtained from diet (vitamin D_2 or D_3) is metabolized firstly in the liver to form 25-hydroxyvitamin D (25D), the main circulating form of vitamin D. Target cells such as monocytes/macrophages and dendritic cells (DC) expressing the vitamin D-activating enzyme CYP27B1 and the vitamin D receptor (VDR) can then utilize 25D for intracrine responses via localized conversion to active 1,25-dihydroxyvitamin D (1,25D). In monocytes/macrophages, intracrine synthesis of 1,25D promotes antibacterial response to infection. In DCs, intracrine synthesis of 1,25D inhibits DC maturation, thereby modulating helper T-cell (Th) function. Th responses to 25D may also be mediated in a paracrine fashion, with DC-generated 1,25D acting on VDR-expressing Th-cells. Intracrine immune effects of 25D also occur in CYP27B1/VDR-expressing epithelial cells. However, other cells such as neutrophils do not appear to express CYP27B1 and are therefore likely to be affected by circulating levels of active 1,25D synthesized by the kidneys. VDR-expressing Th are also potential targets for systemic 1,25D, although intracrine mechanisms have also been proposed. In a similar fashion epithelial cells, trophoblasts and decidual cells are all able to respond in an intracrine fashion to 25D, but may also respond to systemic 1,25D to promote antibacterial responses.

Figure 2. Effects of Vitamin D binding protein (DBP) on endocrine and intracrine actions of vitamin D. Three common allelic forms of the DBP, known as group-specific component (Gc) 1F, 1S and 2, are present in serum at varying concentrations (Gc1F>Gc1S>Gc2) and exhibit varying affinities for 25-hydroxyvitamin D (25D) and 1,25-dihydroxyvitamin D (1,25D) (Gc1F>Gc1S>Gc2). DBP influences renal synthesis of 1,25D by facilitating glomerular reabsorption of 25D for subsequent metabolism by kidney CYP27B1. This effect appears to be more efficient for high abundance/affinity Gc1F. DBP also transports vitamin D metabolites to peripheral target cells such as monocytes where its actions appear to be the opposite of those observed in the kidney. Intracrine conversion of 25D to 1,25D and associated induction of antibacterial responses (e.g. enhanced production of cathelicidin) is more effective in the presence of low concentrations of DBP. Likewise, for any given concentration of DBP monocyte responses to 25D are more pronounced in the presence of low affinity forms of DBP such as GC2 and Gc1S, compared to high affinity Gc1F.

