Exposure to excessive oral vitamin D in youth: a risk factor for celiac disease in later life?

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Abstract
Celiac disease is an autoimmune disease initiated by an allergic reaction to gliadin a component of the protein gluten that is found in wheat and other grains. Vitamin D is a prohormone with a number of biochemical functions including immunomodulatory functions in its active form. Supplementation with large doses of vitamin D induces symptoms that are similar to celiac disease in some of the population. Some researchers have noted that consumption of large doses of oral vitamin D early in life is associated with increased incidence of allergic diseases later in life. An examination of celiac disease suggests that an allergy is fundamental to its development and it features Th2 cytokine elevations which typically characterize allergic diseases. In addition it has comorbidity with allergic diseases where exposure to large doses of vitamin D early in life is a risk factor. This raises the possibility that large doses of vitamin D early in life could be a risk factor for inducing celiac disease later in life as well. The comorbidity between Williams syndrome, which is characterized by spikes in blood levels of vitamin D, and celiac disease gives additional credence to this hypothesis. Epidemiological evidence supports this hypothesis as well. Vitamin D consumption among the young and celiac disease prevalence are high in Sweden, Finland, and the United States. Vitamin D consumption among the young and celiac disease prevalence are low in Russia and Germany. The timing of the increases in prevalence in the United States and Sweden also coincides with increasing vitamin D consumption. This is most striking in Sweden where a law required significant vitamin D fortification of food starting in 1983 and the start of the celiac epidemic in Sweden has been independently dated from 1984. This hypothesis also provides a potential explanation for some seemingly contradictory results in the literature regarding breastfeeding and risk of celiac disease.

Keywords: Th2, allergy, allergic, immunology, milk, formula

Introduction
Celiac disease is an autoimmune disease of the small intestine initiated by an allergy to gliadin which is a component of the protein gluten found in wheat and some other grains [1]. There is significant variability in the estimates of prevalence of celiac disease, but as of 2012 one estimate was approximately 1% of the world-wide population [2], with significant variation between countries [1,2]. Looking at similar cohorts over time shows that the prevalence of celiac has increased significantly in recent decades in some countries [3-5]. Ludvigsson and Green recently hypothesized that there is a “missing environmental factor in celiac disease” that is responsible for this increase [6]. Vitamin D is a fat soluble vitamin that in its active form enhances calcium absorption, raises blood levels of calcium, and affects the immune system. It can be synthesized in the skin through sunlight and in this sense it is not a vitamin as enough can be synthesized from sunlight to promote good health. Vitamin D produced in this way will not result in toxicity due to self-regulating mechanisms. Vitamin D may also be absorbed orally, where there is no similar self-regulating absorption mechanism [7].

Hypothesis
Biologic plausibility
Celiac is typically characterized by atrophy of the intestinal villi and is frequently accompanied by abdominal pain, bloating, diarrhea, constipation, and sometimes weight-loss [8-10]. In rats where extremely high doses of oral vitamin D have been tested (2 mg/kg per day orally), the digestive effects include
42,000 IU per week through supplementation. One need not An allergic disease is a disease in which a hypersensitivity
infants and toddlers in much of the developed world con-
states infant formula averages about 535 IU per liter, whole
vitamin D have been consumed, gastrointestinal effects have
been significant. For example, in one trial of supplementa-
tion in women who were at risk of breast-cancer, in a cohort
receiving 30,000 IU per week for one year, 9% experienced
abdominal distension, 14% experience abdominal pain, 27%
experience constipation, 9% experienced diarrhea, and 18%
experienced nausea. By comparison the only gastrointestinal
complaint observed in a lower dose (20,000 IU) cohort was
abdominal pain in 11% [14].

