Beyond Bones: A Review of Pre-natal Vitamin D Levels and Allergy Development in Children

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Abstract

Although the connection between vitamin D, the immune system, and allergies encompass a large area of research, a consensus about the specifics of the vitamin's role in the developing immune system has yet to be reached. At the same time, prevalence of allergies and hypersensitization have seen a dramatic increase in the last 50 years, especially in developed nations, with very little understanding as to why. Some have connected the purported allergy pandemic to vitamin D, placing the blame on either the equally concerning vitamin D deficiency prevalence or the rise in supplementation of the vitamin (and thus, an argued excess). Through conducting a non-exhaustive review of the literature, the aim of this paper was to answer the question: Does prenatal vitamin D insufficiency or exposure result in increased risk of developing an atopic condition, including eczema, asthma, and food allergy sensitization? For food allergies and eczema, there is support for both increased and decreased exposure causing each condition, as well as support for vitamin D having no effect at all. The debate around asthma is more specific and focuses on whether elevated vitamin D has a detrimental effect. The current evidence is largely based in observational research and findings are still very inconsistent, but as new intervention studies are conducted, a more definitive answer should eventually emerge.

Keywords: vitamin D, 25(OH)D, asthma, food allergy, eczema

Vitamin D is well known for its role in healthy bone maintenance, but the last decade has seen a rapid increase in investigation into the multitude of other areas this vitamin serves in the body. The discovery of vitamin D receptors on immune cells in the 1980s revealed a place for vitamin D in immunity and defense structures, but the pathways and mechanisms by which it exerts its effects are still being determined. It follows that the vitamin would plausibly be involved in the development of the fetal immune system, and by further extension, the development of irregularities in immunity. Allergies are one such defect, since they are an over-reaction of the immune system to a normally harmless foreign substance, resulting in symptoms that present all over the body and can range from mildly annoying to life threatening. Current recommendations for the vitamin D intake of pregnant women address the needs of the growing fetal skeleton, but it is unclear if 15 µg per day is adequate for proper immune

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development (Institute of Medicine, 2011). This uncertainty is partially due to the sheer complexity of the immune system, but also because studies on vitamin D's involvement in immunity development are largely observational and lack cohesion in an agreement on the best methodologies to use. This paper will address the unresolved issue of whether Vitamin D exposure or insufficiency *in utero* increases the risk of the later development of conditions related to allergic response, such as food hypersensitivity, asthma, and eczema

Inefficiency Background and Rationale

Much of the focus of prenatal vitamin D research centers on the premise that insufficient levels for proper immune system and lung maturation (but which may be enough to prevent rickets) ultimately cause defective immune responses after birth and that vitamin D would be protective against allergy development. Clinically, vitamin D deficiency is defined as serum 25(OH)D levels at or below 25-30 nmol/L, which is typically the level at which rickets can be observed (Institute of Medicine, 2011). At this stage, it is unclear if the point of deficiency (or insufficiency) is higher or lower for vitamin D's non-bone related roles. The main support for insufficiency as a culprit in the development of allergy comes from epidemiological observations along geographic latitudes. Allergies seem to be much more common in areas of higher latitude, which is where vitamin D deficiency occurs more often due to lower exposure to UVB rays (Rueter, Siafarikas, Prescott, & Palmer, 2014). A correlation between allergies and Westernized, indoor lifestyles has also been proposed as a way to explain the high prevalence of asthma, in particular, in the more developed countries of the world (Litonjua & Weiss, 2007)

