Published in final edited form as:
Inflamm Bowel Dis. 2013 September ; 19(10): 2245–2256. doi:10.1097/MIB.0b013e31828a3b6f.

Linking Vitamin D Deficiency to Inflammatory Bowel Disease

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Abstract

Inflammatory bowel disease is associated with industrialization, and its incidence has increased markedly over time. The prospect of reversing these trends motivates the search for the agent(s) involved. Modernity entails several physical and behavioral modifications that compromise both the photosynthesis of cholecalciferol in the skin, and of its bioavailability. Although deficiency in this "vitamin" has therefore emerged as a leading candidate, and despite the publication of a randomized control trial that showed a trend towards statistically significant benefit in Crohn's disease, its causal agency has yet to be demonstrated by an adequately powered study. We discuss the strengths and weaknesses of the case being made by epidemiologists, geneticists, clinicians and basic researchers, and consolidate their findings into a model that provides mechanistic plausibility to the claim. Specifically, converging data sets suggest that local activation of vitamin D coordinates the activity of the innate and adaptive arms of immunity, and of the intestinal epithelium, in a manner that promotes barrier integrity, facilitates the clearance of translocated flora and diverts CD4 T cell development away from inflammatory phenotypes. Since smoking is an important risk-altering exposure, we also discuss its newly established melanizing effect, as well as other emerging evidence linking tobacco use to immune function through vitamin D pathways.

Keywords

Vitamin D; Inflammatory Bowel Disease; Crohn's Disease; Ulcerative Colitis

Introduction

Vitamin D deficiency is not an "answer in search of a question". It is one of a limited set of variables credibly proposed to mediate the observed association between environmental exposures and the inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis (UC). The rising incidence rates of these diseases over time, as well as their association with industrialization, limits plausible explanations to those that invoke variables that have changed over that time and with economic development[1]. The evidence concerning a role for vitamin D deficiency in promoting IBD should, then, be viewed with an appreciation for the burden shared by the IBD field collectively to explain these trends, and researchers must be prepared to address the question "if not vitamin D deficiency, then what?" Although not explored here, several environmental risk factors have been proposed to link IBD to its increasing incidence and to industrialization. These include antibiotics,

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oral contraceptives, dietary changes (including increased reliance on infant formula over breastfeeding), and improved hygiene[1-5]. Here, we discuss the evidence and rationale that implicate vitamin D deficiency in the pathogenesis of IBD.

The perceived credibility of vitamin D deficiency as a common contributor to IBD rests on the understanding that the molecule in question was poorly named. The word "vitamin" was originally meant to denote a dietary micronutrient, the absence of which results in disease. The notion that countries populated by affluent and obese citizens could experience widespread deficiency in any vitamin would, then, seem counterintuitive. However, vitamin D is something of a misnomer[6], insofar as exposure of the skin to ultraviolet B (UVB) light leads to the production of vitamin D at levels that notably exceed what can be obtained from most foods. For perspective, one minimal erythemal dose of sunshine can generate as many as 20,000 international units (IU) of vitamin D, which is, for example, 200-fold more than the amount in 8 ounces of milk that has been deliberately fortified with vitamin D[7]. The functional consequence of the cutaneous production of vitamin D is implied by one of the most overtly variable of phenotypic human traits: pigmentation. Positive selective pressure appears to have favored depigmentation in early Eurasians[8, 9], and the driving force for this is most commonly attributed to the enhanced rate of vitamin D synthesis afforded by pale skin in the face of reduced exposure to UVB[10-12].

Our use of the term "deficiency" likewise warrants clarification. Although the definition of "deficiency" and "insufficiency", in the context of bone health, is a matter of some debate[13, 14], in the context of immune-mediated disease such threshold values can only be guessed at, and attempts to do so might risk erroneously implying a discontinuous relationship between serum levels of vitamin D (specifically 25(OH)D, described in the next section) and disease. Here we use the word deficiency to denote a presumed, and as-yet undefined suboptimal range of serum 25(OH)D values that may place an individual, or her offspring, at an incrementally greater risk for a given disease as that individual's vitamin D status falls. By this definition, the relationship between serum 25(OH)D concentrations and immune-mediated disease is not known. Furthermore, we do not frame this discussion in terms of a putative ability of vitamin D to ameliorate IBD, referring instead to vitamin D "deficiency" and "repletion" in order to highlight the basic premise that vitamin D deficiency may describe an average state of the population, but does not describe the state of each individual within that population. If deficiency influences the onset or course of IBD, then it does so in a subset of patients. This is in contrast to what is implied by the various randomized controlled trials (RCTs) that do not employ relatively low vitamin D status as an inclusion criterion.