Yet even at more modest doses (400 IU per day and 700 IU
per day), some in human trials of vitamin D supplementation
have dropped out due to complaints of stomachache, diarrhea,
or constipation [15, 16]. In one trial of vitamin D supplementa-
tion among 171 girls in Finland one girl who started supple-
menting was not able to complete the trial due to the onset
of celiac disease [17]. One may disregard this example alone
as coincidental, but the other evidence above strongly sug-
gests that large doses of vitamin D will cause effects that are
similar to the symptoms of celiac disease in some of the popu-
lation and hints of such effects occur at more modest doses.

Infants and toddlers in much of the developed world con-
sume large amounts of vitamin D relative to that which is
obtainable through natural sources. For example, total vitamin
D in human milk is about 45 IU per liter and in unfortified cows’
milk is about 40 IU per liter [18, 19]. By comparison in the United
States infant formula averages about 535 IU per liter, whole
milk averages about 525 IU per liter, the standard daily dose of
vitamin D drops recommended for breastfed infants starting
at birth is 400 IU, and the most popular brand of children's
multivitamin contains 600 IU [20-23]. In addition substantial
doses of vitamin D are also present in fortified foods such as
cereals, orange juice, and yogurt [24, 25]. These doses are
large by comparison to those available in human milk and
provided at high frequency to infants and toddlers who are
small by weight. If one assumes that the effects of a dose are
proportional to IUs consumed per pound of weight, then a 10
pound infant receiving the standard 400 IU per day dose via
vitamin D drops is equivalent to a 150 pound adult receiving
42,000 IU per week through supplementation. One need not
make this simplifying and perhaps unjustified assumption to
see that the doses given to infants and toddlers are large.
So it seems likely that the aggressive vitamin D supplementa-
tion and fortification which typically accompanies infancy
in the United States will induce gastrointestinal effects in
some infants and toddlers as seen in some adult trials and
that these effects as already mentioned mirror many of the
symptoms of celiac disease.

Oral vitamin D as a risk factor for allergic disease

An allergic disease is a disease in which a hypersensitivity

immune reaction is fundamental to its development [26]. The
relationship between vitamin D and allergic disease is complex
[27]. Littonjua among others has suggested that low serum
levels of 25-hydroxy vitamin D are a causative factor in allergic
disease [28]. Yet Wjst has highlighted that both extremely low
and extremely high serum levels of 25-hydroxy vitamin D are
associated with allergic disease [29]. For example while Baek
et al., found that low serum levels are associated with atopic
allergy in infancy [30], Heimbeck et al., found that children
and adolescents with high serum levels had higher rates of
atopic dermatitis than those with low vitamin D serum levels
[31], and Kang et al., found that 25-hydroxy vitamin D serum
levels were correlated with dust mite allergy based on serum
analysis [32].

Other research suggests that oral vitamin D supplementa-
tion in the young is associated with allergic disease in later
life. For example Hypponen et al., found that oral vitamin D
supplementation early in life is associated with higher rates
of allergies, asthma, and atopic dermatitis in later life [33]. Nja
et al., found that early life supplementation with cod liver oil
and vitamins was associated with increased prevalence of al-
ergic sensitization and asthma later in life [34]. Cod liver oil
contains some vitamin D and supplemental vitamins often
do as well. Back et al., also found that oral vitamin D supple-
mament in infancy results in greater prevalence of atopic
allergies in later life [35]. Interestingly Kull et al., found that
vitamin A and vitamin D supplementation in water-soluble
form were much more likely to be associated with allergic
disease in children than the same vitamins in peanut oil [36].

Wjst found that low levels of allergies among those in
isolated rural communities in Bavaria could be explained by
low levels of oral vitamin D consumption in those same com-
unities [37]. In separate research Wjst provided evidence
that allergic diseases were rare before the introduction of
vitamin D supplementation and suggested that oral vitamin
D is the key factor in the allergy pandemic that has engulfed
the civilized world [38].

