HYPOTHESIS

Elevated Levels of 1,25-Dihydroxyvitamin D in Plasma as a Missing Risk Factor for Celiac Disease

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Abstract: The prevalence of celiac disease (CD) has increased significantly in some developed countries in recent decades. Potential risk factors that have been considered in the literature do not appear to provide a convincing explanation for this increase. This has led some researchers to hypothesize that there is a "missing environmental factor" that increases the risk of CD. Based on evidence from the literature, the author proposes that elevation in plasma levels of 1,25-dihydroxyvitamin D [1,25(OH)$_2$D] is a missing risk factor for CD, and relatedly that significant oral vitamin D exposure is a "missing environmental factor" for CD. First, elevated plasma levels of 1,25(OH)$_2$D are common in CD, especially in the newly diagnosed. Second, nine distinct conditions that increase plasma levels of 1,25(OH)$_2$D are either associated with CD or have indications of such an association in the literature. Third, a retrospective study shows that sustained oral vitamin D supplementation in infancy is associated with increased CD risk, and other studies on comorbid conditions support this association. Fourth, large doses of oral vitamin D upregulate many of the same cytokines, chemokines, and toll-like receptors that are upregulated in CD. Fifth, epidemiological evidence, such as the timing of the inception of a CD "epidemic" in Sweden, the increased prevalence of CD in Finland and the United States in recent decades, the unusually low prevalence of CD in Germany, and the differential in prevalence between Finnish Karelians and Russian Karelians, may all be explained by oral vitamin D exposure increasing CD risk. The same is true of some seemingly contradictory results in the literature on the effects of breastfeeding on CD risk. If future research validates this hypothesis, adjustments to oral vitamin D consumption among those who have genetic susceptibility may decrease the risk of CD in these individuals.

Keywords: vitamin D, vitamin D3, coeliac, gluten, epidemiology, calcitriol

Plain Language Summary

Prevalence of CD has increased significantly in some countries in recent decades. Existing explanations that have been postulated for this increase in prevalence are inadequate. Based on evidence from the medical literature, the author proposes that high levels of 1,25(OH)$_2$D in blood plasma increase the risk of CD. In addition, as consumption of oral vitamin D increases the levels of 1,25(OH)$_2$D in blood plasma, significant vitamin D supplementation or fortification will increase the risk of CD. This hypothesis is supported by data from the literature on CD comorbidity, gastrointestinal and immunological effects of vitamin D consumption, and CD epidemiology.

Introduction

Celiac disease (CD) is a chronic small intestine enteropathy induced by exposure to gluten.[1] Both genetic and environmental factors contribute to the risk of CD.[2]

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Global prevalence of CD has been estimated to be 0.7% with considerable variation between countries.[3] Prevalence has increased significantly in recent decades in some developed countries,[4,5] and serological studies show that a substantial portion of this increase in prevalence is real, in that it is not solely due to factors such as increased awareness and testing.[6–8] As genetic factors do not change over short time periods, there is a consensus that this rise in real prevalence of CD is due to environmental factors.[2,9] Yet, the environmental factors in the existing literature do not appear to provide a satisfactory explanation for this increase in real prevalence.[2,9,10] As Ludviggson and Green have suggested, there is a "missing environmental factor" in CD,[10] and it is crucial that this factor be identified.[10] Others have echoed this sentiment.[2,9]

Vitamin D is a secosteroid that has a number of biological effects including regulating calcium absorption and modulation of the immune system.[11] Two forms are 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] and its precursor, 25-hydroxyvitamin D [25(OH)D].[12] While the level of 25(OH)D in plasma is commonly used as an indication of vitamin D status, it is $1,25(OH)_2D$, which is the biologically active form of vitamin D.[12] Vitamin D can be ingested orally and absorbed through the digestive tract or synthesized in the skin through sunlight exposure.[12] Oral vitamin D supplementation, even in modest doses, generally has a greater effect on plasma levels of vitamin D than sunlight exposure.[13]

Based on evidence from the literature that will be explored in this article, elevation in plasma levels of $1,25(OH)_2D$ is hypothesized to be a significant missing risk factor for CD. Specifically, the author proposes that in a substantial number of cases of CD, three primary factors are involved in the induction of the disease. These three factors are: 1) gluten exposure, 2) genetic predisposition in the form of the genetic variant human leukocyte antigen (HLA) DQ2 or HLA DQ8, and 3) elevated levels of $1,25(OH)_2D$ in plasma. As gluten exposure is a necessary condition for the development of CD,[1] and at least one of the two genetic variants HLA DQ2 or HLA DQ8 is present in almost all cases of CD,[1] the novel part of this hypothesis is the third factor. Consumption of oral vitamin D raises plasma levels of $1,25(OH)_2D$ in a dose-dependent manner.[14] Therefore, a corollary to the above hypothesis is that significant exposure to oral vitamin D through supplementation, fortification, or a combination will increase the risk of CD in those who are exposed to gluten and have at least one of the genetic variants that are associated with CD.

