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REVIEW

Potential links between the emerging risk factors for food allergy and vitamin D status

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Summary

A variety of hypotheses have been proposed to explain the recently described increase in food allergy among children living in developed countries. In this study, we summarize the emerging risk factors for IgE-mediated food allergy in early life, and then review the evidence for and against an association between low vitamin status (VDS) and food allergy. We consider whether each of the epidemiological variables that have been associated with food allergy may also be associated with VDS; and argue that future studies must adequately account for the potential relationships between risk factors for food allergy and VDS, and must also discriminate between vitamin D derived by sun exposure, diet and oral supplementation.

Introduction

The rise in prevalence of food allergy is a phenomenon that has occurred in the last 20 years with evidence of increased hospital admissions for food-induced anaphylaxis, particularly under the age of 5 years [1], a dramatic rise in epinephrine autoinjector prescription [2] and most recently reports from developed countries that up to 10% of infants have evidence of challenge-proven food allergy [3].

Broadly speaking, it has been proposed that the increase in food allergy in early life among children living in the developed world may relate to factors associated with hygiene and microbial experience, infant-feeding practices, maternal dietary intake and more recently, vitamin D status (VDS) [4–6]. At first glance, these hypotheses appear disparate. It is, however, plausible that low VDS may represent a point of confluence for some of the epidemiological variables that we and others have identified as risk factors for food allergy. Alternatively, relationships between food allergy risk factors and VDS may be a source of confounding. In either case, the potential relationships between the emerging risk factors for food allergy and VDS warrant consideration.

Emerging risk factors for IgE-mediated food allergy

The Australian Healthnuts study has recently published data showing the highest prevalence of challenge-proven infant food allergy in the world [3]. In this population-based cohort study, in which food allergy status was determined by formal food challenge, we have examined the hypotheses that the risk of food allergy is reduced by (a) factors associated with increased microbial exposure (the 'hygiene hypothesis') and (b) early introduction of allergenic solids. With regard to microbial exposure, dog ownership, early attendance at child care in the first 6 months of life and an increased number of siblings were all independently protective against egg allergy (the most common food allergy in our cohort) [7]. We also found that early introduction of egg (between 4–6 months) was highly protective against later-onset egg allergy [8]. Less directly, other groups have found an association between proxy markers of

food allergy, parent-reported food allergy and/or food antigen sensitization and a range of epidemiological variables including lower maternal intake of oily fish during pregnancy [9], black American ethnicity [10] and obesity [11, 12].

Is low VDS a risk factor for food allergy?

A putative link between low VDS and food allergy is a plausible hypothesis worthy of evaluation because vitamin D is an important immunoregulator, and low VDS is common among modern populations and amenable to relatively simple public health interventions. To date, however, no study has directly linked low VDS with challenge-proven IgE-mediated food allergy and the existing indirect evidence is conflicting.

The case for a link between low VDS and food allergy

Concurrent with the increase in food allergy over recent decades is a well-documented temporal decrease in vitamin D levels in many parts of the world [13]. Sunlight-derived ultra violet radiation (UVR) is estimated to provide over 90% of vitamin D in humans [14]. Low VDS has become more common in modern communities over time due to increased indoor electronic leisure activities, skin cancer concern, personal safety issues and the modern built environment [15]. Indeed, in a number of centres, around a third of pregnant women [16, 17], infants [17] and young children [18] have been found to have a serum 25 hydroxyvitamin D (25(OH)D) level in the 'insufficient' range (less than 50 nmol/L [19, 20]). Several observations suggest the concordant increase in low VDS and food allergy may be linked. Autumn or winter birth appears to be associated with an increased risk of food allergy. In a study from Boston, children attending the emergency department with a food-related acute allergic reaction were more likely to have been born in autumn/winter than spring/summer ($P = 0.002$) [21]. This season of birth pattern may reflect altered ambient UVR levels, and hence, seasonal differences in vitamin D stores. In both North America and Australia, there is also a latitude gradient for the prescription of epinephrine autoinjectors for the treatment of anaphylaxis (higher rates further from the equator where UVR ambient levels are lower) [22, 23]. This appears to be independent of longitude, physician density or socio-economic status. A similar latitude gradient was found in the prescription of hypoallergenic infant formulas in Australia [24]. More recently, we have also described a latitude gradient for parent report of food allergy but not asthma in a population cohort of 10 000 children in Australia. After adjusting for confounders, those residing in the most Southern states were two to three times more likely to have peanut or egg allergy than those residing in the North and closer to the Equator (Osborne et al., JACI revisions requested and submitted).