There is a strong theoretical basis for why large doses of
oral vitamin D may induce allergic diseases in some as sug-
gested by the empirical evidence. Th1 cells focus the immune
system primarily on intracellular pathogens, while Th2 cells
focus the immune system primarily on extracellular pathogens
[39]. Consumption of oral vitamin D generally induces a Th2
skew to the immune system [40]. Therefore consumption of
oral vitamin D will tend to elevate Th2 cytokine activity which
will upregulate immune reactions to external stimuli. So it
should not be surprising that allergic conditions typically
feature elevated levels of Th2 cells. Among these are atopic
dermatitis and asthma [41, 42].

Despite the empirical evidence outlined above and the
theoretical rationale, other trials suggest that modest sup-
plementation of oral vitamin D may decrease the risk of or
ameliorate the symptoms of certain allergic diseases [43].
While this may seem contradictory it seems plausible that
the effect of supplementation depends upon a number of factors including dosage, duration, age, weight, sunlight exposure, antigen exposure, past antigen exposure, stores of vitamin D in the body, and maternal vitamin D levels in utero. In addition vitamin D has many effects on the immune system and they act over different timeframes. For example, vitamin D downregulates Th17 cell production which decreases the current levels of inflammation in some allergic diseases [44]. Yet vitamin D through Th2 cytokines upregulates production of B cells that imprint on antigens and form enduring humoral immune memory [45]. So the effect of vitamin D supplementation in some circumstances may be an immediate decrease in inflammation through downregulation of Th17 while simultaneously inducing or reinforcing a lifelong allergy through B cell upregulation. For this reason one would expect contradictory long term and short term effects in some allergic diseases from oral vitamin D supplementation. In any case the evidence above suggests that oral vitamin D supplementation among the young increases the risk of allergic diseases over long time frames for some of the population via upregulation of Th2 cytokines.

**Celiac as a Th2 mediated allergic disease**

While celiac is often categorized as an autoimmune disease, an excessive immune reaction to the protein gliadin is fundamental to its development. In fact an IgA blood test for antibodies to gliadin is often the initial step in diagnosis [46]. So while it is not normally categorized as an allergic disease, it is an allergic disease based on the classical definition of allergy as an excessive immune reaction to external stimuli [47]. In fact Dietert et al., consider celiac to be primarily an allergic disease with an autoimmune component [48]. Interestingly while most have considered activation of Th1 cell cytokines to be of greater importance in celiac disease, it appears that elevations in Th2 cell cytokines are also fundamental to it. Lahat et al., found that both Th1 and Th2 cell cytokines are activated in celiac [49]. Manavalan et al., found higher levels of Th2 cell cytokines in those with celiac disease than controls and that those who had been on a gluten free diet less than a year had higher levels of Th2 cytokines than those who had been on a gluten free diet for more than a year [50]. Manavalan et al., commented that the role of Th2 cell “cytokines in [celiac] pathogenesis is not well understood, but immune regulatory functions at the mucosal level have been suggested”[50]. This suggestion was inferred from a study by Chowers et al., analyzing cytokine levels in colonic mucosa immediately following gluten challenge [51]. Separately Mastrandrea et al., found that among a group of 28 celiac patients all but three had a Th2 skew expressed in the chemokine receptor pattern of their circulating CD3+CD4+ lymphocytes [52].

Kohler et al., has described the IgG and IgA antibody response to gluten that is fundamental to celiac disease as a humoral response caused by the activity of B cells, which are upregulated by Th2 cytokines [53]. Recently Corouge et al., have presented evidence that this humoral response in many cases may be associated with a Th2 induced allergy to candida albicans which results in cross reactivity with gluten leading to the development of celiac disease [54].

This data shows that celiac is an allergic disease using the broad definition of allergy and Th2 cell activation plays a significant role in its etiology. So based on the prior section and specifically based on the effect of vitamin D supplementation on Th2 cytokines it would seem that large doses of vitamin D among the young could be a risk factor for inducing celiac disease as well.