Exposure Background and Rationale

Exposure to vitamin D also appears to be correlated with the development of atopic conditions. Vitamin D in this context is generally defined by maternal serum and/or cord-blood 25-hydroxyvitamin D (also known as 25(OH)D) levels elevated above 50 nmol/L. The mechanism by which this relationship occurs is uncertain, though, largely due to the complexity of the immune system and its components. Wjst, a prolific writer on the subject, suggested that signalling and metabolism thresholds of the vitamin in a fetus may be impacted by maternal levels, perhaps via the upregulation of vitamin D response in the infant, resulting in eventual hypersensitivity to atopic materials (2012). In an earlier paper, he postulated that individuals with specific genetic mutations, particularly in those of Northern European descent, whose overall vitamin D system is already heightened, may be even more susceptible to these epigenetic effects caused by *in utero* vitamin D exposure. One proposed mechanism for vitamin D's immune system effects is through calcitriol (also known as 1,25(OH)D), the activated hormonal form of the vitamin. Calcitriol stifles Helper T1 (Th_1) cell maturation by blocking dendritic cell development and subsequent Interleukin (IL)-12 production. Impeded Th_1 growth has been linked to allergy development separately (Wjst, 2006). In a retrospective analysis, Wjst examined historical epidemiological literature, highlighting that in industrialized countries the 1880s saw a high number of rickets cases but a nonexistent allergy prevalence, while by the 1980s incidences of rickets had dropped to near zero and allergy rates had risen dramatically. He concluded that although the relationship could be merely correlative and not causative, vitamin D nonetheless seems to be a "factor repeatedly associated with allergic sensitization" (Wjst, 2009).

Findings and Discussion of Primary Research

Eczema

Atopic eczema (or dermatitis) is a common condition that generally occurs in the first year of life and is often seen in conjunction with the development of allergies or asthma in the infant (American Academy of Dermatology, 2015). How and if vitamin D affects the development of eczema is unclear, as the data are conflicting. A 2014 study of Japanese pregnant mothers' intake of dairy products, calcium, and vitamin D found that a higher ingestion of vitamin D was associated with an increased risk of eczema in the infant by the age of twelve months (Miyake, Tanaka, Okubo, Sasaki, & Arakawa, 2014). Further, Gale et al. (2008) concluded that infants were more likely to have experienced eczema in the first nine months if maternal serum 25(OH)D levels in late pregnancy were above 75 nmol/L. To put the Gale et al. results into context, the Institute of Medicine recommends a serum 25(OH)D level of 50 nmol/L as optimal for bone health (2011), but others argue that a target of 75 nmol/L is more desirable, considering vitamin D's non-bone roles (Vieth, 2011). Thus, both studies demonstrate increased risks of eczema with presumably reasonably healthy exposure to vitamin D. On the other hand, a higher incidence of eczema was observed in Australian one year olds born with lower 25(OH)D cord-blood levels , but the study found no association between eczema incidence and maternal supplemental intake (Jones, Dip, Palmer, Zhang, & Prescott, 2012), indicating that both vitamin D has a protective effect and that supplementation may not play a role in providing such an effect.

Since all three studies employed different ways to measure and define exposure, comparing them directly is challenging. While each group administered food frequency questionnaires to their participant mothers, only Miyake et al. (2014) used this data directly to draw their conclusions. Gale et al. (2008) and Jones et al. (2012) collected intake data for the purpose of validating their maternal serum and cord-blood 25(OH)D measurements, respectively. Since sunlight exposure can be a major source of vitamin D but is also highly lifestyle dependent, Miyake et al.'s failure to consider sources other than dietary ones, coupled with the fact that they directly compared intake to allergic risk, means that their results provide a potentially incomplete picture of actual exposure to vitamin D by the fetus. Although some consider serum 25(OH)D to be a poor indicator of active, biological effects in the body (Wjst, 2012), the prohormone is widely used as a more precise measurement of body levels of and fetal exposure to vitamin D, which makes Gale et al.'s results more specific and potentially more valuable. Cord-blood 25(OH)D levels are typically lower than maternal serum 25(OH)D, but are generally consistent with maternal levels and are considered another good biomarker of exposure to vitamin D within the last trimester (Rueter et al., 2014).Thus, Jones et al.'s methodology was comparable with that of Gale et al.'s, despite coming to a different conclusion. As such, the vitamin D level associated with increased risk of eczema remains contentious, which may be a result of methodological inconsistencies in the way the correlation has been tested thus far.