Of course, UVR has a range of immunological effects, in general enhancing innate immune responses and suppressing adaptive immune responses, and only a proportion of these effects are mediated by vitamin D [25]. Therefore it is entirely possible that sunlight exposure may influence the risk of food allergy via mechanisms other than cutaneous synthesis of vitamin D.

At the individual level, data from National Health and Nutrition Examination Survey (NHANES 2003–2006) demonstrated an inverse association between 25(OH)D levels and allergic sensitization to peanut and shrimp, but not egg or cow's milk [26]. Children with 25(OH)D less than 37.5 nmol/L of blood were more likely (odds ratio = 2.39; 95% CI, 1.29–4.45) to have allergic sensitization to peanut than children with 25(OH)D levels greater than 75 nmol/L. In the preceding NHANES (1988–1994), however, there was no association between peanut sensitization and vitamin D level among subjects aged 12–19 years [27]. A possible reason for the discrepancies between NHANES 1988–1994 and 2003–2006 is the finding that 25(OH)D data from the 2003–2006 survey may have been affected by drifts due to reagent and calibration lot changes in the assay [28]. Indeed, variation in the laboratory measurement of vitamin D is an important general consideration when comparing vitamin D levels from different studies [29].

Gene–environment interactions may be relevant. A recent study found that while vitamin D deficiency at birth (defined by the authors as a cord blood 25(OH)D levels < 11 ng/mL) was not associated with subsequent food sensitization overall, associations were evident among children with four specific genotypes, including CYP24A1 (rs2762934) [30], the gene regulating the degradation of the active form of vitamin D [31]. The finding that an association between vitamin D status and food allergy is modified by vitamin D-related gene polymorphisms provides some evidence against the assertion that the putative association between low VDS and food allergy is simply due to confounding.

The case against a link between low VDS and food allergy

Perhaps the most striking epidemiological evidence against a link between low VDS and food allergy is the parallel increase in food allergy and vitamin D supplementation that has occurred in developed countries. Wjst points out that English cities in the 1900s were characterized by a high rate of rickets due to hypovitaminosis D and a low rate of documented allergic disease [32]; and further, that from the 1980's to 2000 vitamin D was introduced nationwide in all industrial-

ized countries as a supplement to industrial baby food, and during the same period, the allergy prevalence has reached an all-time high [33].

In support of Wjst's argument, several studies have found that oral vitamin D supplementation may increase the risk of allergic disease in general, but not food allergy specifically. Hypponen et al. found in the Northen Finland Cohort that a history of regular vitamin D supplementation during the first year of life was associated with atopic sensitization (OR 1.46, 95% CI 1.4–20), allergic rhinitis (OR 1.66, 95% CI 1.1–1.6) and asthma (OR 1.35, 95% CI 0.99–1.8) at age 31 years [34]. However, they were unable to adequately discount confounding factors or reverse causation. Similarly, a cross-sectional analysis of a population-derived sample of 558 Australians aged 18–61 years found that a history of oral supplementation with cod liver oil (high in vitamin D) during childhood was associated with an increase in the odds of asthma and hayfever (OR 2.87, 1.00–8.32) [35]. This was independent of a range of potential confounding factors, but once again, may have been the result of reverse causation. Finally, Kull et al. found that supplementation of vitamin A and D in water-soluble form, as compared to the same vitamins in peanut oil, was associated with a twofold increase in food sensitization and food reactions during the first 4 years of life [36]. The mechanism is unknown, but it should be noted that the immune effect of vitamin D from oral supplementation may differ to that of vitamin D from other sources such as sun exposure [33].