Ress et al., has found that celiac is about four times more common among children with atopic dermatitis [55]. Ludvigsson et al., has found that asthma is about 1.6 times more common among those with celiac [56]. The comorbidity with celiac of both of these allergic diseases suggests the possibility of a common underlying risk factor. As previously noted oral vitamin D supplementation among the young has been found to be a risk factor for inducing both atopic dermatitis and asthma based on the work of Hypponen et al., and Back et al., among others [33,35]. So the high comorbidity with celiac also suggests the possibility that oral vitamin D supplementation among the young could be a risk factor in inducing it as well.

**Williams syndrome**

Williams syndrome is a genetic syndrome that features hypercalcemia, short stature, narrowing of the blood vessels of the heart, modest deficits of intelligence, and sometimes autism [57]. It is typically caused by a deletion of part of chromosome 7 including the WSTF gene. This results in spikes in 1,25-dihydroxy vitamin D in the blood which cause the hypercalcemia [58]. Given background on vitamin D and allergic disease from a prior section, it should not be surprising that Annaz et al., in a survey on Williams syndrome patients found that asthma and allergies are often comorbid with it as well [59]. Williams syndrome also features high comorbidity with celiac disease. Giannotti et al., found in a cohort of Italian patients with Williams syndrome that 9.5% tested positive for celiac compared to 0.54% of controls [60]. As a defining characteristic of Williams syndrome is its spikes in 1,25-dihydroxy vitamin D in the blood, this supports the possibility that such spikes in vitamin D metabolites may be a risk factor for celiac disease as well. As consumption of large doses of vitamin D may increase levels of vitamin D metabolites in the blood, this further suggests that consumption of large doses of vitamin D among the young could be a risk factor in inducing celiac disease.