Some of the concepts and evidence explored in the present article were initially proposed in a much less developed form 4 years ago in a paper by the author.[15] Additional evidence was obtained and analyzed as part of a retrospective survey study by the author and a collaborator on risk factors for CD in children.[16] The present article further develops this hypothesis, provides additional evidence for it from the literature, and explores how it may explain a number of features of CD epidemiology.

Plasma Levels of $1,25(OH)_2D$ and CD

Plasma levels of 25(OH)D are often low in adults with CD who are not on a gluten-free diet (GFD).[17,18] Based on this, it is a common medical practice to test plasma levels of 25(OH)D in CD patients and prescribe supplemental oral vitamin D to those who have low levels of this metabolite in plasma.[19,20] However, the low plasma levels of 25(OH)D that sometimes occur in CD will usually normalize after some time on a GFD without vitamin D supplementation.[17,21]

Plasma levels of $1,25(OH)_2D$ are often elevated in CD, and this is especially true in those who are not on a GFD.[17,22,23] In contrast to 25(OH)D, the elevation in plasma levels of $1,25(OH)_2D$ in CD often does not completely normalize, even for those on a GFD.[17,23] For example, Corrazza et al found that median plasma levels of 25(OH)D in those with CD on a GFD are just 9% lower than controls, while median plasma levels of $1,25(OH)_2D$ in those with CD on a GFD are 68% higher than controls.[17] Separately, Selby et al in a cohort of 35 middle-aged patients with CD on a GFD, who had been diagnosed on average about 10 years previously, found that no cases had levels of 25(OH)D that were below the reference range and 44% of cases had levels of $1,25(OH)_2D$ that were above the reference range.[23]

Yet, as mentioned in the Introduction, $1,25(OH)_2D$ is the biologically active form of vitamin D.[12] Based on this fact and the evidence above that this metabolite is often elevated in CD, the rationale for vitamin D supplementation in CD seems questionable. Zingone and Ciacci have made this same observation.[24] The elevation in $1,25(OH)_2D$ that is often observed in CD has traditionally been attributed to secondary hyperparathyroidism due to inadequate absorption of calcium.[18,23] To the author, this seems unlikely to be a significant factor after treatment on a GFD as serum calcium levels are generally unremarkable in those with CD on a GFD, even when the plasma levels of $1,25(OH)_2D$ are high.[17,23] Another possibility is that some portion of the

elevation in plasma levels of 1,25(OH)$_2$D that persists in some of those with CD years after initiating a GFD was present prior to the development of CD in these individuals.

Conditions That Cause Elevated 1,25(OH)$_2$D and CD Risk

Many conditions in the medical literature cause elevations in 1,25(OH)$_2$D in plasma. For at least nine such conditions, there are indications in the medical literature of comorbidity with CD. Table 1 enumerates these nine conditions, and for each condition it provides the magnitude of the elevation in 1,25(OH)$_2$D relative to controls, information on the comorbidity with CD, and the odds ratio (OR) and 95% confidence interval (CI) for CD. The ORs in Table 1 are mostly expressed for the outcome of CD subsequent to the diagnosis of the condition in question. For some of the conditions in Table 1, an OR for CD has not been published in the literature. In two such conditions, ORs and CIs were calculated using data from the literature with standard formulas;[25] in two other conditions, ORs were approximated by risk ratios (RRs) from the literature using the rare disease assumption;[26] and in one condition, an OR was approximated by an RR from the literature using the rare disease assumption and the commutative nature of ORs.[26,27]

Table 1 does not include conditions where the elevation in plasma levels of 1,25(OH)$_2$D is merely associated with the condition, rather than being a result of the condition. For example, elevation in 1,25(OH)$_2$D is a risk factor for kidney stones,[49] and kidney stones have significant comorbidity with CD.[50] However, since there is no evidence that kidney stones cause the elevation in plasma levels of 1,25(OH)$_2$D that is associated with them,[49] kidney stones are not included in Table 1.

The nine disparate conditions in Table 1 include genetic conditions (Williams syndrome, Turner syndrome, and Klinefelter syndrome),[28,34,45] infectious diseases (sarcoidosis and tuberculosis),[36,40] and other non-infectious diseases (hypothyroidism, primary hyperparathyroidism, lymphoma, and polycystic ovary syndrome [PCOS]).[31,38,42,47]

The elevated plasma levels of 1,25(OH)$_2$D observed in these nine conditions are caused by a variety of mechanisms. In Williams syndrome, the elevated levels of 1,25(OH)$_2$D are due to haploinsufficiency of the *WSTF* gene, which normally plays an important role in vitamin D homeostasis.[28,51] The elevated levels of 1,25(OH)$_2$D observed in sarcoidosis, tuberculosis, and lymphoma are caused by macrophage activation due to the underlying disease.[52–54] In sarcoidosis and tuberculosis, the disease is bacterial,[52,53] and in lymphoma, the disease is cancer.[54]

The elevated levels of 1,25(OH)$_2$D observed in primary hyperparathyroidism are due to high levels of parathyroid hormone, which upregulates the conversion of 25(OH)D to 1,25(OH)$_2$D.[47,55] In the case of primary hyperparathyroidism, the high levels of parathyroid hormone are generally caused by an adenoma, a non-cancerous tumor on the parathyroid gland.[56]