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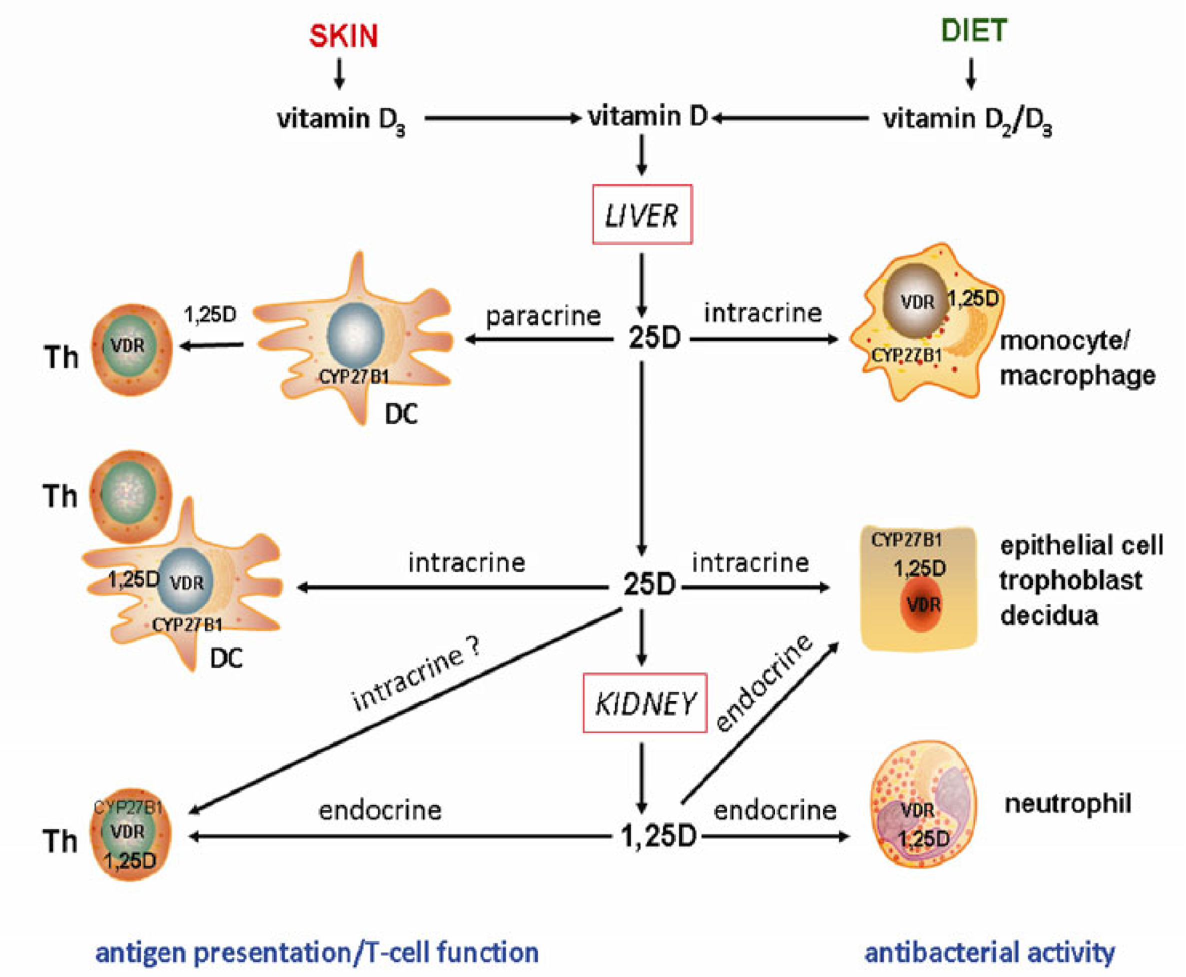
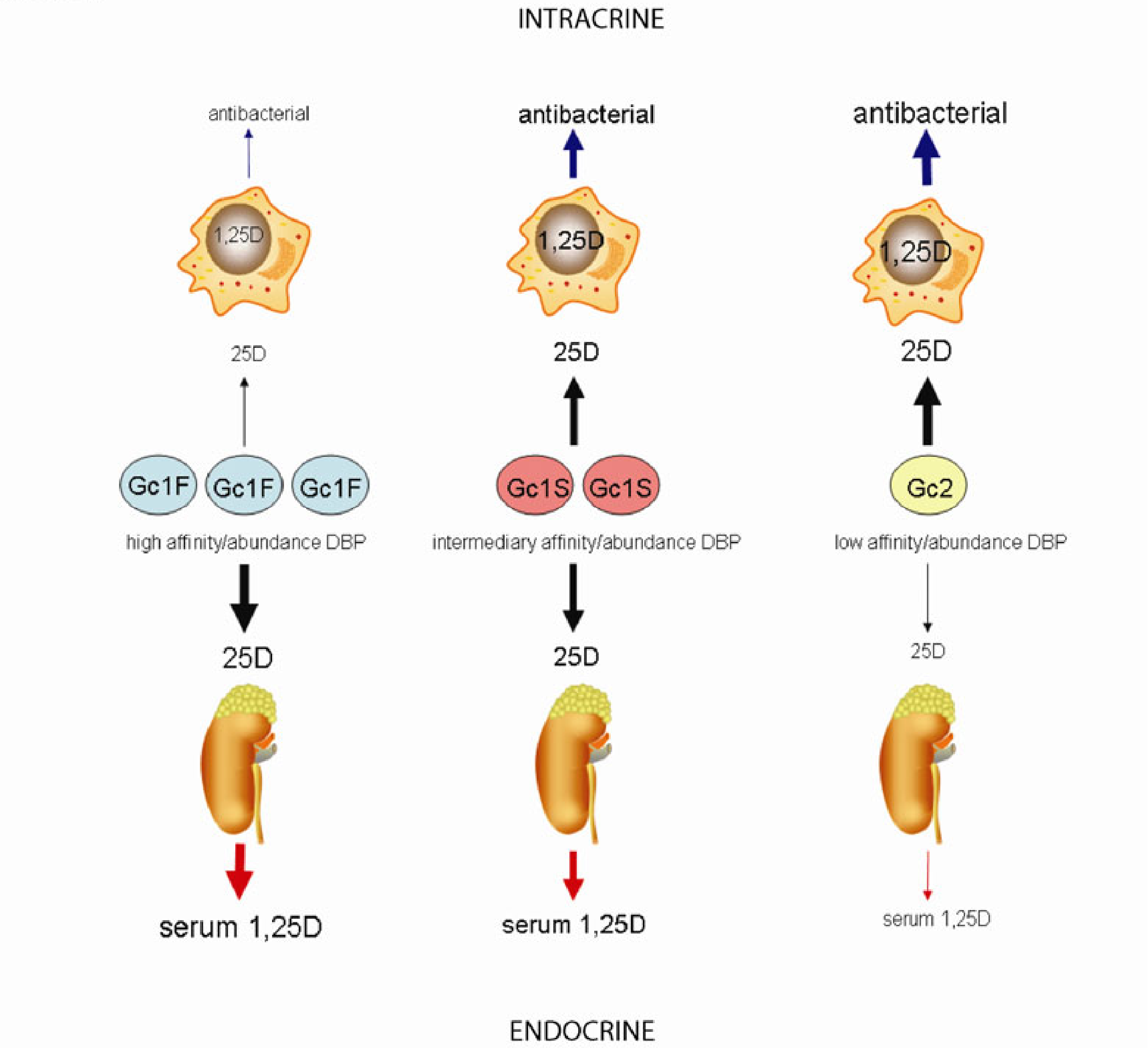
Figure 1



SKIN
DIET
vitamin D_3
vitamin D
vitamin D_2/D_3
LIVER
1,25D
Th
VDR
CYP27B1
DC
paracrine
25D
intracrine
VDR
1,25D
CYP27B1
monocyte/ macrophage
Th
1,25D
VDR
CYP27B1
DC
intracrine
25D
intracrine
CYP27B1
1,25D
VDR
epithelial cell
trophoblast
decidua
intracrine ?
KIDNEY
endocrine
CYP27B1
VDR
1,25D
Th
endocrine
1,25D
endocrine
VDR
1,25D
neutrophil
antigen presentation/T-cell function
antibacterial activity

Figure 2


INTRACRINE
antibacterial
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Gc1F
Gc1S
Gc1S
Gc2
high affinity/abundance DBP
intermediary affinity/abundance DBP
low affinity/abundance DBP
25D
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serum 1,25D
ENDOCRINE