**Epidemiology of celiac disease and vitamin D**

**United States**

Murray et al., found that the prevalence of celiac disease had increased substantially between the 1950s and the year 2000 based on a cohort from Olmsted County, Minnesota. In addition Murray et al., found that much of the increase occurred in recent decades [3]. Some of this increase could
be explained by increased detection of celiac in the population. However, using historically collected blood samples from the army between 1948 and 1954 and comparing them to blood samples collected between 2006 and 2008 also in Olmsted County, Rubio-Tapia et al., found that the incidence of undiagnosed celiac disease had increased by a factor of four [61]. In other words, while the rate of diagnosis of celiac disease has increased substantially, the percent of the population that has celiac and remain undiagnosed has also increased substantially. So there has been a true increase in the prevalence of celiac disease. Using the same Minnesota population Ludvigsson et al., has found that the incidence of celiac has continued increasing through 2010. Specifically, between 2000 and 2010 there was about a 70% increase in the incidence [4]. A recent study based on serological testing of a mostly adult population estimated prevalence of celiac in the United States at 1 in 113 [62]. Since the 1930s vitamin D supplementation of milk has been common in the United States [63]. As noted in a prior section most infants and toddlers receive large amounts of oral vitamin D through fortification and supplementation. However, this is primarily a modern phenomenon. Here are some key events with dates that have pushed consumption of oral vitamin D among the young in the United States to high levels: 1. 1968: Flintstones, the first children's multivitamin to develop a significant market were introduced. Flintstones vitamins were fortified with 400 IU of vitamin D during the 1980s and 1990s and are now fortified with 600 IU of vitamin D [23,64-66]. 2. 1980: The Infant Formula Act required all infant formula to include at least 40 IU / 100 Kcal (about 280 IU per liter) of vitamin D [67]. It also established penalties for manufacturers who do not meet the minimum level. Zhou et al., among others has observed that it created incentives for over-fortification [68] and indeed testing since the passage of the act has found that infant formula is typically significantly over-fortified relative to what the act required [20]. 3. June 1992: American Academy of Pediatrics Committee on Nutrition published a recommendation that all non-breast fed infants be fed formula through 12 months of age [69]. This increased the amount of formula consumed [70]. 4. December 1992: Due to vitamin D levels in most milk samples being significantly below levels listed on the label, the FDA decreed that vitamin D levels in milk were to be targeted at levels significantly above the label which resulted in much higher levels of fortification of milk [21,71,72]. 5. April 2003: American Academy of Pediatrics published guidelines for vitamin D consumption of 200 IU per day starting at 2 months of age for infants who are breastfed [73]. 6. November 2008: American Academy of Pediatrics raised the guidelines to 400 IU per day starting at birth further increasing the consumption of vitamin D by those who are breastfed [22]. These data suggest that vitamin D consumption among the young in the United States rose gradually through the 1970s and 1980s and increased dramatically in the 1990s and has continued increasing since. This pattern is very similar to the gradual increase in celiac rates through the 1980s which preceded much greater increases in celiac prevalence in recent decades. Thus, the trend in vitamin D consumption by the young in the United States is consistent with the hypothesis that vitamin D consumption by the young may be a risk factor for celiac disease. Sweden Sweden has very high rates of celiac disease. Myleus et al., found among a group of 12-year olds the rate was 1 in 34 based on serum testing [74]. Sweden did not always have high rates of celiac disease though. In fact researchers date the onset of the celiac disease epidemic in Sweden to 1984 when rates increased significantly [5]. Vitamin D consumption is very high in Sweden. About 75% of Swedish infants receive vitamin D drops, and Swedish public health recommendations are that they be taken until 6 years of age [75]. As of 2009 among American infants about 16% received vitamin D drops [76]. In addition Swedish children receive significant amounts of vitamin D through fortified foods including porridge, fortified margarine, milk, and milk cereal drinks [75]. Historically Sweden had not required whole milk and spreads to be fortified with vitamin D, but in 1983 Sweden by law required whole milk, all butter, and all margarine to be fortified with vitamin D [77]. This decision undoubtedly led to a significant increase in consumption of oral vitamin D. So if the hypothesis regarding vitamin D and celiac is true one would expect a surge in celiac cases in Sweden starting in 1984 which is exactly what happened. Interestingly there was a decline in new celiac cases in Sweden in the mid-1990s. Myleus attributed this to earlier introduction of gluten in small amounts during breastfeeding, increased duration of breastfeeding, and decreased gluten content of cereals [5]. More recent research has called into question these explanations as controlled trials in other populations have found that neither the timing of introduction of gluten nor breastfeeding have significant effects on incidence of celiac disease [6]. However in the case of Sweden those who are breastfed received less vitamin D than those who formula fed as both receive vitamin D drops [75] and formula is also fortified with significant doses of vitamin D. In addition cereals which are competing sources of calories are fortified with vitamin D in Sweden [75]. Therefore, in Sweden these steps would have resulted in aggregate in less vitamin D consumed and especially less vitamin D consumed at the time of introduction of gluten. Based on evidence presented previously on allergic disease, it may be inferred
that the combination of a Th2 skew to the immune system at the time of antigen introduction makes the development of allergy to the antigen more probable. If this is true, then the reduction in the incidence of celiac disease in the mid-1990s coincident to the changes in feeding practices in Sweden is also consistent with the vitamin D hypothesis.

**Finland**

Finland has a high prevalence of celiac disease. Kondrashova et al., found that 1 in 107 Karelian children in Finland had celiac disease based on biopsy following serologic testing. Using a serologic definition solely would give a higher estimate of prevalence [78]. Tylavsky et al., found in an examination of vitamin D consumption in Denmark, Finland, Ireland, and Poland that Finland had the greatest per capita vitamin D consumption among the young [79]. In Finland 86% of infants take vitamin D drops as they are provided by the Finnish Health Service [80,81]. In addition cooked cereals, margarine and milk are fortified with vitamin D [80]. So the high prevalence of celiac and high levels of vitamin D consumption in Finland also fit with the hypothesis.