The Basic Biology of Vitamin D

The evidence regarding vitamin D and IBD cannot be appreciated without an understanding of the basic aspects of vitamin D biology, comprehensively reviewed elsewhere[7, 15-18]. In this section, we provide an abbreviated, but conventional view of vitamin D metabolism and signaling. As depicted in figure 1, UVB light converts cutaneous 7-dehydrocholesterol (7-DHC) to cholecalciferol (i.e., vitamin D). Vitamin D is an inactive precursor that is converted to yet another inactive precursor, 25-hydroxyvitamin D [25(OH)D]. The most commonly cited genes that encode the 25-hydroxylase(s) that catalyze this reaction are *CYP27A1* and *CYP2R1*, though other genes have been implicated. 25(OH)D circulates in the blood with a half-life of, roughly, one month, and serves as the reservoir of substrate from which cells that activate vitamin D can draw. To do so, these cells express 1α-hydroxylase from *CYP27B1*, thereby converting 25(OH)D to the active form of vitamin D, 1α,25-dihydroxyvitamin D [1,25$(OH)_2$D]. In practice, the term vitamin D is sometimes used to refer, depending on the context, to 25(OH)D or 1,25$(OH)_2$D, but formally denotes

cholecalciferol. Thus, for example, one's vitamin D status, which can be measured in the clinic, refers to the serum concentration of 25(OH)D, even though 25(OH)D is not, formally, vitamin D. In target cells, $1,25(OH)_2D$ binds and activates a transcription factor, the vitamin D receptor (VDR). Ligand-activated VDR heterodimerizes with the retinoid X receptor (RXR), and this heterodimer subsequently binds DNA at vitamin D response elements (VDREs) that are distributed across a target gene's extended locus (i.e., not exclusively at the proximal promoter). Binding of the heterodimer to VDREs leads to the recruitment of cofactors that subsequently induce or repress gene expression. *CYP24A1* encodes 24-hydroxylase, which converts 25(OH)D and $1,25(OH)_2D$ to 24,25-dihydroxyvitamin D [$24,25(OH)_2D$] and 1,24,25-trihydroxyvitamin D [$1,24,25(OH)_3D$], respectively. $1,24,25(OH)_3D$ is also formed from $24,25(OH)_2D$ by the action of CYP27B1. These latter molecules retain activity[19-21], but the functional consequences of these metabolites are less well characterized than for $1,25(OH)_2D$.

Vitamin D is commonly referred to as an endocrine molecule, since that is the first mode of signaling that was identified for it. However, as the concentration of serum 25(OH)D falls, the concentration of serum $1,25(OH)_2D$ changes only modestly, if at all[22-24], except when 25(OH)D becomes very low[25]—lower than is experienced by the large majority of modern humans. The maintenance of serum $1,25(OH)_2D$ concentrations reflects the secondary hyperparathyroidism that increases CYP27B1 activity when 25(OH)D levels fall. If VDR that is expressed in immune cells is liganded by $1,25(OH)_2D$ that is produced by the kidneys, then the activation of VDR in those cells should change only modestly as vitamin D status fluctuates through the range that is typical for the industrialized world, and the incentive for investigating vitamin D "deficiency" as a cause of IBD is diminished. However, subsequent to the discovery of vitamin D activation in the kidneys numerous laboratories have reported the expression of *CYP27B1* in extra-renal tissues, including macrophages and dendritic cells, thereby supporting the view that intracrine and paracrine roles for vitamin D signaling may be commonplace[26]. Various endpoints that were measured in cultured antigen-presenting cells (APCs), and in humans, correlated with 25(OH)D concentrations when those concentrations were manipulated to vary across the normal human range[27-31], indicating the biological relevance of the local activation of vitamin D by tissues other than the kidneys.

Observational Studies

Epidemiology

Depending on the study, the vitamin D status of IBD patients is[32, 33], or is not[34, 35], lower than that of healthy controls, and does[36, 37], or does not[33, 38], correlate with disease severity. The studies that report a relationship between vitamin D status and IBD entail the possibility that vitamin D deficiency is a cause of the disease, but it is also possible that low vitamin D status marks the influence of causal confounders (see below) or that vitamin D deficiency is a consequence of disease (i.e., reverse causation). At least three forms of reverse causation may be operative here. First, sickness may lead patients to spend less time outdoors photosynthesizing vitamin D. Second, CD may result in the malabsorption of vitamin D[39, 40]. Finally, the expression of CYP24A1 and CYP27B1 in inflamed tissue (as with the expression of CYP27B1 in colonic tissue of CD patients[41]) results in the consumption of 25(OH)D thereby placing downward pressure on vitamin D status. Consistent with this, lipopolysaccharide (LPS) induces the expression of CYP27B1 in human monocytes and dendritic cells[29, 42], and induced endotoxemia causes vitamin D status to fall in dogs[43]. For some perspective on the likelihood of vitamin D deficiency as a cause of IBD, we turn first to the field of epidemiology.

Several factors that influence vitamin D status fall within the purview of epidemiological investigations, and would be expected to co-vary with IBD, assuming that vitamin D deficiency is one of its causes. That is, vitamin D status is, or may be, non-randomly allocated, in part, by industrialization, urbanization, pollution, time, ethnicity, body mass, geography and the orbit of our tilted planet around its sun. More specifically, vitamin D status is set largely by the availability of UVB radiation (e.g., by season, latitude and pollution), the time spent outdoors exposed to that radiation (e.g., by industrialization), the rate at which exposure results in the photosynthesis of vitamin D (e.g., by pigmentation) and the effect that the production of vitamin D has on vitamin D status (e.g., by body mass). Since the interpretation of epidemiological data sets is especially vulnerable to confounding, biases and reverse causation[44, 45], the presence or absence of an association between IBD and any of the vitamin D status-modifying exposures is only suggestive of a link, or its absence, between vitamin D deficiency and IBD. These studies are, however, available and informative.