Asthma

Asthma is considered an atopic disease because it is often suffered alongside traditional allergies, and asthmatic attacks can be triggered by allergens. Vitamin D's role in the development of asthma is unknown, although animal models have demonstrated that *in utero* deficiency changes how lung structures mature (Zosky et al., 2011), indicating that the vitamin is required in some way. With asthma, the disagreement in the literature seems to focus on whether elevated levels of vitamin D produce an asthmatic effect or not. Along with more eczema, Gale et al. (2008) observed an increased risk of asthma by the age of nine when maternal serum 25(OH)D was in excess of 75 nmol/L (2008). By comparison, Maslova et al. (2014) found no association between asthma and maternal serum at 75 nmol/L, instead observing a higher prevalence of asthma by hospital admission when serum levels were above 100 nmol/L. However, it should be noted that the two studies differed in the information they collected. The Danish Maslova et al. (2014) study combined data gathered from 1497 maternal 25(OH)D measurements at 25 weeks gestation with lifestyle and diet information to create a "vitamin D status prediction score" (p.707) that was then applied to the larger sample size of 32,465 mother-baby pairs to represent exposure to the fetus. Gale et al. (2008) used only the maternal 25(OH)D results to draw their conclusions. Maslova et al. (2014) had a large sample size, but their use of modeled estimations rather than a biological measurement of exposure does not quite match up to the more standardized measurements used by Gale et al., and subsequently, the results of each study really only apply to their own context.

In addition, a longitudinal Danish study reported more asthma-caused hospitalizations by the age of 25 if the individual was exposed to maternal serum levels of 25(OH)D above 125 nmol/L and fewer cases of both hospitalizations and medicine use for asthma in 25 year olds when maternal levels had been below 50 nmol/L (Hansen et al., 2015). Long term studies like these are lacking in the vitamin D and allergy-related literature, potentially elevating the value of Hansen et al.'s (2015) findings. Still, a birth cohort study with an 89% five-year follow-up (Camargo Jr. et al., 2011), and a 2014 review paper (Rueter et al.,) found no link between maternal or cord-blood 25(OH)D levels and later incidences of asthma in children. Most notably, a 2013 supplementation randomized controlled trial (in general, a research format also missing from the vitamin D and immune system literature, despite its position as the gold standard of scientific evidence), did not support the existence of an association (Goldring et al., 2013). A number of sources of error may have skewed the results of this particular study, including that their intervention began too late (at 27 weeks) in the participants' gestation to have any effect. As well, the form of administered vitamin (daily ergocalciferol or a single quantity of cholecalciferol taken once) may have been inappropriate, or the dose (800 IU daily or 200,000 IU taken only once) could have been too low for the purpose of raising newborn cord blood levels. Goldring et al. (2013) also acknowledged that since four different ethnic groups took part in the study, the design did not account for genotypic variations among participants, and therefore some positive findings may have been obscured . Regardless, these researchers were unable to find a protective effect of maternal gestational supplementation at 27 weeks against asthma, casting doubt on whether interventions under similar conditions are suitable. Similarly, an American trial published in 2016 found that daily doses of 4,400 IUs of vitamin D managed to increase maternal third trimester 25(OH)D levels to above 75 mmol/L, but did not show any significant reduction in asthma recurrence in the children by the age of three, as compared to mothers given 400 IUs per day (Litonjua et al., 2016).

Again, inconsistencies within the design of these studies make comparisons among the findings difficult. Gale et al. (2008) and Hansen et al. (2015) analyzed direct maternal 25(OH)D serum concentrations, while Maslova et