Table 1 Conditions That Cause Elevated 1,25(OH)$_2$D in Plasma and Have Indications of Comorbidity with CD

Condition	1,25(OH)$_2$D in Plasma (% Higher Relative to Controls)	CD Comorbidity	OR of CD
Williams syndrome	602[a,28,29]	9.4% with Williams syndrome have CD[30]	19.36 (8.15–46.02)
Lymphoma	107[b,31,32]	RR 2.4 (0.7–8.5) for CD after or with lymphoma[33]	2.4 (0.7–8.5)
Turner syndrome	91[c,29,34]	6.4% with Turner syndrome have CD[35]	12.63 (8.03 −19.89)
Sarcoidosis	88[d,36]	OR 3.58 (1.98–6.45) for CD after sarcoidosis[37]	3.58 (1.98–6.45)
Hypothyroidism	74[38]	OR 2.20 (1.21–4.01) for undiagnosed CD[39]	2.20 (1.21–4.01)
Tuberculosis	49[40]	OR 2.50 (1.75–3.55) for CD after tuberculosis[41]	2.50 (1.75–3.55)
Polycystic ovary syndrome	35[e,42]	3x greater IgG seropositivity for gliadin;[43] infertility often comorbid with CD[44]	Likely > 1
Klinefelter syndrome	30[f,45]	RR 3.0 (0.8–7.8) for CD[46]	3.0 (0.8–7.8)
PHPT	27[47]	RR 1.91 (1.44–2.52) for PHPT, 5 years after CD[48]	1.91 (1.44–2.52)

Notes: [a]in infancy; [b]among hypercalcemic cases; [c]among girls provided with estrogen therapy; [d]among hypercalcemic cases; [e]among those of normal weight; [f]among older boys.
Abbreviations: 1,25(OH)$_2$D, 1,25-dihydroxyvitamin D; CD, celiac disease; IgG, immunoglobulin G; OR, odds ratio; PHPT, primary hyperparathyroidism; RR, risk ratio.

Likewise, elevated levels of parathyroid hormone are a characteristic of hypothyroidism,[38] Turner syndrome,[57] Klinefelter syndrome,[45] and some cases of PCOS.[42] As parathyroid upregulates conversion to $1,25(OH)_2D$ as previously mentioned,[47,55] it seems certain that the elevation of $1,25(OH)_2D$ observed in these conditions is at least partly caused by the elevated levels of parathyroid hormone that are common to them. In Turner syndrome and Klinefelter syndrome, the hormone replacement therapy that is often provided to patients with these conditions also contributes to elevation in $1,25(OH)_2D$. Specifically, it is considered best medical practice for Turner syndrome patients to receive estrogen and for Klinefelter syndrome patients to receive testosterone,[58,59] and each of these therapies increases plasma levels of $1,25(OH)_2D$.[34,60]

For eight of the nine conditions in Table 1, there is evidence in the literature that the condition in question often precedes the development of CD in cases of comorbidity. As Williams syndrome, Turner syndrome, and Klinefelter syndrome are all genetic conditions that are present prior to birth,[28,34,45] and CD cannot be present prior to gluten exposure,[1] it is clear that these three genetic conditions precede the development of CD in cases of comorbidity.

For the conditions that are not purely genetic, the relationship is less clear. While CD is typically viewed as a risk factor for lymphoma,[33] the converse is also true. Specifically, patients who are diagnosed with lymphoma are at greater risk of being diagnosed with CD after or simultaneously with a diagnosis of lymphoma.[33] Similarly, CD is sometimes viewed as a risk factor for tuberculosis, but a population-based study shows that tuberculosis is a risk factor for subsequent diagnosis of CD.[41] Likewise, CD is typically viewed as a risk factor for primary hyperparathyroidism.[48] However, much of the increased risk of diagnosis of primary hyperparathyroidism following a diagnosis of CD occurs in the first year following CD diagnosis, which suggests that CD may have "unmasked" unrecognized cases of primary hyperparathyroidism.[48] In hypothyroidism, undiagnosed CD is about 2.2 times as common as in the general population.[39] Likewise, prior diagnosis of sarcoidosis is associated with subsequent diagnosis of CD.[37,61]

With PCOS, there are indications of an association but limited data on whether PCOS precedes or follows CD. Specifically, a small study found that immunoglobulin G positive antibodies to gliadin are about three times more common among those with PCOS than controls,

but biopsy did not confirm this association.[43] Yet separate research shows that there is a significant association between female infertility and CD,[44] and PCOS is the cause of about 70% of the cases of anovulatory infertility.[62]

At least four of the conditions in Table 1 are significantly more common in adults than children. Specifically, sarcoidosis and primary hyperparathyroidism are much more common in those who are of age 40 or over,[63,64] and the risk of tuberculosis and lymphoma increases with age.[65,66]

Interestingly, among the conditions in Table 1, there is a correlation between the average level of $1,25(OH)_2D$ in plasma relative to controls and the magnitude of comorbidity with CD as measured through the OR. Specifically, the Pearson correlation coefficient between these two columns in Table 1 is 0.858, and the p-value is 0.006. PCOS was excluded from this analysis as its OR with CD is unknown. While this correlation is strong, the data suggest that Klinefelter syndrome and especially Turner syndrome have relatively high ORs for CD compared to the levels of $1,25(OH)_2D$ that are observed in these conditions. If elevation in $1,25(OH)_2D$ is a causative risk factor for CD, higher ORs might be expected for these two genetic conditions than indicated by a point in time analysis of plasma levels of $1,25(OH)_2D$ due to the lifelong persistence of these two conditions and volatility in $1,25(OH)_2D$ levels from hormone replacement that is commonly provided as treatment for them.