The industrial revolution heralded an age of rickets, which led to the discovery of vitamin D and of its production by UVB. The concentration of children into the factories and narrow streets of heavily polluted cities compromised access to sunlight to such an extent that adequate calcium metabolism for some children was lost[6]. Even today, city dwellers typically have lower vitamin D status than do residents of outlying areas[46-53], and this has been attributed either to absorption of UVB by pollution[54-58] or to the physical obstruction of sunlight by tall buildings[59]. Furthermore, the amount of time spent indoors dramatically affects vitamin D status[60]. If vitamin D deficiency is a cause of IBD, then it might be expected that industrialization, urbanization and pollution are associated with IBD. Industrialization[1, 2, 4, 61-63] and urbanicity[64] are indeed clear risk factors for IBD, and two of three studies also link air pollution to IBD[65-67].

Furthermore, in the United States and globally, vitamin D status is declining, at least in recent years[68-70]. To estimate the change in vitamin D status over a longer time frame, it was recently established that traditionally living Maasai and Hadzabe have an average serum 25(OH)D concentration of 46 ng/ml (i.e., 115 nM)[71], whereas the mean level in the US is roughly half that[69]. If vitamin D deficiency is a cause of IBD, then it might be expected that IBD has increased over time, which it clearly has[72]. The incidence of pediatric IBD, for example, doubled between 1991 and 2002 in the US[62].

Since fat sequesters[73], or body mass dilutes[74], vitamin D, the aforementioned obesity that is associated with affluent societies is itself a risk factor for vitamin D deficiency. If deficiency contributes to IBD, then obesity might be expected to correlate with IBD. In fact, IBD is generally associated with reduced weight[75], and recent weight loss is a common feature at presentation[76], though the relationship between the two may be more complex than conventionally believed[77, 78]. Attempts to link obesity to IBD are, however, confounded by the anorexia and malabsorption that result from disease[76].

Since melanin absorbs UVB, slowing the rate at which the skin photosynthesizes vitamin D, African Americans have a collective vitamin D status that is lower than that of Caucasian Americans[79]. If vitamin D deficiency is a cause of IBD, then it might be expected that African Americans would be at enhanced risk for this disease, as they clearly are for rickets[80]. It is commonly believed, however, that their risk for IBD is lower, not higher. However, concerns have been raised that this could reflect under-diagnosis of this population[81]. Additionally, ethnic groups differ not only with respect to pigmentation, but with respect to non-pigmentation-related genetic variations as well. Ashkenazi Jews, for example, have genetically-determined greater risk for CD than do other Europeans[82].

Both the position of people on the earth and the migration of the earth around the sun are additional parameters that affect vitamin D status, and for the same reason. The higher the sun appears off of the horizon (i.e, the lower the solar zenith angle) the less atmosphere the sunlight travels through before striking the earth's surface. Since the atmosphere absorbs UVB, this results in a latitudinal gradient of UVB radiation, with UVB intensity decreasing as the distance from the equator is increased. Furthermore, the axial tilt of the earth establishes, in a manner dependant on latitude, a seasonal oscillation of the UVB radiation to which people are exposed. Thus, the amount of UVB radiation that is available to catalyze the production of vitamin D varies with season and latitude[83, 84].

Despite rare reports to the contrary[85, 86], a north-south gradient of IBD is now well established for both CD and UC[87-94], with risk positively correlated with latitude. In France, however, the effect of latitude was noted only for CD, not UC[91, 92]. Vitamin D status is being considered as a candidate variable to explain the latitude effect on IBD[2, 93]. However, the presumed relationship of vitamin D status to latitude needs further investigation[95]. For example dietary intake of vitamin D in Europe positively correlates with latitude[96]. Furthermore, much of the human population has not migrated far from where their ancestors resided, and therefore exhibit a level of pigmentation that is adapted to their environment. This would be expected to reduce or nullify the effect of latitude on vitamin D production, and may be why a latitude gradient of vitamin D status was reported only for Caucasians[97]. Although vitamin D status *negatively* correlated with latitude in the adult urban population of France[98], and in postmenopausal women worldwide during winter[99], when Europe was analyzed separately, vitamin D status of these women *positively* correlated with latitude, and this was accounted for almost entirely by per capita Gross Domestic Product (GDP)[99]. Indeed, per capita GDP increases with latitude[99], and this correlation was documented as a potential confounder of the IBD latitude gradient[89].

Of all the commonly cited risk factors for vitamin D deficiency that are discussed here, only season seems to vary independently of the others. Although the seasonal fluctuation of vitamin D status[100, 101] makes season an especially attractive variable to follow, the studies that have investigated IBD as a function of season are so numerous, and their conclusions so conflicting, that we leave it to the reader to evaluate them in detail[102-121]. Instead we segue directly into a discussion of their weaknesses in order to aid in the interpretation and planning of existing and future studies, respectively. Firstly, where studies showed seasonal variations in IBD, causal agency was usually suggested of pathogens, not vitamin D. For example, periodicity of IBD tracks with bacterial infections[120, 121]. Secondly, where studies failed to find a correlation between season and diagnosis, the null results may be explained away by the variable and sometimes long time lag between onset and diagnosis, which would decouple the time of diagnosis from a seasonal effect on disease onset[109, 122]. Thirdly, if vitamin D deficiency provokes IBD, but a relatively long and variable time lag separates vitamin D deficiency from the onset or exacerbation of disease, then seasonal fluctuations in vitamin D status will not impact the seasonality of IBD. Fourthly, the magnitude with which vitamin D status varies across the seasons is influenced by latitude and race[123]. Furthermore, in locations where heat and humidity become extreme, summer may lead people to take shelter, away from UVB, resulting in a counterintuitive relationship between season and vitamin D status[124].

