Medical Hypotheses 127 (2019) 154–158

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

The vitamin D positive feedback hypothesis of inflammatory bowel diseases

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ABSTRACT

While it appears that there are a variety of factors that exacerbate IBD, it is frustrating that symptoms can persist and worsen even when environmental insults are removed. We suggest that there may be a positive feedback loop which perpetuates the inflammatory response in IBD patients. The loop is triggered by vitamin D deficiency which reduces calcium uptake. Lowered vitamin D and calcium interfere with anti-inflammatory pathways. Inflammation of the mucosa inhibits absorption of calcium and thus perpetuates the reduced anti-inflammatory response. A number of predictions follow from this hypothesis and are supported by geographic and lifestyle patterns in IBD incidence and prevalence.

History of IBD and current understanding

Inflammatory bowel disease (IBD) describes two separate conditions: ulcerative colitis (UC) which is a mucosal inflammation limited to the colon, and Crohn's disease which is a disease of transmural inflammation with skip lesions that may involve any part of the GI tract from mouth to anus. It was not until the late 19th century that distinctions could be made in identifying IBDs. Ulcerative colitis was first described in 1888 by Sir William Hale White. Soon after, the electric sigmoidoscope was invented allowing conclusive diagnosis of ulcerative colitis. It was not until 1932 that Crohn's disease (CD) was recognized as a separate entity from UC [1]. Historically, the difficulty of diagnosis stems from the subjectivity of patient histories, the reduced likelihood of patients presenting their IBD-related symptoms to their primary care physicians, and the absence of a non-invasive "gold standard" diagnostic criteria [2].

There appears to have been an increase in incidence of IBD over the past 50 years [3,4], but it has not been clear whether this reflects a true rise in IBD or merely improved diagnosis and reporting. Physicians have typically employed several diagnostic tools to differentially diagnose IBD and its various forms; namely, the patient's symptoms are paired with results from an endoscopy, during which biopsies are taken for histological examination [5]. The standardization of endoscopies given to patients at 50 years of age has established the exam as the most reliable method for diagnosing IBD [6]. However, in younger patients, the presentation of IBD clinical features, such as diarrhea, abdominal pain, and rectal bleeding, do not immediately prompt the physician to order an endoscopy. Discomfort to patients, risk of perforation, and cost deter the use of endoscopy.

The Inflammatory Bowel Disease (IBD) Expanded Profile blood test, is a newer diagnostic tool in general practice and emergency medicine settings in diagnosing IBD. Currently, the most common serological markers associated with IBD are anti-*Saccharomyces cerevisiae* antibody (ASCA) and atypical perinuclear antineutrophil cytoplasmic antibody (pANCA) [7]. The use of the ASCA and pANCA antibodies allows physicians to differentiate Crohn's disease from ulcerative colitis with a specificity as high as 99% [2].

Naturally, the association between disease prevalence and diagnostic expansion is strong. Improved diagnostic tools and methods increases the likelihood that a patient presenting with IBD symptoms is diagnosed with IBD. Furthermore, the risk of false positives and false negatives decreases with the development of more reliable serological and histological markers. However, a real increase in IBD has been seen in countries that are not historically linked with the disease and that have adequate healthcare systems. For example, the first case of Crohn's disease in Korea was discovered in the late 1980s, but the country now reports 3 cases per 100,000, and there are similar trends in India, China, and Japan [8].

Broader trends show major increases in IBD that cannot be explained by the reversal of missed diagnoses. In a longitudinal study of IBD in Olmsted County, Minnesota the prevalence for ulcerative colitis and Crohn's disease increased by 34% and 41%, respectively, in the period from 2000 to 2011 [9]. In a *meta*-analysis of 260 population based studies of IBD, 75% of CD studies and 60% of UC studies reported an increasing incidence [10]. This trend began as early as 1950 and is consistent worldwide with prevalence peaking in the past decade [10]. A variety of contributing factors have arisen in parallel during the same timeframe: Vitamin D deficiency, reduced exposure to enteric bacteria, increased stress, appendectomy, and use of NSAIDs, antibiotics, and oral contraceptives [11]. Although environmental factors and Vitamin