Vitamin D Supplementation and CD

Animal studies show that vitamin D supplementation in extremely high doses can have significant negative gastrointestinal effects, and these effects or variants of them are often observed in CD in humans. For example, high-dose vitamin D supplementation in mice increases the propensity for colitis and decreases bacterial diversity in the microbiome.[67] CD and colitis have significant comorbidity,[68] and decreased bacterial diversity of the microbiome is a characteristic of CD.[69] Extremely high-dose chronic oral vitamin D exposure in rats, at doses that are eventually lethal, causes sloughing of the intestinal villi.[70] Flattened intestinal villi are one of the defining characteristics of CD.[71]

Three human studies have directly measured the impact of oral vitamin D supplementation on CD risk in modest doses. First, a multi-site diabetes study examined the effects of prenatal supplementation on CD risk.[72] Second, a Norwegian cohort study examined the effects of supplementation up to 18 months of age and prenatal

supplementation on CD risk.[73] Third, a retrospective US survey study by the author and collaborator examined the effects of supplementation in infancy and between ages 2 and 3 years on CD risk.[16]

The multi-site diabetes study concluded that there was no association between prenatal vitamin D supplementation and CD risk.[72] The Norwegian cohort study found no association between supplementation up to 18 months of age and CD risk or prenatal supplementation and CD risk.[73] The retrospective study by the author and a collaborator found a statistically significant association between vitamin D supplementation for greater than 3 months in infancy and CD risk but found no association between supplementation between ages 2 and 3 and CD risk.[16]

Superficially, these three human studies would seem to provide only modest support for a connection between vitamin D supplementation and CD risk. However, additional analysis is revealing. Regarding the multi-site diabetes study, it actually found an association between any prenatal vitamin D supplementation and CD autoimmunity in the child with a p-value of 0.04.[72] The authors of this multi-site study did not appear to view this result as worthy of comment, likely because other measures of vitamin D supplementation from this same study were not observed to have statistically significant associations with CD or CD autoimmunity. As maternal vitamin supplementation is associated with supplementation in childhood,[74] one might interpret this finding from the multi-site study as providing some support for the hypothesis that vitamin D supplementation in infancy is associated with CD.

Regarding the Norwegian cohort study, while the underlying dataset was large, the subset on which the analysis was conducted consisted of 416 cases and 570 controls, and many of these had missing data for some variables.[73] Specifically, of these, 108 cases and 176 controls were missing data on vitamin D supplementation,[73] which represents a disproportionately greater share of controls than cases. If vitamin D supplementation among those with missing data for this variable differed materially in aggregate from those where data were present, this could impact the results.

During the majority of years when data for this Norwegian cohort study were gathered, the recommended daily intake of vitamin D in Norway was 5 micrograms, which is equivalent to 200 international units (IU),[75,76] and during the remaining years, the recommended daily intake of vitamin D was 7.5 micrograms.[75] Subsequent to the

data collection period, the recommended daily intake in Norway was raised to 10 micrograms.[75] Also, it was and is a common practice in Norway to provide supplemental vitamin D through cod liver oil capsules.[77,78] Thus, any effect of vitamin D supplementation on CD risk may be obscured or reduced in this study, if 200 IU is not a material dose with respect to risk, or if other compounds in cod liver oil have confounding effects on CD risk.

Regarding the result on supplementation among 2- to 3-year-olds from the survey study by the author and a collaborator, the study did not collect information on the dose of vitamin D provided through supplementation or the quantity of vitamin D consumed through fortified foods.[16]

With respect to the dose, multivitamin supplements for children typically provide much smaller doses of vitamin D per pound than infant vitamin D drops provide to an infant. Specifically, as of 2008, multivitamins in the US for young children typically contained between 200 IU and 400 IU of vitamin D,[79] while vitamin D drops for infants typically provided doses of 400 IU of vitamin D.[80] Thus, if used as directed, a 2- to 3-year-old child would receive an equal or slightly smaller dose than an infant, but a 2- to 3-year-old typically weighs over twice as much as a 3-month-old infant.[81] Hence, the typical dose of vitamin D per pound in infancy from vitamin D drops will be much greater than what a 2- to 3-year-old would receive through a multivitamin.