Although epidemiologists typically make efforts to correct for the influence of confounders[44], the extent to which the exposures discussed above confound each other bears emphasizing. Obesity is becoming more prevalent[125], and is associated with industrialization[125] and ethnicity[126]. Pollution, urbanization and industrialization are likewise related, and, as noted above, latitude correlates with both vitamin D status of Caucasians and per capita GDP[89, 97, 99]. Thus, on the one hand, the ability to rationalize

many of these risk exposures in terms of mechanistically independent causes of vitamin D deficiency seems to lend some credence to the notion that vitamin D deficiency promotes IBD. On the other hand, these risk exposures appear highly interdependent, making the value of rationalizing their influence over vitamin D status by independent mechanisms unclear. Modernity may embody various environmental exposures that conspire to enhance the risk for IBD through the agency of vitamin D deficiency, but possibly also presents a myriad other candidate exposures that may promote IBD independent of this deficiency.

Since vitamin D is not only generated by exposure to UVB, but is a marker of that exposure as well, vitamin D-independent effects of that exposure may be the most difficult group of confounders for which to control[127]. Cutaneous urocanic acid (UCA), for example, is converted, by exposure to UVB, from its inactive *trans* conformer to the active, systemically-immunosuppressive *cis* conformer. Importantly, subcutaneous injections of *cis*-UCA ameliorated disease in the dextran sodium sulfate (DSS) mouse model of colitis[128].

Genetic Association Studies

Although Mendelian randomization studies are correlative in nature, the random assignment of parental alleles to offspring at the moment of conception minimizes confounding, precludes reverse causation, and may justify causal inferences[45]. If we equate variations in vitamin D status with variations in vitamin D signaling, then genetic association studies may qualify as Mendelian randomization studies, where genetic variants that influence vitamin D signaling serve as instrumental variables that proxy for vitamin D status. In this regard, *VDR* is localized to a region of chromosome 12 that has been linked to IBD susceptibility, and, given the biological plausibility of relatively weak VDR activation in the etiology of IBD, its associated polymorphisms have been selected for analysis. Until recently, it was mainly the restriction fragment length polymorphisms (RFLPs) *ApaI, BsmI, FokI* & *TaqI* that were analyzed, and, for the most part, study results are highly discrepant[129-134]. Two groups have, however, reported that the *TaqI* variant (consisting of a synonymous change in codon 352 of exon 8) is more frequent in male CD patients than in female CD patients or in healthy controls[135, 136]. It has also been reported that variants of the open reading frame for the vitamin D binding protein may influence IBD[137]. As a cautionary note, early reports linking *VDR* RFLPs to bone mineral density and fracture risk appear not to have survived close scrutiny[138]. More recently, a very large study that combined genome-wide association scans and network-based analyses implicated VDR in the pathogenesis of both CD and UC[139].

Intervention Studies

Animal Experimentation

To formally test a causal relationship between vitamin D status and IBD, serum 25(OH)D must be experimentally manipulated and the consequences of this on IBD measured. To the extent that vitamin D status influences vitamin D signaling, the manipulation of vitamin D pathways in animal models also informs the causal relationship between 25(OH)D and colitis. In the context of IL-10 deficiency, mice rendered vitamin D deficient developed diarrhea and began dying by 9 weeks of age, in contrast to vitamin D sufficient mice[140]. Oral administration of $1,25(OH)_2D$ to the IL-10/vitamin D double-deficient mice was therapeutic[140, 141]. Deficiency in VDR aggravates IBD in the $CD45RB^{hi}$ transfer model[142], an effect we confirm here (Fig. 2), as well as in IL-10 KO mice[142, 143]. VDR and $1,25(OH)_2D$ had similar effects on colitis induced by DSS[144]. DSS-induced colitis is likewise exacerbated by deficiency in either *Cyp27b1* or vitamin D[145, 146], and, when administered intraperitoneally, $1,25(OH)_2D$ or a low calcemic analog of $1,25(OH)_2D$ reduces the severity of colitis induced by trinitrobenzene sulfonic acid[147, 148].

Granting that, when examined in isolation, several of the experimental designs that were used to collect the data reported above may be suspected to suffer demonstrated (i.e, calcemic effects) or potential (e.g., ligand-independent effects of VDR[15]) confounders, vitamin D deficiency, which was shown in studies referenced above to worsen disease in two colitis models, cannot be its own confounder. By whatever pathway(s), then, vitamin D deficiency aggravates IBD in mouse models. Instead, the main weakness of these studies is that the results obtained from mouse models do not always generalize to humans. We know, for example, that $1,25(OH)_2D$ induces the expression of CAMP (an antimicrobial peptide; AMP) in human, but not mouse, cells and that this difference mirrors a VDRE within a retroelement that is present in the promoter for human, but not mouse, *CAMP*[149].