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https://doi.org/10.1016/j.mehy.2019.04.005
Received 25 December 2018; Accepted 11 April 2019
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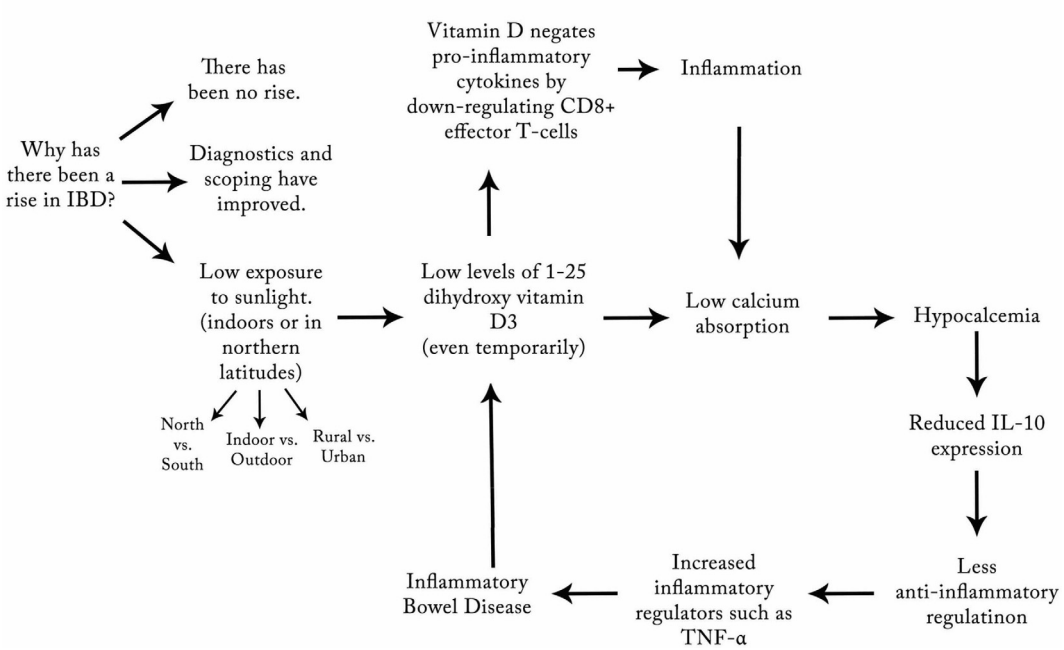

Fig. 1. IBD may be caused by a cascade of events, initiated by reduced exposure to sunlight and resulting in chronic inflammation. This can be perpetuated by malabsorbtion of calcium.

D deficiency have been implicated, neither Molodecky nor Ye discuss sunlight exposure or feedback loops that might explain general resistance to treatment.

The vitamin D positive feedback hypothesis

WE PROPOSE that subchronic, reduced exposure to ultraviolet (UV) light, and consequent 1–25 dihydroxyvitamin D3 deficiency, can initiate a feedback cycle that may manifest as inflammatory bowel disease (IBD) and which can persist even after sun or UV exposure is normalized (Fig. 1). This results from a cascade of physiological dysregulations and feedback loops. Reduced sunlight exposure, in the absence of supplemental vitamin D, causes temporary hypocalcemia [12,13]. Calcium and 1–25 dihydroxyvitamin D3 deficiencies reduce IL-10 suppression [14], which leads to an increase in tumor necrosis factor alpha (TNF-α), IL-6, and possibly IFN-gamma [15], which in turn increases the likelihood of inflammatory bowel disease [16]. Once inflamed, the bowel mucosa absorbs less calcium, even if sun exposure and active 1–25 dihydroxyvitamin D3 levels are restored [17,18]. The cycle can be self-maintaining and can even escalate over time as the microbiome changes in response to general malabsorption and the consequent availability to the gut flora of unabsorbed micronutrients [19]. The resultant immune shift due to reduction of anti-inflammatory factors may manifest as persistent inflammation, as is seen in the autoimmune etiologies of IBDs. Low UVB exposure (across spatial and temporal gradients) may be a valuable predictor of IBD epidemiologically, may explain global patterns of IBD, and may explain the etiology in many cases currently classified as idiopathic.