Other studies have found associations between oral vitamin D supplementation in infancy and the risk of atopic dermatitis and asthma.[82–85] Both of these conditions have comorbidity with CD.[86,87] As comorbidity suggests the possibility of a common underlying risk factor, and vitamin D supplementation in infancy is associated with both of these conditions, these findings serve as additional circumstantial evidence that vitamin D supplementation in infancy may be a risk factor for CD.

Some additional studies in the literature that highlight the effects of oral vitamin D supplementation on the gastrointestinal tract are worthy of highlighting in this context. First, in a study designed to test the effects of vitamin D supplementation on bone in prepubescent girls, one of the participants who received supplemental vitamin D dropped out of the study due to the development of CD.[88] It is possible that this finding of a single case of CD onset during a vitamin D supplementation trial could be coincidental, but it is tantalizing given the evidence that oral vitamin D supplementation in infancy may be associated with CD. Second, some trials of high-dose vitamin D supplementation have inadvertently

highlighted that vitamin D supplementation causes constipation in some of the population. In some trials, researchers acknowledged that constipation was a complaint of a modest number of the participants,[89–91] and in at least one trial constipation was found to be a statistically significant outcome in the highest dose cohort.[92] Constipation has become an increasingly common symptom of CD in recent decades and as of 2013 was a symptom of CD in 27% of Finnish children at the time of diagnosis.[93] This data suggest that significant vitamin D supplementation is a risk factor for constipation, and constipation and CD are often comorbid. As comorbidity suggests the possibility of a common risk factor, the above is consistent with the hypothesis that significant vitamin D supplementation may be a risk factor for CD as well.

To summarize this section, evidence from animal studies suggests that high-dose vitamin D supplementation has significant negative gastrointestinal effects that are characteristic of CD. Evidence in human studies is mixed, but one human study found a statistically significant association between vitamin D supplementation for greater than 3 months in infancy and CD, and another study found an association between a measure of any prenatal vitamin D supplementation and CD autoimmunity in the child. In addition, the literature suggests that significant vitamin D supplementation in infancy is associated with two conditions that are often comorbid with CD, which is supportive of the hypothesis that vitamin D supplementation in infancy is associated with CD.

Select Effects of Vitamin D on the Immune System

The effects of $1,25(OH)_2D$ on the immune system are complex.[94] One of its effects is to upregulate allergic response to foreign proteins.[95] In mice, injections of $1,25(OH)_2D$ coincident to exposure to egg albumin have been found to increase the production of immunoglobulin E and upregulate interleukin (IL) 13, a proinflammatory cytokine.[95] In baby pigs, high-dose vitamin D supplementation significantly increases the number of leukocytes in blood and upregulates mucosal antimicrobial activity.[96] These findings are consistent with in vitro studies on human macrophages, which also show that $1,25(OH)_2D$ upregulates antibacterial immune activity.[97,98] Separately, Leonard et al have suggested that the initiation of CD may be due to the immune system confusing the gliadin proteins in gluten with a pathogenic bacteria.[99] In this light, it is conceivable that increased antibacterial immune activity in the mucosa of the small intestine caused by high

plasma levels of $1,25(OH)_2D$ may increase the risk of a dysfunctional immune reaction to gliadin in this same tissue, which may ultimately result in CD autoimmunity.

While the above seems plausible, much of the medical literature on vitamin D suggests that greater vitamin D exposure leads to less inflammation and more measured immune response.[100,101] However, many of the studies in the literature on vitamin D and the immune system have some substantial limitations. First, some studies are observational and only measure the 25(OH)D metabolite,[102,103] and relatedly, it is the 25(OH)D metabolite that is typically used to define deficiency.[12] Yet, as previously highlighted, $1,25(OH)_2D$ is the active vitamin D metabolite,[12] and in CD, 25(OH)D can be low or normal, while $1,25(OH)_2 D$ may be high.[17,22,23] Thus, observational studies which use the typical definition of vitamin D deficiency are likely to produce questionable results in the context of CD.

Second, some studies that analyze the effects of vitamin D on the immune system are in vitro studies.[97,98,100,101] While these have real value in illuminating the functions of the various components of the immune system, due to the complexity of the immune system and how real-world exposures may interact with it, in vivo studies are likely to be more reliable indications of real-world effects.[104]

Third, some studies on the effects of oral vitamin D exposure are based on protocols that use modest doses of vitamin D.[105,106] While such studies may be safer for participants than studies with larger doses, a stronger signal on effect will undoubtedly be observed through studies that use larger doses.

Table 2 includes some of the effects on the immune system of very high-dose vitamin D supplementation in humans from a non-systematically selected subset of studies in the literature. One of the studies is based on supplementation with $1,25(OH)_2 D$ rather than 25(OH)D,[107] and two measure effects in umbilical cord blood after significant maternal vitamin D supplementation.[109,112] Collectively this set of studies suggests that in very high doses vitamin D upregulates many of the cytokines, chemokines, and toll-like receptors that are associated with immune activation and relatedly are also associated with CD. Specifically, these studies show that oral vitamin D in very large doses upregulates TLR2, TLR4, IL-17A, CCR4, CXCR4, IL12RB1, IL12RB2, and TGF beta.[107,109,112,113,115] The upregulation of each of these has also been observed in CD.[99,108,110,111,114]