Clinical Trials

Although we are not aware of any clinical trials that have evaluated the effects of vitamin D on UC, two trials published the effects on CD[150, 151]. One of them[150] compared vitamin D to an active analog, not a placebo, and will not be discussed here. In the second study—a double-blind, placebo-controlled trial—94 remitted CD patients had been randomized to receive either 1,200 IU vitamin D or placebo once daily for one year[151]. Both groups also received 1,200 mg calcium daily. Treatment insignificantly reduced ($P = 0.06$) the rate of clinical relapse, which was defined in terms of a Crohn's Disease Activity Index. The decision to set alpha at 0.05 as the criterion of significance[151] does not follow from mathematics, but reflects the tolerance of the investigators for committing a type I error. That is, one can conclude from this study that 1,200 IU vitamin D (with 1,200 mg calcium) daily is therapeutic for CD, with a 6% chance of doing so in error.

A primary weakness of this study is that, by convention[152], it was underpowered (i.e, at 70%)[151], and the authors recommended larger sample sizes for future studies. We also note that this study's design is not consistent with the premise that the increasing incidence of CD over time, and its association with the Western lifestyle, reflects restricted exposure to sunshine with an attendant *average* decline in serum 25(OH)D within the population. Relative to placebo, treatment of the CD patients with 1,200 IU vitamin D daily increased serum 25(OH)D concentration by 40% (i.e, 38.4 ng/ml versus 27.6 ng/ml)[151]. The selection criteria for this study did not exclude patients with relatively high vitamin D status, and the study did not dose for what may now be considered an ancestral level of 25(OH)D[71]. If, for example, selection of study subjects had resulted in an average initial serum 25(OH)D concentration of 15 ng/ml and subjects in the treatment arm had received enough vitamin D to increase 25(OH)D to 45 ng/ml, then 25(OH)D would have increased 300%, not 40%, and this difference may have increased the study's statistical power. Finally, it is possible that vitamin D deficiency may promote disease onset without influencing the course of disease, such that vitamin D repletion will not reverse pathology that was initiated by deficiency. Vitamin D repletion will not, for example, reverse limb deformities in adults who suffered childhood rickets, and adaptive immunity is well known for its memory.

Mechanistic Plausibility

Vitamin D is locally activated in disease-affected tissue of CD patients[41], and data from several areas of enquiry converge to suggest that this signaling coordinates the activity of multiple cell types, intervening at several stages, to promote homeostatic coexistence between the host and its intestinal microbiota. We present a preliminary model that incorporates what are most likely to be core elements involved in the putative failure to maintain this tolerance during the vitamin D deficient state in otherwise predisposed individuals.

The intestinal epithelium and its associated mucus constitute a barrier that physically separates the host from its gastrointestinal commensal microorganisms. Intestinal permeability is a hallmark of IBD[153], and a role for mucus is indicated by the identification of *MUC1*, which encodes a constituent of mucus, as a candidate gene whose locus harbors a CD risk-conferring variant[154]. In this regard, vitamin D deficient mice have 50-fold more bacteria in colonic tissue than do non-deficient controls and this was attributed in part to reduced expression of the Paneth cell-produced AMP angiogenin 4[146]. This bacterial translocation may also reflect the loss of VDR-dependent intercellular tight junctions that aid gut epithelial barrier integrity[155].

Dysregulated innate immunity also contributes to the pathophysiology of CD. Genome-wide association studies (GWASs) have, for example, implicated the genes *NOD2* and *ATG16L1*, whose products interact within DCs and macrophages to facilitate autophagy, antigen presentation and bacterial clearance[156]. NOD2 is a receptor for peptidoglycans from Gram-positive bacteria, and it has been reported that, in the absence of a NOD2 ligand, $1,25(OH)_2D$ induces expression of NOD2 in human monocytes (and other cells) by directing VDR to distal VDREs along the *NOD2* locus[30]. Furthermore, in normal human macrophages, $1,25(OH)_2D$ and liganded NOD2 synergistically induce the expression of CAMP and β-defensin 2 (i.e, DEFB4A; formerly DEFB2 and HBD-2), but not in macrophages obtained from CD patients homozygous for loss-of-function variants of *NOD2*[30]. LPS, a toll-like receptor (TLR) 4 ligand, induces CYP27B1[29] and IL-6[31] in human monocytes, and addition of 25(OH)D reduces IL-6[31]. TLR2/1 activation induces CYP27B1, VDR and IL-1β, along with its receptor, in human monocytes, with VDR inducing CAMP independent of IL-1β signaling, but inducing DEFB4A, which may be important in IBD[157], in concert with IL-1β-activated NF-kB[158]. $1,25(OH)_2D$ induces the expression of CAMP in human monocytes, which in turn promotes autophagy through transcriptional activation of autophagy-related genes, including ATG5[159]. Similar effects have been recorded in human macrophages[160]. ATG5 interacts with ATG16L1 in this process[159, 160]. CAMP not only facilitates the formation of autophagosomes that sequester *Mycobacterium tuberculosis* (Mtb), but also promotes fusion of these structures with lysosomes, and subsequently enters the lumen of the resulting autophagolysosomes to effect direct anti-Mtb activity as well[159]. Induction of CYP27B1 and VDR similarly links IFN-γ signaling in human monocytes/macrophages to AMP expression and autophagy, with IL-15 serving as an intermediary[161].