Studies have also reported an association between elevated maternal 25(OH)D during pregnancy and allergic outcomes in general, but once again, not food allergy specifically. In a prospective study of 466 children who had information on maternal 25(OH)D concentrations in late pregnancy, 440 (94%) were followed-up at the age of 9 months, and 178 (38%) at 9 years [37]. At the 9-month review, infants whose mother's 25(OH)D was greater the 75 nmol/L, compared with those less than 30 nmol/L, were more likely to have visible eczema (odds ratio 3.26; 95% CI 1.15–9.29), and there was a trend towards greater likelihood of atopic eczema (modified UK Working Party criteria) (OR 1.62; 95% CI 0.67–3.89). However the numbers were small: across these two 25(OH)D categories, only 20 infants had visible eczema and 23 had atopic eczema. There was no reported difference in eczema rates between infants whose mother's 25(OH)D was in an intermediate range (30–49, or 50–74 nmol/L) in comparison to those in the lowest or highest categories. At the 9-year review, maternal 25(OH)D 75 nmol/L or greater was positively associated with parent-reported 'asthma', but not parent-reported 'eczema'; but by 9 years, the follow-up rate was only 38% and the outcome measures had low discriminatory value.

To reconcile these conflicting data regarding vitamin D and food allergy, it has been proposed that both high and low VDS may predispose to allergic disease – a so-called 'u-shaped' association. A study published in 2009 conducted among 7,288 participants aged 45 years found that relative to the reference group (25(OH)D 50–74 nmol/L), serum IgE levels were elevated among participants with 25(OH)D levels less than 25 nmol/L or greater than 135 nmol/L [38]. Although the data satisfied a test for non-linear association (*P*-value for curvature = 0.0001), fewer than 1% of participants actually had a 25(OH)D level greater than 135 mmol/L. Of greater relevance, a recent study among 219 participants involved in the Tuscon Infant Immune Study found that relative to the reference group (25(OH)D 50–74.9 nmol/L) both low ($<$ 50 nmol/L) and high ($\geq$ 100 nmol/L) cord blood 25(OH)D levels were associated with increased serum IgE levels and increased aeroallergen sensitization during the first 5 years of life [39]. There was no association between 25(OH)D levels and the clinical outcomes of allergic rhinitis or asthma – although this aspect of the analysis was underpowered. To date, no study has specifically linked both high and low VDS with either food allergy or its proxy markers.

A potential explanation of a u-shaped association between 25(OH)D and allergy is that 25(OH)D may promote a TH2 immune skew at the systemic level, while simultaneously promoting an anti-inflammatory effect at the local/organ level [40], and the balance between these effects may vary at different 25(OH)D levels. Alternatively, the apparent U-shaped association may simply be evidence against the more biologically common linear dose–response relationship, and could therefore be evidence against a causal association between VDS and allergy.

While the potential association between elevated vitamin D and allergic outcomes are insufficient to dismiss the hypothesis that low VDS is a risk factor for food allergy, they certainly highlight the need for improved data before proceeding with interventional trials or changes in public health policy.

Are the emerging risk factors for food allergy linked to low VDS?

It is important to consider whether the emerging risk factors for food allergy may also influence the likelihood of low VDS, and/or whether low VDS may influence the child's response to the emerging risk factors. Such links would introduce the possibility of confounding and or mediating pathways. The potential links between the emerging risk factors for food allergy and vitamin D are discussed below according to whether the risk factor for food allergy might be linked to low VDS

via (i) oral intake of vitamin D, (ii) sun exposure and cutaneous synthesis of vitamin D, (iii) bioavailabilty or metabolism of vitamin D; or in terms of the (iv) biological activities of vitamin D (potentially modifying the host response to a given risk factor) (Table 1).