Vitamin D deficiency

Vitamin D deficiency can be viewed as a nutritional-environmental-immunological risk factor for developing or relapsing IBD [20]. Vitamin D deficiency is not uncommon and the standards for this micronutrient deficiency, or inadequacy, are largely based on the skeletal and not immunological effects of vitamin D and its receptors [21]. In the United States, “prevalence of vitamin D deficiency and vitamin D inadequacy in 2001–2010 were 28.9% and 41.4%, respectively” where vitamin D deficiency is defined as a 25(OH)D concentration of < 50 nmol/L and inadequacy as 50–75 nmol/L. [22]

There are two sources of the precursors to the active, hormonal form of Vitamin D: 1–25 dihydroxyvitamin D3. The first source begins with cholesterol in the skin where UVB converts 7-dehydrocholesterol into vitamin D3 in a non-enzymatic reaction. The second source is dietary vitamin D. Both of these species go through two metabolic steps before becoming the active form of $1,25(OH)_2D_3$ which binds to the vitamin D receptor (VDR) and activates the paracrine effects of the vitamin D pathways. These receptors are found in bone as well as “skin, lymph nodes, pancreatic islet cells, adrenal medulla, brain, and colon.” [23] Notably, the rate-limiting step in maintaining $1,25(OH)_2D$ levels is the final hydrolysis of 25(OH)D to the active, $1,25(OH)_2D$. Because the reservoir of circulating serum 25(OH)D is not quickly replaced by the precursors, local deficiency of $1,25(OH)_2D$ can occur for hours or days [23].

Predictions and empirical support

Recent studies have already implicated low sunlight exposure as a risk factor for Crohn’s disease [24] and pointed to a broader role of vitamin D in the natural history of IBD [21]. “The incidence of chronic inflammatory disorders such as IBD correlates with low serum Vitamin D levels.” [25] and vitamin D deficiency also increases the severity of IBD [26], indicating a cascading immune response. We tested our general prediction that prevalence of IBD, UC and CD will be higher in populations living further from the equator, where people are spending more time indoors and receiving less direct UV for a longer proportion of the year. Using published prevalence data [10], we examined the association between the absolute value of latitude and IBD, UC, and CD (Figs. 2, 3, 4). We found that prevalence of IBD, UC and CD are all significantly correlated with distance from the equator ($r^2 = 0.4073$ {for IBD (UC + CD)}, $r^2 = 0.3335$ {for CD}, and $r^2 = 0.4245$ {for UC}, Pearson correlation $p < .005$, $n = 48$ cities/regions).

Our hypothesis also suggests that a variety of environmental and lifestyle factors that lower exposure to sunlight and UVB should correlate with incidence of IBD. We expect pediatric incidence to increase in populations where children are spending more and more time in front of screens or indoors studying rather than playing outdoors. We also expect incidence of IBD to increase with active avoidance of