A role for adaptive immunity is also well established. Flagellin-derived antigens expressed by the host microbiota are immunodominant in patients, CD4 T cells that recognize these antigens are pathogenic in an animal model of colitis[162], and CD4 T cell depletion during AIDS limits relapse of CD[163]. GWASs and animal data suggest that Th1 and Th17 cells are especially relevant CD4 T cell subsets, but their relative contribution, and their relationship to each other, has not been fully elucidated[169]. The development and maintenance of Th1 cells is directed by the cytokine IL-12, and by the transcription factors T-bet, STAT1 and STAT4, whereas the development and maintenance of Th17 cells is directed by the cytokines TGF-β, IL-1β, IL-6 and IL-23, and by transcription factors, the most important of which are STAT3 and RORγt (encoded by *RORC*). Th1 cells produce IFN-γ, whereas Th17 cells produce IL-17A, IL-17F and IL-22. On the one hand, a variant of IL-23R, a receptor whose activation by IL-23 promotes Th17 cell development, is protective for CD[164], *RORC* and *STAT3* are associated with IBD[139], and the loss of *Rorc* function in CD4 T cells strongly limits colitis in a mouse model[169]. On the other hand, *STAT1, STAT4* and *IFNG* are associated with IBD[139], and T cell-deficiency of either T-bet or STAT4 reduces disease severity in transfer models of colitis[169]. The gene that encodes p40, the subunit that is common to both IL-12 and IL-23, is implicated in CD by GWAS[154], and the neutralization of p40 is therapeutic for CD[165, 166]. These and other data suggest that elements of Th1 and Th17 cells are jointly protagonistic, which may reflect the transition of Th17 cells to a Th1

phenotype, the co-expression of T-bet in some Th17 cells, or both[169]. Importantly, GWASs also implicate IL-10 in CD[154] and UC[167], and mice deficient for IL-10 in CD4 T cells spontaneously develop colitis comparably to mice globally deficient in IL-10[168].

As discussed above, T cell expression of VDR limits colitis, and we have shown that $1,25(OH)_2D$ partially suppresses *in vitro* Th17 cell developmental programming (including suppression of mRNA that encodes RORγt and IL-23R), while increasing the expression of IL-10. Importantly, this suppression occurred even when IL-1β and IL-23 were used for polarization. In contrast to previous reports, $1,25(OH)_2D$ has negligible effects on Th1 cell development in our hands and we further reported that VDR mRNA was ~30 fold lower in Th1 cells than in Th17 cells[170]. The failure to inhibit Th1 cell differentiation from naïve murine precursors was corroborated by another recent study[171]. In dendritic cells, however, $1,25(OH)_2D$ suppresses the expression of p40[172], which is expected to reduce the polarization of both Th1 and Th17 cells.

Collectively, these data suggest that vitamin D sufficiency assists epithelial barrier integrity, and that, when the barrier is breached by luminal microbiota, activation of TLRs on APCs solicits intracrine vitamin D signaling to further contain these microbes through autophagy and the expression of AMPs, while also limiting the development and maintenance of Th1 and Th17 effector CD4 T cells through paracrine signaling (Fig. 3), and enhancing IL-10 production. Conversely, in the vitamin D deficient state, flux through CYP27B1 is likely reduced and the formation of tight junctions, as well as the responsiveness of APCs to bacteria, is thereby diminished. Ligands to TLRs and NOD2 subsequently accumulate, and the production of IFN-γ is increased. Consequently, expression of CYP27B1 and VDR, and engagement of NOD2, increases still further, until enough autophagy and AMPs are recruited by VDR to place an upper limit on the microbial excess. In this scenario, inordinate inflammation occurs in the deficient state as Th1 and Th17 cell effector functions are favored over innate mechanisms of homeostatic control.

A model for vitamin D sufficiency-mediated protection against UC is more tentative. Many of the same loci are implicated in both CD and UC, and this includes roles for autophagy, Th1/Th17 pathways, IL-10 and VDR[139]. Thus, some of the mechanisms proposed in figure 3 may apply to UC as well. Importantly, however, a few polymorphisms have opposing effects on CD and UC[139], and this includes risk-altering polymorphisms that implicate *NOD2*, a gene whose expression is induced by $1,25(OH)_2D$.

Vitamin D and Smoking

New links between smoking, vitamin D signaling, multiple sclerosis (MS) and IBD have become apparent recently, and are worth highlighting separately. Immune-mediated diseases are related to each other[173], and we note here overlapping areas of interest with MS. As with IBD, the distribution of MS exhibits a latitude gradient[174], and recent GWASs identify risk-conferring polymorphisms that implicate CYP24A1 and CYP27B1 in MS[175, 176], thereby giving more weight to the idea that the latitude effect reflects vitamin D status.