al. (2014) developed an exposure score based on maternal levels, diet, and lifestyle, Camargo Jr. et al. (2011) considered cord-blood measurements, and Goldring et al. (2013), the lone intervention study, compared supplementation amounts to outcomes. As no two studies examined exactly the same thing, it follows that each conclusion made may not directly correspond to the conditions of the others, and may explain the disagreement between Gale et al. (2008) and Maslova et al. (2014) regarding the precise serum 25(OH)D level that causes concern (75 nmol/L and 100 nmol/L, respectively). Similarly, each study experienced varying sample sizes and rates of follow-up, and targeted different groups in recruiting of participants, calling into question the generalizability of some of the findings. For example, Gale et al.(2008) also faced problems with maintaining follow-up, especially to age nine, and the results of an increased risk of asthma by nine years is based on data from 178 children of the original 440, which causes uncertainty into whether this data is a true representation of the original cohort . Finally, the last notable concern in much of the methodology was the use of a single serum (or cord-blood) 25OHD measurement to represent fetal exposure to vitamin D. Since both dietary sources and skin synthesis (which depends on sun exposure) of this vitamin contributes to body stores, serum levels typically vary throughout the year. Hansen et al. (2015) acknowledged this limitation explicitly, noting that pregnancies typically span three seasons and one measurement may not reflect the mother's status over the entire gestational time span. These weaknesses in study design both complicate comparisons among results and further obscure a definitive answer as to whether prenatal vitamin D exposure results in asthmatic offspring or not.

Food Allergy

For food allergies, the question remains as to whether they are caused by increased or decreased levels of vitamin D. Two similar observational studies, one American and one Australian, reported a larger number of participants with food allergies had been born during fall and winter months, when UVB rays and sun exposure is typically lowest, than in the spring or summer (Vassallo, Banerji, Rudders, Clark, & Camargo Jr., 2010; Mullins et al., 2011). Although neither one does more than illustrate an association between low UVB immediately leading up to birth and food allergy incidence, epidemiological results such as these have provided the basis for the exploration of *in utero* insufficiency resulting in atopy. Likewise, a cohort paper that pulled participants from a Finnish Type 1 Diabetes prevention study analyzed maternal diet and reported that vitamin D had a protective effect against food allergy development (Nwaru et al., 2010). Interestingly, Liu et al. (2011) found no association between prenatal vitamin D deficiency (based on cord-blood levels) and risk of food allergies until they accounted for vitamin D and immunity-related genetic mutations in the participants, as a reversal of the previous three studies. Vitamin D deficiency only increased the likelihood of food sensitization in children with one or more of four particular single nucleotide polymorphisms tested for . In support of prenatal exposure being detrimental, Weisse et al. (2013) observed that children in their study saw an increase in food allergy prevalence by the age of two when maternal and cord-blood 25(OH)D was higher. Inspired by previous research, regulatory T cell (Treg) numbers in the cord-blood were also measured, and this data showed a negative correlation between cord-blood vitamin D and Treg count, allowing Weisse et al. (2013) to postulate that vitamin D may have an inhibitory effect on the development of these cells, which may change the newborn's immune tolerance, resulting in eventual atopic outcomes.

Conclusion

The question of whether increased or decreased prenatal exposure to vitamin D results in atopic conditions in a child does not yet have a simple answer. It is highly likely that vitamin D plays some role in the development of the fetal immune system, but since the location and the mechanisms have yet to be identified, it will be very hard to determine the dose required until more research is done. Epidemiological evidence for both scenarios exists, which further complicates matters and can make it difficult to distinguish theory from reality. The most plausible answer is that a U-shaped response curve exists (as suggested by Maslova et al., 2014) , and that outcomes are highly dependent on individual genetics. Since the immune system and all the places where vitamin D may fit into it is so complex, the maternal and fetal genetic variability likely will make optimal levels of exposure dependent on the individual metabolic efficiencies and quirks. Part of the reason why there seems to be so much inconsistency in the literature likely has to do with the majority of the studies having been designed with a one-level-fits all attitude, instead of recognizing (as Liu et al., 2011 found and Goldring et al. 2013 conceded), that heterogeneity among the population group may disguise any influences of individual and ethnic differences. As well, since a host of different observational study designs make up the biggest portion of the literature, many of the studies lack similar enough conditions for proper comparison, and most can only provide correlative conclusions, not cause-and-effect ones. Despite having some limitations to overcome, data from randomized controlled trials are beginning to trickle in, and this will ideally help to clarify much of the confusion. The data concerning eczema is inconsistent, while asthma may either be a result of higher exposure or not have

anything to do with vitamin D at all, and food allergies could develop from deficient levels, but have also been shown to occur following higher exposure. As we enhance our understanding of the immune system and work to improve our research methodology, the answers to these questions may emerge.

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