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Editorial

The vitamin D slant on allergy

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Oral vitamin D supplementation has been introduced into modern medicine to prevent rickets without the knowledge that this may have profound immunological consequences. The main vitamin D metabolite calcitriol suppresses dendritic cell maturation and consecutive Th_1 cell development, which has independently described as a key mechanism of allergy development. Animal studies and epidemiological surveys now provide a first link of early vitamin D supplementation and later allergy where several vitamin D regulated genes seem to be involved. A randomized clinical trial of vitamin D supplementation could be a further step to follow up the vitamin hypothesis.

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Vitamin D supplementation in newborns is a success story of modern medicine. It eradicated rickets that had been endemic at the beginning of the last century (1). Simple or common rickets, also called 'English disease,' emerges from deprivation of sunlight by air pollution, skin coverage or restricting children from playing outdoors.

Preventive vitamin D doses were introduced in the 1950s by 'what has been the equivalent of a tablespoon liver cod oil' that had been proven safe for the prevention of rickets. Vitamin D_3 (cholecalciferol but also vitamin D_2, ergocalciferol) is now used for oral rickets prophylaxis (2). In some countries milk, cereals or infant formula are fortified with up to 1000 IU cholecalciferol per liter; in other countries pregnant women or newborn children are prescribed between 500 and 1000 IU daily (1) where a clear distinction of 'physiological' or pharmacological doses is difficult. Natural sources of vitamin D are scarce, mainly fatty fish, which is not part of the newborn's diet (3). Breast milk contains little vitamin D, usually less than 20 IU/l (4, 5). Importantly, oral doses are fully resorbed in the intestinal tract while vitamin D production in the skin by UV exposure reaches an equilibrium after 20 min (6). Oral exposure can therefore bypass regulatory mechanisms in the skin and elicit strong effects in the gut mucosa (7).

It was only in 1983 that vitamin D receptors were described in lymphocytes (8). Following extensive research, the endocrine action is now seen only as tip of the iceberg while the main effects are observed in the immune system. Calcitriol suppresses dendritic cell maturation and consecutive Th_1 cell development mainly by blocking the IL-12 signal (9). Such a delayed Th_1 maturation has been independently implicated in allergy (10) and finally led to the hypothesis that allergy development may be a delayed side effect of early rickets prophylaxis (11–14).

Allergy prevalence rates follow to some extent the geographical and temporal trend (15) of rickets prophylaxis in industrialized countries. Also some observations like the lower prevalence in anthroposophic communities (16), the farming environment (14), or the convergence of East and West German allergy rates (13) can be explained by the use or avoidance of vitamin D. Some high allergy prevalence countries like the United States of America generally fortify milk while in the United Kingdom and Germany only margarine (17) and baby food is being fortified. Any ecological comparison, however, is difficult as vitamin D supplementation varies even within countries. Most industrialized countries now use commercial baby milk preparations that contain vitamin D supplements. The ongoing Europrevall baby cohort study will provide a first overview of vitamin D exposure in several European countries.

This is urgently needed as already several studies now support the vitamin hypothesis: A study by Moneret-Vautrin et al. (18) showed a

9.0-fold increased risk for sensitization under combined peanut and calcidiol exposure. The Milner et al. study (19) described in a cohort of 8285 3 yr old a 1.6-fold increased risk for food allergy by multivitamin drops while the Hyppönen et al. study (20) of 12,058 live-births showed a similar 1.7-fold atopy risk if babies were treated regular rather than irregular with vitamin D. As both, the Milner and Hyppönen study, did not test exposed vs. never exposed children, the risk estimate by Moneret-Vautrin seems to be even more realistic.

Further evidence for the vitamin hypothesis comes from genetic studies (21) as genes have been well-known risk factors for rickets development (22, 23). This is in accordance with more recent molecular data where baseline expression of several vitamin D related genes segregate in families (S. Monks 2004, personal communication). It is therefore not unexpected, that DNA variants in many vitamin D regulated genes have now been associated with allergy (Table 1). Newborn mice can be sensitized more rapidly under calcitriol load (56) while vitamin D receptor knockout mice fail to develop allergic asthma (36).

Are there any arguments against the vitamin hypothesis? Clearly, vitamin D metabolites inhibit differentiation, maturation, activation, and survival of dendritic cells leading to impaired T cell activation in different models of allo- and autoreactivity (57). Inhibition of Th_1 type immune response, however, does not necessarily imply allergy promotion. Also previous reports of inhibition or enhancement of Th_2 response by vitamin D or its metabolites are not fully conclusive. The existing immunological literature on vitamin D and Th_2 response is difficult to interpret, with studies performed in the presence or absence of antigen presenting cells, at different T cell maturation state, under variable co-stimulation, changing dose and duration of vitamin D exposure (58). Nearly all studies neglected the genetic background of laboratory animals [where mice might not be a particular suited model as fur bearing and night active animals that show different expression in vitamin D regulated genes (59)]. A detailed experimental work-up of allergy induction by vitamin D is therefore a future challenge.