Moreover, smoking is one of the clearest risk factors for both MS[174] and CD[177]. Very recently, and very surprisingly, the lungs have been reported to be an immunological staging ground in a rodent model of MS[178], and it has therefore been speculated that smoking may activate auto-reactive, pulmonary T cells that subsequently traffic to the central nervous system (CNS)[179]. Importantly, a recent GWAS of lung cancer provides evidence that links smoking to vitamin D signaling, and suggests a mechanism that, we speculate, might apply to MS and IBD as well. Dong et al. report that the single nucleotide polymorphisms (SNPs) rs48009957 and rs1663689 confer risk for lung cancer[180]. The former occurs in the 3′ UTR of *CYP24A1* and interacts with smoking to contribute to lung cancer risk. Although the

latter SNP is almost one megabase downstream of the nearest gene, that gene is *GATA3*, which encodes an essential Th2-programming transcription factor. Furthermore, a third SNP (i.e., rs247008) was found to interact with smoking to contribute to lung cancer risk, and occurs just downstream from *IL3* and *CSF2*, and near the Th2 cytokine cluster. Consistent with a relationship between Th2 cells and CYP24A1, the Th2 cytokine IL-4 has been shown to enhance the monocyte-mediated catabolism of vitamin D in a manner dependent on CYP24A1[181]. Collectively, these data suggest interactions not only between vitamin D signaling and the immune system, which was already well established, but also between these variables and smoking. Dong et al. noted[180] that benzo[a]pyrene (BaP), a component of tobacco smoke and a ligand for the aryl hydrocarbon receptor (AhR), enhances, within a human monocyte/macrophage-derived cell line, the induction of CYP24A1 by $1,25(OH)_2D$ in an AhR-dependent manner[182]. Perhaps, then, smoking promotes MS by inducing the CYP24A1-mediated catabolism of 25(OH)D and $1,25(OH)_2D$, with loss of VDR-mediated regulation of auto-reactive T cells that subsequently migrate to the CNS. It will be interesting to see if the lungs likewise harbor colitogenic T cells, and if this could link smoking and vitamin D to CD. Alternatively, BaP may distribute systemically[183], directly affecting immune cells residing in the gastrointestinal tract. We also wonder how this may be related to the observation that smoking cessation actually increases risk for UC[177]. Liganding of the nicotinic receptor on macrophages may underpin this latter effect[184].

To this we would add a simpler putative mechanism relating smoking to vitamin D-mediated effects on IBD and MS. Nicotine accumulates in melanin-expressing tissues[185] and activates amphibian dermal melanocytes *in vitro*[185], while cigarette smoking promotes pigmentation in humans[186, 187]. That surplus melanin should slow the rate of UVB-mediated vitamin D production, thereby lowering vitamin D status. Smoking is indeed associated with lower vitamin D status[188-193]. This suggests a causal relationship between tobacco use and reduced vitamin D status, but further research is needed to formally demonstrate this link and to assess the extent to which the risk of IBD and MS that is conferred by smoking is mediated by effects on the photosynthesis of vitamin D.

Directions for Future Research

In conclusion, we remain agnostic regarding any causal relationship between vitamin D status and human IBD, and emphasize, instead, the need to accelerate the research efforts that can generate the answers that physicians and patients await. Repeating the aforementioned RCT, but with a design that increases the study's power, should be a priority. To expand on the recent analyses that implicate VDR in IBD[139], while minimizing the multiple testing burden innate to GWASs, it may be useful to target polymorphisms known to affect vitamin D status[194], as well as those that may link vitamin D signaling to MS[175, 176] and lung cancer[180], for future study. A better understanding of vitamin D signaling during mouse models of colitis will inform our efforts to understand the context in which vitamin D status affects human IBD, if that is what it does. The prospect of reversing pathology that arises from the Western lifestyle with something as simple as vitamin D repletion gives this research some urgency.

Acknowledgments

Supported by the US National Institutes of Health (C.T.W. and M.T.P.) and the Crohn's and Colitis Foundation of America (C.T.W. and M.T.P.). The authors thank Daniel D. Bikle for helpful comments, and Yun Kyung Lee for technical assistance.

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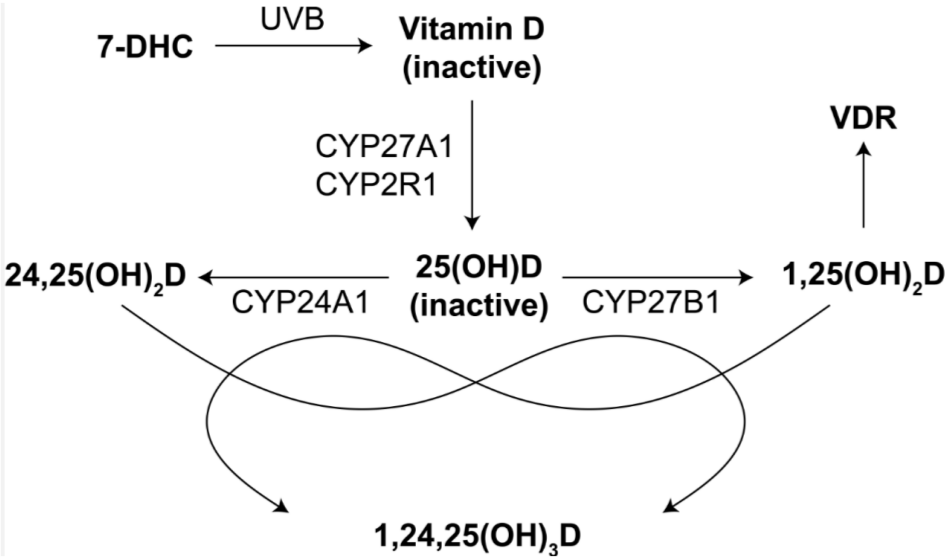

Figure 1. Vitamin D metabolism

As discussed in more detail in the text, the conversion of vitamin D from 7-DHC by UVB is followed by two hydroxylation reactions to generate the active ligand for VDR, a transcription factor that regulates gene expression. Catabolic pathways are also shown.