**Russia**

The prevalence of celiac disease in Russia is low. Kondrashova’s study cited above was designed to measure the difference in celiac prevalence between Russian Karelian and Finnish Karelian children. From this study, the prevalence among Russian Karelians was 1 in 496 based on biopsy following serological testing [78]. This is much lower than the prevalence among Finnish Karelians cited above [78]. Russian food is not fortified with vitamin D and historically there has been little vitamin D supplementation in Russia [82,83]. So consumption of vitamin D among children in Russia is low. So the low vitamin D consumption and low celiac prevalence in Russia also fits the hypothesis.

**Germany**

The prevalence of celiac disease in Germany is relatively low. Unfortunately, no recent study in the literature appears to document prevalence among children in Germany. However, Kratzer et al., found that 1 in 270 adults in Germany tested positive for celiac disease based on serology [84]. While there are some exceptions, vitamin D fortification of foods is generally prohibited in Germany [85]. So based on Germany’s negligible vitamin D fortification and modest prevalence of celiac, it also fits the hypothesis.

**Summary**

The epidemiological data, which are summarized in (Table 1), illustrate that celiac prevalence is highest in countries that have the highest vitamin D consumption among the young and increases in celiac prevalence appear to be associated with increases in vitamin D consumption.

**Breastfeeding and celiac**

A number of researchers have looked at the question of whether breastfeeding reduces the risk of celiac disease. Greco et al., using an Italian cohort from the 1980s found that breastfeeding was protective [86]; Ivansson et al., using a Swedish cohort from the 1990s also found that breastfeeding is protective [87]; yet more recently, Lionetti et al., found in a large randomized trial among genetically at risk Italian infants which began enrolling participants in 2003 that breastfeeding offers no protection against celiac [88]. What could explain these seemingly contradictory results?

Consider the oral vitamin D recommendations in place at the time and location of each of these studies. Swedish public health officials had begun recommending vitamin D drops for all infants independent of whether or not they are breastfed starting in 1978 [75]. Italian physicians began recommending vitamin D drops be given to breastfed babies starting around 1995 [89]. If the hypothesis regarding vitamin D being a risk factor for celiac were true, what would one expect from the study results? Few if any of the Italian children in Greco’s study would have received vitamin D drops as it predated recommendations regarding supplementation in Italy. As infant formula is fortified with vitamin D, those receiving infant formula would have consumed more vitamin D as infants. Hence one would expect them to have had a higher rate of celiac which agrees with what Greco et al., found. The vast majority of the children in Ivansson’s study would have received vitamin D drops based on Swedish recommendations in place at the time. As infant formula is fortified with vitamin D as well those that received it would have received more vitamin D in total than those who were breastfed. Hence those receiving infant formula would

| Country | Prevalence | Population | Testing | Epidemiology | Assessment | Consumption | Comments |
|---------|------------|------------|---------|--------------|------------|-------------|----------|
| USA     | 1:113      | Adults & Children | Serological | Up in recent decades | High | High | Up in recent decades |
| Sweden  | 1:34       | Twelve year olds | Serological | Big increase in 1984 | Very high | Very high | Big increase in 1983 |
| Finland | 1:107      | Karelian children | Biopsy | -- | High | High | D drops from Health Service |
| Russia  | 1:496      | Karelian children | Biopsy | -- | Low | Low | No fortification |
| Germany | 1:270      | Adults | Serological | -- | Low | Low | No fortification |

Table 1. Celiac epidemiology and vitamin D consumption.
be expected to have a higher rate of celiac which agrees with the results. In Lionetti's study it seems probable that many of the breastfed infants would have received vitamin D drops while formula fed infants would not have based on the Italian recommendations. Hence the vitamin D exposure of these two groups may have been comparable which would have resulted in comparable levels of celiac disease which is what was found.

So the hypothesis that vitamin D is a risk factor for celiac offers a plausible explanation for the seemingly contradictory results regarding breastfeeding and celiac in the literature.