Sun exposure and cutaneous synthesis of vitamin D

The emerging risk factors for food allergy, which may also influence cutaneous synthesis of vitamin D include living at higher latitude, winter birth, Black American ethnicity, pet ownership and obesity. Vitamin D (calciferol) refers to both cholecalciferol (vitamin D_3) and ergocalciferol (vitamin D_2). Cholecalciferol is produced by the action of ultraviolet B light (UVB) on 7-dehydrocholesterol in the skin of humans. Sunlight is estimated to provide over 90% of vitamin D in humans [14]. Skin synthesis of vitamin D varies with latitude, season, skin colour, UV protection (clothing, shade, sunscreen) and time spent outside.

As described above, studies have found a latitude gradient in the prescription of epinephrine autoinjectors and hypoallergenic formulas. It has also been reported that food allergy is more common among ethnic groups with darker skin colour [10]. The skin pigment melanin has evolved as a natural sunscreen and effectively absorbs UVB photons; and adults with dark skin require two to seven times the amount of UVB compared with someone with light skin to achieve similar vitamin D levels [55–59]. Thus, those with darker skin pigmentation are well recognized to be more likely to have a lower vitamin D status. Several other allergy-linked factors could potentially relate to the major antecedent of vitamin D, sun exposure, through their influence on the amount of time that the mother and child spend outside [60]. For example, we have recently found that (i) dog ownership and (ii) a greater number of siblings are each associated with reduced risk of food allergy (dog ownership: adjusted OR 0.57, 95% CI 0.33–0.98, increasing number of siblings: OR 0.80, 95% CI 0.65–0.98) [7]. While these factors may operate via other pathways, such as microbial exposure, it is also plausible that pets and siblings are associated with increased vitamin D levels. For example, dog ownership is associated with greater outdoor physical activity [41, 42] (and hence likely sun exposure). Similarly, farm living has been associated with a reduced risk of allergic disease in general [61] (although not food allergy specifically), and while this is thought to relate to microbial exposure, it is also likely that farmers spend more time outdoors and have greater UVB exposure than non-farmers[43].

Obesity has also been identified as a potential risk factor for both food allergy [11] and low VDS in the mother and newborn [12]. The potential association between obesity and food allergy may be via associations with genotype, the microbiome, immune development and/or VDS. The association between obesity and VDS may be due to vitamin D storage in adipose tissue (see below) or an association between obesity and reduced outdoor activity [62], and hence UVB exposure.

Dietary intake of vitamin D

The emerging risk factors for food allergy that may also influence oral vitamin D intake include living in a country that does not fortify the food chain with vitamin D, low oily fish intake during pregnancy, delayed (or absent) introduction of infant formula and delayed introduction of hen's eggs.

As described above, there is a high rate of both low VDS [16, 17] and food allergy [3] among Australian infants. Australia is one of the few countries in the developed world that does not fortify the food chain with vitamin D, and the current Australian recommended vitamin D intake is substantially lower than many other countries [63, 64]. Although there are no current data for dietary intake in Australian children, it is unlikely to be higher than current adult intakes, which are very low at 48–104 IU (1.2–2.6 μg)/day [65].

Maternal intake of fish oil during pregnancy may be associated with a reduced risk of food sensitization and self-reported food allergy. This has been attributed to

Table 1. Possible mechanisms by which the emerging food allergy risk factors may also be associated with low VDS

(i) Sun exposure and cutaneous synthesis of vitamin D	(ii) Dietary intake of vitamin D	(iii) Bioavailability or metabolism of vitamin D	(iv) Biological activities of vitamin D
Higher latitude [22, 23]	Australian residence [3, 17]	Obesity [11,12]	May promote the induction of immune tolerance [47, 48]
Winter birth [5]	Lower maternal intake of oily fish [9]	CYP24A1 gene polymorphisms [46]	Modifies intestinal barrier function [49–52]
Black American ethnicity [10]	Delayed (or absent) introduction of infant formula [44, 45]		Modifies immune response to microbial exposure [46, 53]
Absence of pets [41, 42]	Delayed introduction of hen's eggs [8]		May alter composition of the gut microbiome [51, 54]
Obesity [11,12]			
Not living on a farm [43]			