While the doses involved in these studies are very large, the direction of association suggests that in those

Table 2 Select Human Trials of High-Dose Vitamin D Supplementation and Its Effects

Study	Population	Vitamin D Exposure	Select Findings	Findings on CD from Literature
Protiva et al[107]	Adults at risk of cancer	Supplementation with 1,25(OH)$_2$D at 10 IU per day	"Striking upregulation of genes involved in immune responses, inflammation, extracellular matrix, and cell adhesion" in the rectosigmoid mucosa.	Genes associated with inflammatory response upregulated.[108]
Hornsby et al[109]	Pregnant women	4400 IU per day vs 400 IU per day	In cord blood from neonates, 4400 IU per day increased expression of TLR2, TLR4, and IL-17A.	Increased TLR2 and TLR4 expression,[110] and IL-17A upregulation.[111]
Akhtar et al[112]	Pregnant Bangladeshi women	35,000 IU per week vs placebo during third trimester	In cord blood from neonates, 35,000 IU per week increased expression of TNF alpha, INF gamma, CCR4 gene, CXCR4 gene, IL12RB1 gene, and the IL12RB2 gene.	Upregulation of CCR4, CXCR4, IL12RB1, and IL12RB2 gene activity.[99]
Goncalves-Mendes et al[113]	Vitamin D deficient elderly	100,000 IU per 15 days vs placebo over 3 months with influenza vaccine	Higher levels of TGF beta in plasma.	Higher levels of TGF beta in lamina propia.[114]
Bak et al[115]	Ten healthy adults	480,000 IU over 15 days	Increased RNA expression of TGF beta and TNF alpha.	Higher levels of TGF beta in lamina propia.[114]

Abbreviations: 1,25(OH)$_2$D, 1,25-dihydroxyvitamin D; CCR4, C-C chemokine receptor type 4; CD, celiac disease; CXCR4, C-X-C chemokine receptor type 4; IL-17A, interleukin 17A; IU, international units; TGF beta, transforming growth factor beta; TLR2, toll-like receptor 2; TLR4, toll-like receptor 4; TNF alpha, tumor necrosis factor alpha; vs, versus.

whose plasma levels of 1,25(OH)$_2$D are already elevated or are predisposed to elevation, more modest doses of oral vitamin D may induce a state of increased immune activation that puts such individuals at greater risk for onset of CD. This possibility that small doses of oral vitamin D will have an outsized effect on immune activity seems especially likely to occur in those who are later diagnosed with CD, since a large subset of those who are diagnosed with CD have significantly elevated plasma levels of 1,25(OH)$_2$D independent of supplementation.[17,22,23]

Epidemiology of CD and Vitamin D Exposure

CD epidemiology has a number of idiosyncrasies that appear in the literature, many of which superficially seem improbable. Table 3 catalogs thirteen of these features and how the hypothesized association between elevated 1,25(OH)$_2$D and CD or relatedly the hypothesized association between vitamin D supplementation and CD could provide an explanation for each.

Other Hypotheses

The strength of this vitamin D hypothesis as a significant missing risk factor for CD is especially evident when one compares the breadth of its explanatory power to other hypotheses that have been proposed in the literature. Three such hypotheses are examined in this section.

First, some researchers have suggested that the hygiene hypothesis may explain the increased prevalence of CD.[134] According to this hypothesis, decreased exposure to parasites and infections, especially in the young, negatively impacts the development of the immune system, and as a result increases the risk of CD and other immune-mediated diseases in later life.[134,155] While the hygiene hypothesis could conceivably provide an explanation for the differential in CD prevalence between Finnish and Russian Karelians,[134] some other major features of CD epidemiology from Table 3 do not bear it out. For example, consider the Swedish CD epidemic. The literature shows that its inception was in 1984.[116] If the hygiene hypothesis played a major role in CD epidemiology, then one would expect significant increases in CD prevalence as exposure to