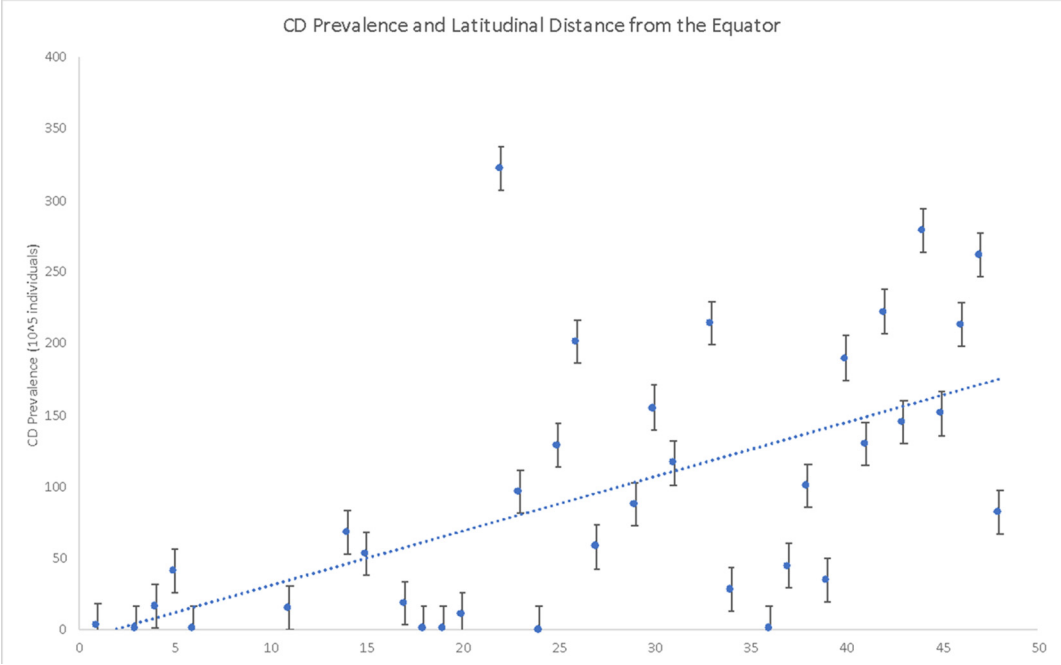

Fig. 2. There exists a strong positive correlation between longitude and prevalence of Chron's Disease ($r^2 = 0.3335p < .005$, n = 48, Pearson correlation).

sunlight as a strategy to reduce the risk of skin cancer. These predictions are consistent with Bernstein and Shanahan's lifestyle environmental factor as a predictor of IBD [27]. In addition, Mukherjee found that the rate of IBD was higher than the background rate in south Asian women who covered their entire bodies for religious convention [28].

Furthermore, a variety of environmental factors that reduce UVB exposure should correlate with prevalence of IBD. At the simplest levels, we would expect low prevalence of IBD near the equator where days are long year round, and low prevalence in people living at high altitudes because the atmosphere is thinner at high altitude and filters out less UVB radiation. These predictions are consistent with the findings reported by Sonnenberg et al., and Hayes, et al. who found associations between latitude, altitude and IBD [29,30]. In addition, Kappelman et al. found that the prevalence of Crohn's disease and ulcerative colitis was significantly lower in southern United States versus the Midwest, West, and Northeast [31]. Nerich et al. found a similar pattern across France, with a strong association between lack of sun exposure and Crohn's disease [24] and Shivananda found a similar pattern across all of Europe [32]. This pattern can be seen even within small countries, as Jussila et al. found "the prevalence of IBD and UC in Finland increased from South to North." [33]

In general, areas close to the equator consistently have 12-hour days (sunlight time). Away from the equator, direct sunlight time varies seasonally. For example, during the winter solstice in Reykjavik, Iceland, the day lasts about 4 h. Liu et al. have shown that Vitamin D deficiency and insufficiency can be seasonal with lower serum Vitamin D levels in winter months [22]. Altitude also impacts sun exposure for a number of reasons. Ozone, water vapor, oxygen, and carbon dioxide