the anti-inflammatory effects of omega-3 fatty acids (n-3 PUFAs), but fish oil is also a good source of vitamin D. A total of three randomized controlled trials have evaluated the effect of maternal fish oil supplementation during pregnancy and or lactation on the offspring's risk of food allergy [9]. There was weak evidence that babies whose mother received fish oil rather than placebo were less likely to develop parent-reported food allergy (6/128 vs. 16/136, OR 0.46, 95% CI 0.16–1.38). Two of these studies (n = 187) also found that maternal fish oil supplementation during pregnancy was associated with a reduced risk of egg sensitization among the offspring at 12 months of age (12/87 vs. 32/100; OR 0.33, 95% CI 0.16–0.70). By contrast, postnatal fish oil supplementation does not appear to modify the risk of food-allergen sensitization [66].

Although controversial, a number of studies have found an association between delayed (or absent) introduction of infant formulae and food allergy [44]. Breast milk, despite its other benefits, is a poor source of vitamin D, with a total vitamin D content of 25 IU/L in mothers with normal vitamin D levels [67], whereas infant formulae are fortified with vitamin D to a concentration of 360–520 IU/L. Prolonged exclusive breastfeeding is associated with low VDS [68, 69], and it is plausible that the protective effect of early introduction of infant formula is due to increased oral vitamin D intake. Recent evidence suggests that early introduction of infant formulae reduces the risk of food sensitization to non-dairy foods, i.e. peanut and perhaps egg [45]. A protective effect of dairy containing formulae on non-dairy food allergy suggests a non-antigenic mechanism of inducing tolerance, as might be expected if the relevant component of the formula was vitamin D rather than cow's milk (or other specific) protein.

Delayed introduction of egg in the infant's diet is also associated with an increased risk of food allergy [8]. There has been a progressive and dramatic delay in timing of the first exposure to solids since the 1960s [70], and it is possible that this may have contributed to the increase in allergic disease over the same period. While early egg exposure may protect against food allergy via induction of immune tolerance, it is also possible that it does so by increasing vitamin D levels. Egg yolk is one of the few sources of dietary vitamin D and delay in the introduction of egg-derived vitamin D at a critical point in immune development may be important.

Bioavailability or metabolism of vitamin D

The emerging risk factors for food allergy that may also influence vitamin D metabolism include ethnicity (and hence genetic factors) and obesity. The risk of food allergy is strongly genetically determined [71, 72]. There are many potential explanations for this, but given that at least one vitamin D-metabolizing gene has been implicated in food sensitization [30], there is a need to better understand the potential relationship between genotype, vitamin D metabolism and food allergy.

As noted, obesity is a potential risk factor for both food allergy and low VDS [12]. Several pathways, including co-association with low VDS, may explain a relationship between obesity and food allergy. While obesity may relate to low VDS via reduced cutaneous synthesis of vitamin D (discussed above), obesity may also be associated with low VDS via reduced vitamin D bioavailability as vitamin D is sequestered in adipose tissue [73, 74].

Biological activities of vitamin D that may link low VDS with other emerging risk factors for food allergy

Vitamin D is a pleiotropic hormone that influences the expression of greater than 200 human genes [75], and in there are a number ways in which vitamin D may modify the host response to other epidemiological variables that have been associated with food allergy. For example, given that vitamin D promotes the induction of IL-10-secreting T regulatory cells [47] which play a key role in establishing and maintaining immune tolerance [76], vitamin D may be relevant to the induction of tolerance following early exposure to a food allergen. Du Toit et al. recently found that Jewish children in Israel have a lower risk of peanut allergy than Jewish children in the United Kingdom [77]. It has been suggested that this finding might relate to the early introduction of peanut in the Israeli diet. Israel is, however, substantially closer to the equator than the United Kingdom, and therefore it is possible that people living in Israel also have greater UVR exposure and vitamin D levels. Accordingly, the apparent protective effect of early introduction of peanuts in the Israeli diet may be intertwined with coexisting vitamin D sufficiency – although it should be noted that recent evidence suggests low VDS is surprisingly common even in Israel [78].