Table 3 CD Epidemiology and the Vitamin D Hypothesis

Area	CD Epidemiology	Possible Explanation Based on the Vitamin D Hypothesis
Sweden	1984 was the inception of the Swedish CD "epidemic."[116]	March 1983 was the inception of mandatory vitamin D supplementation of milk and margarine in Sweden.[117]
Finland	CD prevalence doubled among Finnish adults between 1978 and 2000 based on serology.[6]	Oral vitamin D consumption in Finland increased during this time period primarily due to a significant increase in the proportion of the population using vitamin D supplements.[118–120]
Nordic countries vs Germany	At least five times greater prevalence of CD in Sweden and Finland than in Germany.[6,116,121]	Much greater intake of oral vitamin D in Sweden and Finland than in Germany due to greater use of vitamin D supplementation and fortification in Sweden and Finland than in Germany.[76,117,122,123]
US	Significant increase in prevalence of CD and CD serology in the US in recent decades.[5,8,124]	Increased use of vitamin D supplements, increased doses of vitamin D supplements, and increased levels of vitamin D fortification in the US in recent decades.[125–130]
Burkina-Faso	No case of CD based on serology among 600 adults in Burkina-Faso, despite wheat consumption by all and some genetic susceptibility.[131]	There have historically been no vitamin D supplementation programs or vitamin D fortification programs in Burkina-Faso.[132,133]
Karelians	Finnish Karelian children have a CD risk that is 2.3 times greater than Russian Karelian children based on serology and 4.6 times greater based on biopsy.[134]	Finland fortifies food with vitamin D and encourages vitamin D supplementation in childhood.[76,135] Russia has not historically fortified food with vitamin D or provided supplemental vitamin D to its population.[136,137]
Breastfeeding	Early studies found that breastfeeding decreases risk of CD,[138] while more recent studies do not find such an effect.[139]	Vitamin D fortification and supplementation in infancy has increased during the last three decades in much of the developed world.[76,80,135] Infant supplementation in some countries is focused on breastfed infants.[80,140] These effects may outweigh any positive effect of breastfeeding.
Constipation and CD in Finland	Between the late 1970s and 2013 in Finland, there was a 500% increase in constipation as a symptom of CD among newly diagnosed children.[93]	During this time, vitamin D intake increased significantly in Finland.[76,118–120,135] Vitamin D exposure increases risk of constipation.[92] If vitamin D exposure increases risk of CD, this change in presentation would be expected.
Pregnancy	Greater risk of CD onset during pregnancy and the period immediately following pregnancy.[141,142]	Plasma levels of 1,25(OH)$_2$D are elevated during pregnancy and lactation.[143]
Helicobacter pylori	Significantly decreased incidence of gastric H. pylori infection observed in children with CD.[144]	Plasma levels of 1,25(OH)$_2$D are often elevated in those with CD,[17,22,23] and 1,25(OH)$_2$D activates a lysosomal degradation pathway that is effective in combatting H. pylori infection.[145]
African Americans	CD and CD serology is much less common among African Americans than among non-Hispanic White Americans despite some genetic risk.[4,146,147]	Vitamin supplementation in general is less common in the African American community than among non-Hispanic White Americans.[148]
Smoking	Smoking is associated with decreased risk of CD.[149]	Vitamin supplementation in general is less common among smokers,[150] and plasma levels of 1,25(OH)$_2$D are lower among smokers than non-smokers.[151]
Socioeconomic	Higher socioeconomic status is associated with increased risk for CD.[152,153]	Vitamin supplement use is greater among those of higher socioeconomic status.[154]

Abbreviations: 1,25(OH)$_2$D, 1,25-dihydroxyvitamin D; CD, celiac disease; US, United States; vs, versus.

intestinal parasites diminished with the advent of household plumbing and the modern toilet.[156] These advances in hygiene occurred gradually in Sweden in urban settings in the early and middle decades of the twentieth century.[157,158] Thus, the timing and rapid advance of the Swedish CD epidemic starting in 1984[116] would not appear to be explainable using the hygiene hypothesis. Also, recall that the prevalence of CD is more than five times higher in Sweden than in Germany.[116,121] If this feature of CD epidemiology is due to the hygiene hypothesis, then Sweden must be significantly more hygienic than Germany. As Sweden and Germany are both highly developed European countries, and Germany's spending on healthcare per capita is marginally higher than Sweden's is,[159] this seems improbable.

Second, some researchers have suggested that increased exposure to the pesticide glyphosate may explain the increased prevalence of CD.[160] Consider this hypothesis in the context of Sweden, Finland, and Germany. As previously mentioned, prevalence of CD in Sweden and Finland is about five times higher than in Germany.[6,116,121] If glyphosate is a significant factor in this feature of CD epidemiology, then one would expect negligible glyphosate exposure among those living in Germany and significant glyphosate exposure among those living in Sweden and Finland. Yet, in 1997, glyphosate became the only herbicide used on the German railway system.[161] In the same year, glyphosate was observed in the surface water of two rivers in the North-Rhine-Westphalia state of Germany at a maximum concentration of 590 ng/l,[162] and as of 2009, glyphosate was applied to 39% of all of the arable land in Germany.[163] A groundwater survey in the mid-2000s found no indication that glyphosate exposure was significantly lower in Germany than in Sweden or Finland.[164] Specifically, glyphosate was present in 22% of groundwater samples from Germany, 24.7% from Sweden, and 11.2% from Finland.[164]

Third, some researchers have suggested that increased exposure to manufactured transglutaminase enzymes in food may explain the increased prevalence of CD.[165] An issue with this hypothesis is that the introduction of manufactured transglutaminase in food occurred after much of the increase in the prevalence of CD. Specifically, stable transglutaminases were first isolated from bacteria in 1989,[166] and many of the processes to manufacture transglutaminase for the food industry were developed in the early 2000s.[167] Yet, as previously highlighted, the CD epidemic began in Sweden in 1984,[116] prevalence of CD doubled in Finland between 1978 and 2000,[6] and

a significant portion of the increase in CD prevalence in the US occurred prior to 1989.[124] Thus, it would appear that manufactured transglutaminase in food was not a significant factor in the increased prevalence of CD during the latter decades of the twentieth century in some developed countries.