Table 1. Genes that have been associated with allergy pathogenesis and are regulated by vitamin D metabolites

Gene	Description	Vitamin D regulation	Allergy association
IL12B	Growth factor for activated T and NK cells, stimulates the production of IFN-resting PBMC	Lyakh et al. (24)	Randolph et al. (25), Morahan et al. (26), Hirota et al.(27), Wjst et al. (28)
IL12RB	Low affinity receptor for interleukin12	Mahon et al. (29)	Bassuny et al. (30), Takahashi et al. (31)
SPP/OPN	Secreted phosphoprotein 1 (alias osteopontin)	Shaffer and Gewirth (32)	Personal communication Y. Tanino ATS (2004)
CD14	Mediates together with TLR4 the innate immune response to bacterial LPS	Wang et al. (33)	Baldini et al. (34), Zambelli-Weiner et al. (35) and many more
CD23	Fc fragment of IgE receptor with low affinity	Wittke et al. (36)	Lewis et al. (37)
VDR	Nuclear vitamin D receptor	Wang et al. (33)	Poon et al. (38), Raby et al. (39), Wjst (40)
TNF	Tumor necrosis factor, secreted by macrophages, potent pyrogen by stimulation of interleukin 1	Hakim et al. (41)	Migita et al. (42)
GC	Vitamin D binding protein and many other immunological functions	Wang et al. (33)	Laufs et al. (43), Wjst (44)
IFN	Secreted by lymphocytes, many immunoregulatory functions, activator of macrophages	Mahon et al. (29)	Nagarkatti et al. (45)
IL1RN	Family of proteins and corresponding receptors, involved in the inflammatory response	Wang et al. (33)	Gohlke et al. (46)
IL8	Interleukin-8 is a chemotactic factor that attracts neutrophils, basophils, and T-cells	Wang et al. (33)	Heinzmann et al. (47)
ADRB2	β2 adrenergic receptor activates adenylate cyclase through G proteins	Wang et al. (33)	Dewar et al. (48)
CARD15	Alias NOD2, activates NF B, confers responsiveness to intracellular bacterial LPS	Wang et al. (33)	Weidinger et al. (49)
IL4R	Interleukin 4 receptor, mediates IL4 and IL13 effects by coupling to the JAK1/2/3-STAT6 pathway, IL4 promotes Th_2 differentiation	Wang et al. (50)	Mitsuyuasu et al. (51), Wjst et al. (28)
ALOX5	Arachidonate 5-lipoxygenase, lipid peroxidating enzyme implicated in inflammatory disorders	Wang et al. (33)	Drazen et al. (52)
FLG	Filaggrin, aggregates keratin intermediate filaments	Personal communication Y. Oda Vitamin D workshop (2006)	Palmer et al. (53)
SOCS3	Suppressor of cytokine signaling 3	Ekelund et al. (54)	Morales et al. (55)

Ige, immunoglobulin E.

Second, it could not be shown so far that administration of oral vitamin D suppresses lung dendritic cell development. It seems, however, questionable if a direct effect on lung dendritic cells is being necessary. Primary allergen contact may occur also in the gut mucosa (with food allergy being often the first sign of the allergy career). Swallowed airborne allergens can bypass gastric digestion (60–65). This might be particular important in newborns where both the intestinal barrier function as well as the immune function is not fully developed (66–68). While natural sunlight exposure is leading to a rather distributed vitamin D accumulation, it is only in the GALT where oral supplementation is leading to a high local exposure. Oral vitamin D can already be converted in the gut mucosa in its active metabolites [both colon cells (69) and macrophages (70, 71) seem to have all necessary enzymes], where paracrine effects are leading to a massively down-regulation of CD83 and CCR2 on T cells (50). Both markers are involved in the homing of T cells (72, 73); in a suppressed state they may open new circulation routes of vitamin D exposed lymphocytes to other 'allergen hotspots' like skin, upper and lower airways. So far, a combined *ab initio* exposure of vitamin D and allergen has not been tested in experimental models, although the interaction is likely from allergen (74) and vitamin D studies (7). Any beaten track will last for many years or even decades of specific immunoglobulin E (IgE) memory (75).