Vitamin D may also modify the host response to early food-allergen exposure via effects on intestinal barrier function as first hypothesized by Vasallo et al. [79]. Vitamin D has been shown to have a role in maintaining intestinal barrier function via regulation of tight junction proteins [80] and innate epithelial defences [49–52]; and it has been proposed that low VDS may increase the risk of food allergy via increased antigen exposure in the gut due to effects on intestinal barrier and immune function [79].

In general, vitamin D may influence the interaction between microbial exposure, host immune development and food allergy. A relative absence of optimal microbial stimulation in early life is a proposed risk factor for food allergy [81, 82]. Given the important role vita-

min D plays in both innate and adaptive immunity [46, 53], the interplay between microbial exposure, vitamin D and food allergy requires further evaluation. In a similar vein, vitamin D may influence the putative interaction between the composition of the gut microbiome and food allergy. Gut microbiota plays a key role in shaping the development of the immune system [83, 84], and reduced diversity of early-life gut flora has been associated with subsequent eczema [85], a condition closely linked to food allergy. However, as yet no study has directly assessed the composition of gut microbiota with regards to food-allergy risk, and the evidence that vitamin D may alter gut flora via an effect on enteric defensins is preliminary [51, 54]. Further studies are required regarding the relationship between the gut microbiome, vitamin D and food allergy.

Implications for future studies

Disentangling the relationship between low VDS and other potential risk factors for IgE-mediated food allergy poses a significant challenge. Low VDS has a broad range of recognized environmental associations and biological effects, consequently there is ample scope for both true causal pathways and confounding bias. Studies are required that (i) provide sufficient longitudinal data regarding VDS determinants, and (ii) provide the opportunity to investigate the underlying biological mechanisms. Specifically, studies should include prospective high-quality measurement of sun exposure and skin pigmentation, ethnicity and genotype, body composition, microbial experience and the gastrointestinal microbiome, oral intake of dietary vitamin D and vitamin D supplements, timing of introduction of infant formulae, hen's eggs and other solids and determination of both food sensitization and challenge-proven IgE-mediated food-allergy status. Studies should also include the longitudinal collection of relevant biosamples, such as feces, serum and cryopreserved mononuclear cells. Considered and rigorous analytical strategies will then be required to evaluate the various potential relationships and pathways; and the contribution of UVR-derived, diet-derived and supplement-derived vitamin D should be separately considered.

Some have called for randomized trials of oral vitamin D supplementation for food allergy prevention [79]; however, there are important reasons to first obtain improved observational data. Most notably, current evidence regarding the association between low VDS and food allergy is inconsistent, and indeed, vitamin D supplementation may increase the risk of food allergy. Furthermore, current knowledge is insufficient to adequately design an interventional study. In particular, we know neither the 'optimal' vitamin D level, the preferred timing, nor whether vitamin D should be elevated via oral supplementation or increased UVR exposure. There are also well-recognized feasibility concerns for randomized trials of vitamin D supplementation for disease prevention [86]. These include (i) poor adherence with supplementation among healthy participants and (ii) uncommon outcomes with delayed onset necessitating large cohorts to be maintained in the trial for long periods.

Conclusions

The hypothesis that the increase in food allergy is related to a concordant increase in low VDS is attractive as vitamin D has a variety of immunomodulatory actions, and because low VDS is common and amenable to relatively simple and inexpensive public health interventions. We have reviewed the evidence for and against this hypothesis. We have noted that low VDS may represent a point of partial confluence for a range of emerging risk factors for food allergy, although prospective analytical studies will be required to unravel whether these factors exert their effect partially through vitamin D-dependent pathways or whether in fact these factors are associated with food allergy through different pathways and merely also linked to vitamin D. Furthermore, the relative importance of the major determinant of vitamin D, UVR exposure, remains to be determined and the relative immune modulation of UVR-derived compared to dietary-derived vitamin D requires consideration.

Conflicts of interest

The authors declare no conflict of interests.

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