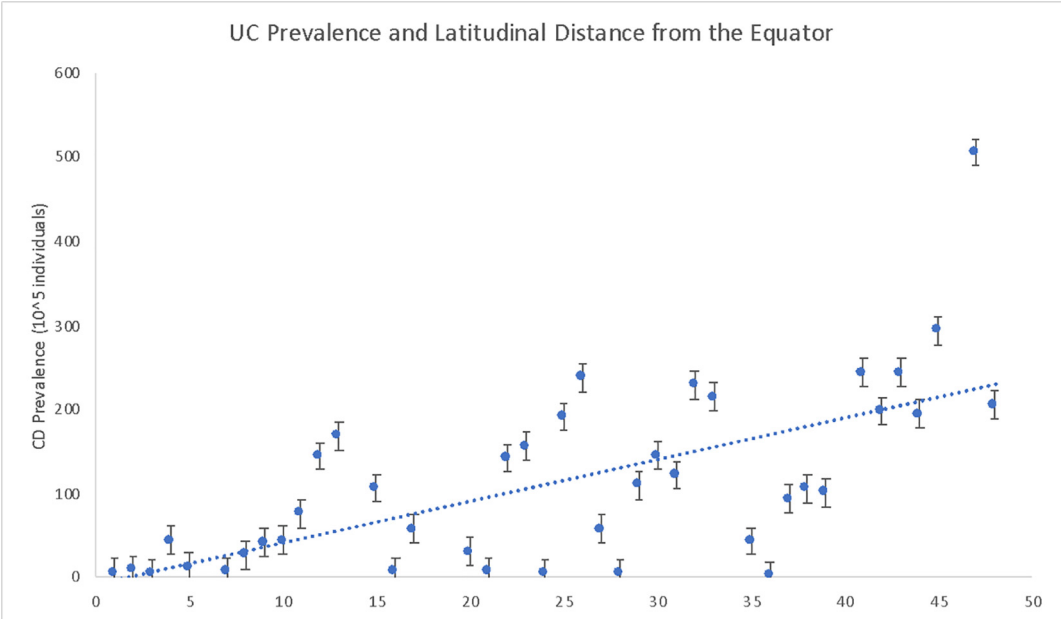

Fig. 3. There exists a strong positive correlation between longitude and prevalence of Ulcerative Collitis ($r^2 = 0.4245$, $p < .005$, n = 48, Pearson correlation).

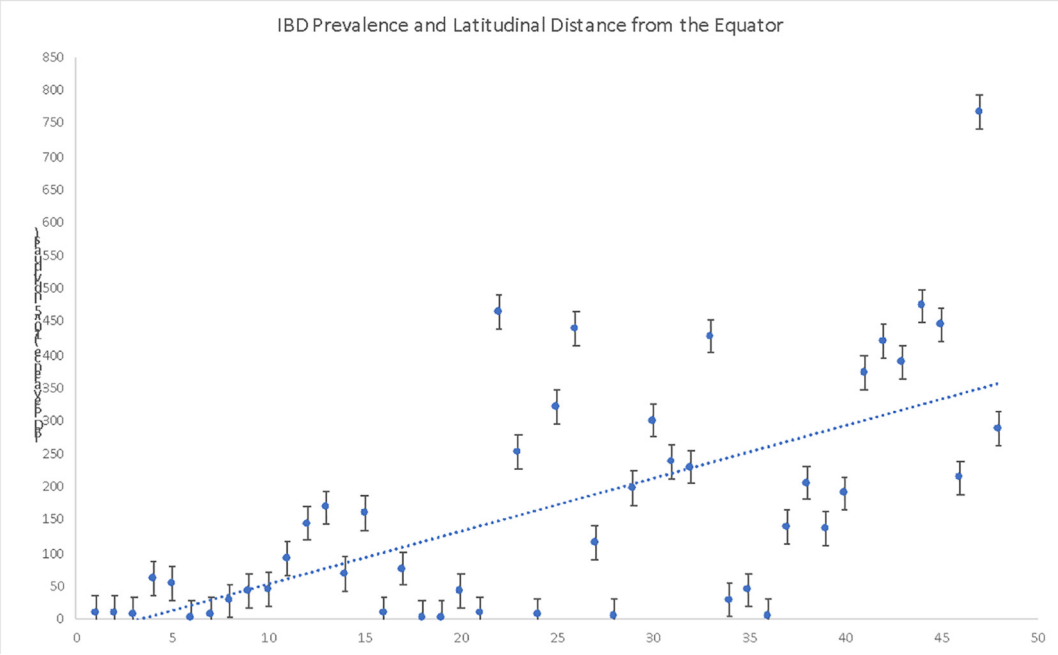

Fig. 4. There exists a strong positive correlation between longitude and prevalence of IBD ($r^2 = 0.4073$, $p < .005$, $n = 48$, Pearson correlation).

filter nearly all UVC radiation and approximately 90% of UVB radiation, therefore higher elevations have greater exposure to UV radiation as a result of the diminishing atmosphere [30].