Third, there are a few reports of a co-occurrence of atopic dermatitis and rickets in the same patient (76). This might be a chance observation as the temporal sequence of events in these patients is not been known. An initial high vitamin D exposure may have triggered atopic dermatitis (leading to consecutive sun deprivation). A concomitant food allergy could have been also responsible for calcium poor diet (leading to rickets). On the other hand, there are also case reports on allergic reactions because of calcipotriol application (77).

Fourth, oral vitamin D supplements have been advocated in asthma therapy to antagonize steroid induced osteoporosis (78) and more recently to boost steroid responsiveness (79). This highlights the diversity of vitamin D actions but does not necessarily conflict with the vitamin D hypothesis where early timing, appropriate dose and allergen co-exposure is being relevant.

Fifth, there is an unexplained observation that a low cord blood vitamin D serum level is associated with low IL-10 serum levels (80). IL-10 has variously been considered as a Th_1-associated mediator, particular in mice, but is also associated with more severe asthmatic disease in humans. Given the potential bias of any observational study, the Zittermann study awaits further confirmation as it also contradicts experimental studies (24).

Sixth, in a recent epidemiological study of mother–child pairs in Massachusetts, the maternal intake of each additional 100 IU vitamin D in the first and second trimester was associated with a lower childhood risk of wheezing and asthma in the child (81). A reduced number of respiratory infections by vitamin D may already be expected from previous studies (82–86). As asthma was defined as two or more reports of wheezing (plus either parental history of asthma or child diagnosis of eczema), it is possible that the protective effect on 'asthma' may simply reflect the fact that vitamin D reduces also the number of multiple wheezing episodes.

Finally, the intricate question is about the relationship to the prevailing hygiene hypothesis. The hygiene hypothesis assumes that improved living standards have lead to less frequent infections, where a less challenged immune system is misdirected to allergens. A reduced rate as well as lower severity of respiratory infections has been observed with vitamin D prophylaxis (G. Soldner 2004, personal communication) which is consistent with the increased infection rates found in many studies of vitamin D deficient children (82–86). The mechanism behind this observation probably relates to lower levels of antimicrobial peptides like cathelicidin (87).

Hygiene and vitamin hypotheses therefore agree on lower respiratory infection rates albeit in a different context. Reduced infection rates are a causal factor in the hygiene hypotheses while they constitute a secondary effect in the vitamin hypothesis. As pointed out earlier, the observation of a lower allergy rate in farm children may be explained either by the under-use of vitamin D supplements in children who consume primarily unpasteurized milk (88) or by a direct antagonistic effect of higher bacterial exposure in the farm environment (14). Calcitriol pulsed dendritic cells show a blunted response to LPS (24, 89) by down-regulating TLR4 expression leading to a hyporesponsiveness to PAMPs (90). Calcitriol is long known to suppress key effector functions of IFN-γ activated macrophages, leaving DCs in an immature state (9) and reduced phagocyte functions (91). Corollary, LPS down-regulates vitamin D receptor levels (92), reduces VDR promoter binding (93) with consecutive NFκb activation (94) while at the same time CD80/CD86 and HLA-DR expression increases (95).

In summary, it might be possible that the ubiquitous oral vitamin D exposure induces allergy in a genetically susceptible subgroup. According to the 'thrifty genotype' hypothesis (96, 97), the European population has been selected for alleles favoring better use of sunlight (98) which could be confirmed very recently by selective sweeps in genes determining skin color (99) and vitamin D metabolism (100, 101). Is the allergy epidemic a drawback that we are now facing by having over-optimized our vitamin D system?

A randomized clinical trial of vitamin D supplementation in newborns could provide an answer to a question where all other explanations failed so far (102). Unfortunately there will be three major problems: The ubiquitous vitamin D occurrence in infant formulas will confound any clinical trial and lead to disease also in the control group. The genetic variants responsible for vitamin D sensitivity needed for block randomization between test groups are also not known. Finally, there is an ethical challenge as such a trial risks inducing rickets in the control group.

The last problem seems to be manageable. Common rickets may not be viewed simply as vitamin D deficiency (103) as many other dietary factors like calcium, phytate, phosphate and fibers are as important as sun exposure (104–106). Current experience in an anthroposophic clinic at 48 ° latitude estimates the annual incidence of observing early rickets signs to be in the range of 1–500 untreated children (D. Hilgard 2004, personal communication) Risks may be further minimized by careful examination of study participants at regular intervals. Also the non-random assortment of risk genes between study groups could partially be overcome by randomization of children with a history of parental allergy. The ubiquitous exposure to supplemental vitamin D seems to be the most difficult challenge where additional actions may be necessary to control any nutritional vitamin D intake. If these difficulties could be overcome, such a clinical trial could provide an explanation to the allergy epidemic.

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