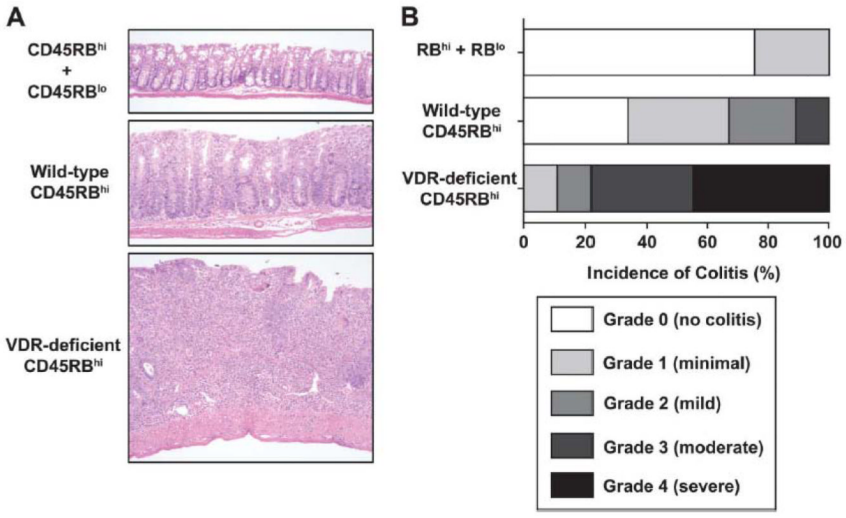

Figure 2. T cell deficiency of VDR aggravates CD45RBhi CD4 T cell-mediated colitis

$CD4^+CD45RB^{hi}$ and $CD4^+CD45RB^{lo}$ T cells were from isolated from secondary lymphoid tissues of WT or VDR-deficient donors by FACS sorting and 3×10^5 of the indicated cells were injected i.p. into congenic, C57BL/6 RAG-deficient recipients. **(A)** Five weeks post-transfer, mice were sacrificed and intestinal tissues collected for histological processing and analysis as previously described[195]. Shown are representative hematoxylin and eosin (H&E)-stained sections of colon from the indicated experimental groups of one of two experiments; all magnifications = 40×. **(B)** Incidence and severity of colitis five weeks post-transfer of the indicated T cell populations. Samples were coded and scored by a pathologist in a blinded fashion, as previously described[195]. Data are pooled from two independent experiments. The total number of recipients in each group were: $CD45RB^{hi}$ +$CD45RB^{lo}$, 4; WT, 9; and VDR-deficient, 9.

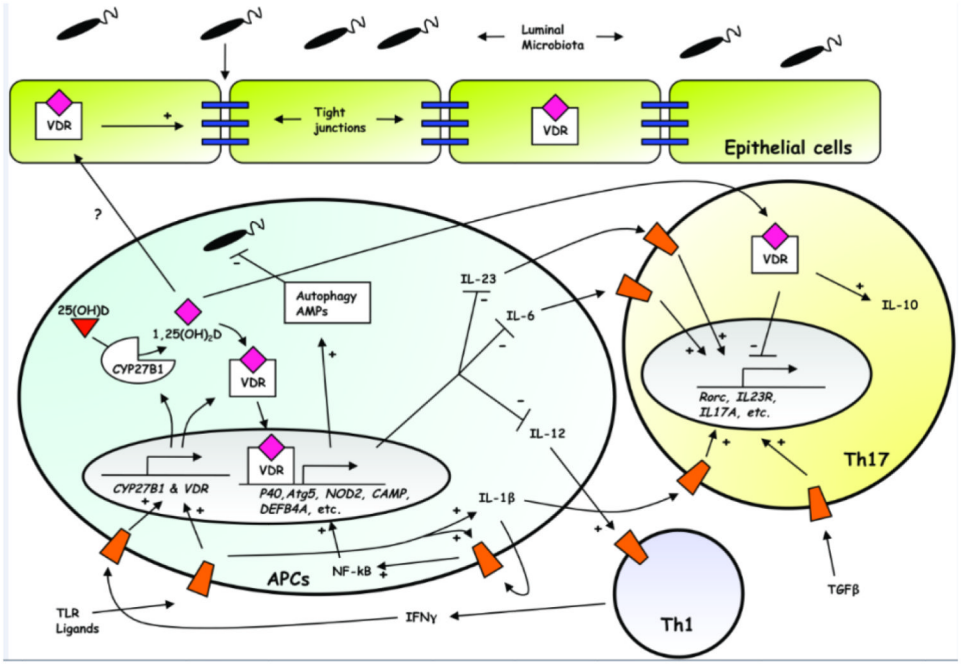

Figure 3. Model for vitamin D-mediated intestinal homeostasis

Induction of CYP27B1 and VDR by TLR and IFN-γ signaling leads to intracrine and paracrine signaling involving the several cell types depicted. Activated VDR alters the expression of downstream target genes which promote the formation of tight junctions (blue rectangles), as well as the expression of AMPs and proteins involved in autophagy, and diverts development of CD4 T cells away from the Th1 and Th17 lineages with enhanced expression of IL-10. Receptors for cognate ligands are shown as orange trapezoids. See text for more details.