**Two counter arguments examined**

A skeptical reader might question whether oral vitamin D could be a risk factor in inducing celiac as a number of cases of vitamin D deficiency have been observed among those with celiac. For example Kemppainen et al., found that the blood level of 25-hydroxy vitamin D in those with celiac were lower on average than in the general population [90]. First the levels of vitamin D in Kemppainen's study were measured in an adult population after the onset of celiac disease. If one looks in younger populations one sees a different result. For example, Villanueva et al., found marginally higher 25-hydroxy vitamin D levels among children with celiac than among controls but the difference seemed to be associated with differences in body mass [91]. Second, Bickle has suggested that elevated 1,25-dihydroxy vitamin D may be common in celiac disease [92]. Therefore the lower levels of 25-hydroxy vitamin D seen in some adults does not conflict with the hypothesis that significant consumption of oral vitamin D among the young may be a causative factor in inducing celiac disease.

Others might question how oral vitamin D could play a role in inducing celiac disease since celiac disease has significantly greater than average comorbidity with some autoimmune diseases such as type 1 diabetes [93] and evidence suggests that supplementation with vitamin D in the young reduces the risk of type 1 diabetes [94]. First, comorbidity between autoimmune and allergic diseases is not uncommon. For example lupus which is considered an autoimmune disease has high comorbidity with atopic dermatitis, an allergic disease [95]. Similarly the autoimmune disease alopecia areata has high comorbidity with atopic dermatitis [96] and the autoimmune disease Kawasaki disease is often comorbid with allergic diseases as well [97]. So celiac's greater than average comorbidity with certain autoimmune diseases does not preclude it from also being an allergic disease.

Second, comorbidity data suggest that supplementation with vitamin D may have very different effects on celiac disease risk and type 1 diabetes risk. As previously highlighted Ress et al., found that celiac is about four times more prevalent in those with atopic dermatitis [55], but Thomsen et al., found that type 1 diabetes has much less than average comorbidity with atopic dermatitis [98]. In addition the study cited above on type 1 diabetes risk reduction from oral vitamin D relies on the same 1966 Finnish birth cohort data and has the same

**lead author, Hypponen, as a study cited earlier in this paper that suggests that oral vitamin D in children increases risk of allergic disease [33,94]. In other word, if one believes the data on oral vitamin D supplementation and disease susceptibility derived from the 1966 Finnish birth cohort, and comorbidity with atopic dermatitis is relevant to the determination of risk factors, then the data suggest that celiac and type 1 diabetes should have opposite risk profiles with respect to the effect of vitamin D supplementation. As oral vitamin D supplementation in the young reduces the risk of type 1 diabetes and increases the risk of atopic dermatitis, one would therefore expect it to increase the risk of celiac disease.

**Conclusion**

A wealth of evidence supports the hypothesis that significant consumption of oral vitamin D among the young is a risk factor for inducing celiac disease. Exposing infants and toddlers to large doses of oral vitamin D has been found to be a risk factor for inducing allergic diseases including atopic dermatitis and asthma both of which have a high comorbidity with celiac. Celiac is an allergic disease using a broad definition of allergic disease and elevations in Th2 cytokines have been shown to be fundamental to celiac disease. As Th2 cytokines are upregulated by oral vitamin D, this suggests that oral vitamin D could be a risk factor in inducing celiac disease as well. The case of Williams syndrome and its spikes in 1,25-dihydoxy vitamin D and high comorbidity with celiac further supports this hypothesis. Epidemiologically, the countries that have the most aggressive fortification and supplementation policies for vitamin D are the countries where the prevalence of celiac is greatest. In addition the increase in supplementation and fortification of vitamin D in recent decades in the United States corresponds with the increasing rates of celiac disease seen in the United States during the same time period. Also the Swedish celiac disease epidemic starting around 1983 corresponds well to implementation of widespread vitamin D fortification in Sweden dating from 1983. Additional research will be needed to confirm this hypothesis.

**Competing interests**

The author declares that he has no competing interests.

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