While the above shows that none of these three hypotheses individually can explain the major features of CD epidemiology as outlined in Table 3, this does not preclude the possibility that one or more of these factors may contribute to CD risk, and perhaps in combination with other factors could explain many of the major features of CD epidemiology.

Summary and Discussion

Studies highlighted in the section on plasma levels of 1,25(OH)$_2$D show that elevated plasma levels of this metabolite are common in CD at the time of diagnosis and that in a substantial proportion of cases these elevated levels persist years after transition to a GFD. Separately, as highlighted above, there are nine disparate conditions in the literature, which cause elevations in 1,25(OH)$_2$D through various mechanisms and for which there are indications of an association with CD in the literature. For eight of these conditions, there is evidence that the condition in question often precedes CD in cases of comorbidity. In the author's opinion, this suggests that the elevated plasma levels of 1,25(OH)$_2$D, which is a common feature of these disparate conditions and is often observed generally in CD near the time of diagnosis, is a causative factor in inducing CD.

As supplementation with oral vitamin D increases plasma levels of 1,25(OH)$_2$D, the above suggests that significant exposure to oral vitamin D will also increase the risk of CD. Indeed, animal studies show that exposure to very high doses of oral vitamin D will induce some gastrointestinal symptoms that are associated with CD, and a retrospective study by the author and a collaborator confirms that vitamin D supplementation in humans in infancy for greater than 3-months duration is associated with increased risk of CD. Other studies suggest that significant oral vitamin D supplementation in infancy is associated with increased risk of two conditions that are often comorbid with CD. While no study in the literature has found direct evidence that vitamin D supplementation in later life increases the risk of CD, there is evidence that large doses of oral vitamin D induce constipation in some, and constipation is often comorbid with CD. Also, as highlighted in the section on the nine conditions, four of

the nine conditions, which are associated with increased CD risk and cause elevations in $1,25(OH)_2D$, are primarily conditions of adulthood. In the author's opinion, this suggests that elevation in plasma levels of $1,25(OH)_2D$ in adulthood, which each of these conditions cause, may also increase CD risk. Since vitamin D supplementation increases the levels of $1,25(OH)_2D$ in plasma as previously mentioned, this supports the hypothesis that significant vitamin D supplementation in adulthood will also increase the risk of CD.

As the section on vitamin D and the immune system highlights, $1,25(OH)_2D$ upregulates the antibacterial actions of the immune system, and the effects of very high-dose vitamin D supplementation on cytokines, chemokines, and toll-like receptors match key aspects of the immune profile that is typically observed in CD. While such immune activation is generally not evident in empirical studies of vitamin D supplementation in low doses, it seems likely to the author that a subset of individuals, who have high plasma levels of $1,25(OH)_2D$ or have propensity to elevations in $1,25(OH)_2D$, will experience such immune activation with more modest doses of oral vitamin D.

Table 3 in the section on epidemiology and CD shows that the breadth of the evidence that this vitamin D hypothesis may explain about CD epidemiology is extraordinary. The hypothesis offers a possible explanation for the timing of the inception of the CD epidemic in Sweden, the increased prevalence of CD in Finland, the significant differential in prevalence between these two countries and Germany, and the apparent absence of CD from Burkina-Faso. The hypothesis also explains some other puzzles of CD epidemiology, including the differential in prevalence between Finnish and Russian Karelians, the trend toward increased incidence of constipation with CD in Finland, the higher risk of CD onset during pregnancy, the decreased risk of *Helicobacter pylori* infection in CD, the decreased risk of CD among smokers, and some seemingly contradictory results in the literature regarding breastfeeding and CD risk in children.

The breadth of the epidemiological evidence that the hypothesis explains acts as additional circumstantial evidence for the hypothesis. In addition, the magnitude of the differentials in CD prevalence that the hypothesis explains suggests that oral vitamin D exposure may be an important variable in CD risk. By comparison, three other potential explanations from the literature for the increased prevalence of CD are inconsistent with some major features of CD epidemiology.

If this vitamin D and CD hypothesis is validated, it has profound practical implications. First, the practice of prescribing oral vitamin D to CD patients based on the low levels of 25(OH)D in plasma that are often observed in newly diagnosed CD patients should be reevaluated. Second, among those who do not have CD but do have genetic risk for it, decreasing exposure to the large doses of oral vitamin D that are frequently consumed in many developed countries may decrease the risk of CD. As this would have important consequences for the health of these individuals with genetic susceptibility, if this hypothesis is validated, practice guidelines should be reevaluated.

Abbreviations

$1,25(OH)_2D$, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; CCR4, C-C chemokine receptor type 4; CD, celiac disease; CI, 95% confidence interval; CXCR4, C-X-C chemokine receptor type 4; GFD, gluten-free diet; HLA, human leukocyte antigen; IL, interleukin; IL-17A, interleukin 17A; IU, international units; OR, odds ratio; RR, risk ratio; TGF beta, transforming growth factor beta; TLR2, toll-like receptor 2; TLR4, toll-like receptor 4; TNF alpha, tumor necrosis factor alpha; US, United States.

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Disclosure

The author declares that he has no competing interest.

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