We further expect people in rural populations to have lower rates of IBD than people in urban environments and we expect people working outdoors to have lower rates than people who work mostly indoors because of their greater exposure to UVB sunlight. These predictions are consistent with Sonnenberg and Ekbon who reported associations between both occupation and environment with prevalence of IBD in Germany [29,34,35].

Discussion

Why does autoimmune dysfunction occur in some vitamin D deficiencies and not others? Although there are two vitamin D receptor polymorphisms which may increase and decrease the risk of CD in Caucasians [36], the tipping point in the imbalance of immune pathways that leads to chronic, persistent inflammation seen in autoimmune diseases is often inscrutable. Our hypothesis suggests an etiology of inflammation that may be under *evolutionarily novel* conditions that involve TNF-α upregulation, low sunlight exposure, vitamin D deficiency and hypocalcemia. As noted in Fig. 1 TNF-α upregulation is one of the downstream effects of Vitamin D deficiency and hypocalcemia. Nielsen also points out that "in addition to T-cell regulation, the production of anti-inflammatory cytokines including IL-4, IL-10, and TGF-Beta, is increased by vitamin D." [21]

Under other conditions, this TNF-α pro-inflammatory pathway serves an adaptive function. "Several viruses and other pathogens encode proteins that inactivate caspase-8, thus preventing the infected cells from undergoing apoptotic death that would otherwise prevent the virus from replicating… [and] necroptosis provide[s] an alternative pathway for cell death… at the cost of inflammation." [37] Thus functional necroptosis enhances inflammation because cell contents are released when dying cells rupture and release their contents into extracellular space.

The microbiome community, which can be affected, not only by the immune system, but also by the use of antibiotics, dietary changes, and even surgery, likely plays a major role in IBD. It is beyond the scope of this article to describe the microbiome role in IBD. However, Huttenhower et al. point out that, "commensal gut microbiota have been found to be ecologically and functionally perturbed during [IBD] with… unexplained heterogeneity between IBD subtypes and patients." [38] While there are likely a multitude of triggers for IBD onset, our hypothesis offers an explanation for the persistence of IBD after the trigger has been removed, namely the inflammatory feedback loop.

Clinical Implications

Other autoimmune diseases show similar pathologies linked to vitamin D, including multiple sclerosis [39]. Multiple sclerosis (MS) and inflammatory bowel disease (IBD) occur because of immune-mediated attacks on self tissue. Interestingly, studies show that Vitamin D, also through exposure from environmental factors such as sunlight, has a critical role in susceptibility to the increase risk of the onset of MS [30]. Ultraviolet (UV) light results in increased production of vitamin D3 synthetic rates and provides a protective effect from the onset of MS [41,42]. This finding also is confirmed through the observed increase in cases of MS patients in locations that are further away from the equatorial regions or in lower altitudes [30].

This hypothesis has implications for both prevention and treatment of IBD. Incidence of IBD may be reduced in vulnerable populations by either promoting more time outdoors or prescribing oral vitamin D supplementation. A variety of treatments for IBD may be more successful if combined with Vitamin D and Calcium supplementation in order to break the feedback cycle. Only two clinical trials with small sample sizes have directly tested Vitamin D supplementation for therapeutic use in existing IBD, finding potential but inconclusive support, as noted by Nielson in a recent review[21]. This dearth of evidence was surprising in light of the fact that "suboptimal circulating levels of 25-hydroxyvitamin D are common in IBD and appear to be associated with an increased risk of flares, IBD-related hospitalizations and surgeries, an inadequate response to tumor necrosis factor [TNF] inhibitors." [21] Taken together, this research gap and the physiological basis we describe lend credence to the usefulness of our new hypothesis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2019.04.005.

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