

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/280872673>

Vitamin D, Breastfeeding and Food Allergy

Article in *Mini Reviews in Medicinal Chemistry* · October 2015

DOI: 10.2174/138955751512150731112039 · Source: PubMed

CITATIONS

4

READS

103

4 authors, including:



Sophia Tsabouri

University Hospital of Ioannina

39 PUBLICATIONS 259 CITATIONS

[SEE PROFILE](#)



Anna Challa

University of Ioannina

47 PUBLICATIONS 554 CITATIONS

[SEE PROFILE](#)

Vitamin D, Breastfeeding and Food Allergy

Sophia Tsabouri¹, Anna Challa², Vasilios Giapros³ and Nikolaos Chaliasos¹

¹Department of Paediatrics, Child Health Department, University of Ioannina School of Medicine, Ioannina, Greece; ²Pediatric Research Laboratory, Child Health Department, University of Ioannina, Ioannina, Greece; ³Neonatal Intensive Care Unit, Child Health Department, University of Ioannina, Ioannina, Greece

Abstract: Inasmuch as many infants develop allergic symptoms early in infancy, and exposure to allergens may be important in the development of food allergies, there is great interest in maternal dietary strategies during pregnancy and lactation that may prevent food allergies, and thus reduce the burden of disease. Vitamin D levels are known to be associated with atopic disease development in early infancy; however, existing data are controversial. The aim of this review was to investigate any possible effect of vitamin D on the onset of neonatal allergy via breast feeding.

Keywords: Breast feeding, breast milk, food allergy, infancy, nutrition, vitamin D.

INTRODUCTION

Breast milk is considered the gold standard for infant nutrition, offering a complement of antibodies, macronutrients, and nutritional balance unsurpassed by any substitute. However, as human milk contains low vitamin D amounts, the drive to promote and increase the rate of exclusive breastfeeding in early infancy without adequate sunlight exposure and appropriate vitamin D supplementation leads to some risk factors. Hence, except of the significant skeletal deformities and poor growth seen in children with long term vitamin D deficiency there is increasing evidence for risk of atopic disorders, including food allergy, indicating the importance of vitamin D to infant health [1-3]. 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 [4], a dramatic rise in epinephrine autoinjector prescription [5] and most recently reports from developed countries that up to 10% of infants have evidence of challenge proven food allergy [6]. 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 [7-9]. Furthermore, 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 [10]. The case becomes attractive as vitamin D has a variety of multiple biological roles, including immunomodulatory actions, and because low

vitamin D is common and amenable to relatively simple and inexpensive public health interventions [11].

VITAMIN D IN HUMAN BREAST MILK

After birth, exclusively breastfed infant may produce vitamin D using the UV radiation or receive it directly by human milk [12]. Breast milk of healthy unsupplemented lactating women contains relatively small amounts of vitamin D and 25(OH)D and is usually considered insufficient to prevent vitamin D deficiency in exclusively breast-fed infants if their exposure to sunlight is limited [13]. In industrialised countries the mean breast milk concentration of vitamin D ranges from undetectable to 2 µg/l (80 IU/L) [14, 15]. However, well-fed mothers receiving vitamin D supplements have a up to 90-fold increase in vitamin D in their milk [16] suggesting that the nutritional status of lactating mothers affects the vitamin D sterol potential of her milk which, in turn, would likely have an effect on the vitamin D status of her nursing infant [17]. Thus, exclusively breastfed infants are at increased risk of vitamin D deficiency if vitamin D supplementation is lacking and sun exposure is limited [18].

The question is whether vitamin D supplementation during lactation may increase vitamin D levels in breast milk as to ensure the adequate vitamin D status for her breastfed infant. It is estimated that 20% of maternal vitamin D is transferred through milk to the exclusively breastfed infant [14]. Cancela *et al* reported that circulating 25(OH)D levels in breastfed infants were directly related to the vitamin D content of mother's milk [19]. Available evidence indicates that if the vitamin D status of the lactating mother is adequate, her nursing infant will maintain a "minimally normal" nutritional vitamin D status [20]. Studies in the 1980s showed that supplementation of nursing mothers with 2000 IU rather than 1000 IU of vitamin D had a significant

Please provide
corresponding author(s)
photograph
size should be 4" x 4" inches

*Address correspondence to this author at the Department of Paediatrics, Child Health Department, University of Ioannina School of Medicine, Ioannina, Greece; Tel: +302651099793; Fax: +302651044062; E-mail: stsabouri@gmail.com

effect on the breastfeeding infant's vitamin D status as measured by infant serum 25(OH)D levels [17]. Expanding these findings, two later pilot studies involving lactating women supplemented with high-dose vitamin D of up to 6400 IU/day for 6 months, showed that the vitamin D content of milk increased to levels as high as 873 IU/l without any evidence of maternal vitamin D toxicity [14,15]. The serum 25(OH)D levels in the infants of mothers on 6400 IU/day increased from a mean of 32.5 nmol/l to 115 nmol/l and were similar to those of infants receiving 300–400 IU vitamin D/day whose 25(OH)D levels increased from a mean of 35 nmol/l to 108 nmol/l. Similarly, the vitamin D status of the mothers on high-dose supplementation increased from a mean serum 25(OH)D level of 85 nmol/l at baseline to 147 nmol/l after supplementation [15].

The parent compound cholecalciferol (vitamin D₃) is the major vitamin D metabolite that passes from maternal serum into breast milk. The quantity of the downstream metabolite -25-hydroxyvitamin D, 25(OH)D in human milk is negligible because of the avid binding of 25(OH)D to vitamin D-binding protein [21]. But maternal milk and serum cholecalciferol concentrations are related. It has been shown that infant mean serum 25(OH) D concentration increased from 16±12 to 39±12 ng/mL to mothers supplemented with 5000IU vitamin D in a daily-dose for 28 days (the mean 28-day value in a daily-dose group of 5000IU/d correspond to 320 IU/L) [22]. Breast milk cholecalciferol concentrations increased to 8 ng/mL whereas all infants achieved serum 25(OH)D concentrations of more than 20 ng/mL [22]. Hence infants, receiving milk from mothers replete in vitamin D, have circulating 25(OH)D levels comparable to infants receiving oral vitamin D supplementation [15].

Still, despite the fact that vitamin D levels can be increased in the milk of lactating women taking large vitamin D supplements, such high dose supplementation must be validated and demonstrated to be safe in larger, more representative populations of lactating women.

VITAMIN D IN HUMAN BREAST MILK AND ITS DUBIOUS LINK WITH FOOD ALLERGY: WHAT DOES THE EVIDENCE SAY?

Because many infants develop allergic symptoms early in infancy, and exposure to allergens may be important in the development of food allergies, there is great interest in maternal dietary strategies during pregnancy and lactation that may prevent childhood allergies, and thus reduce the burden of the disease. Little evidence, mostly indirect, exists on the potential link between vitamin D in human breast milk and food allergy.

Studies Against a Link Between Low Vitamin D and Food Allergy

Perhaps the most striking epidemiological evidence against a link between low Vitamin D and food allergy is the parallel increase of food allergy and vitamin D supplementation that has occurred in developed countries.

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 [23]. 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). On the other hand, 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 [24]. The mechanism is unknown, but it has been suggested that the immunomodulatory effect of vitamin D from oral supplementation may differ to that of vitamin D from sun exposure [25]. In a recent randomized, double-blind, placebo-controlled trial from Japan, daily supplementation with 800 IU of vitamin D₃ for 6 weeks from 1 month after birth for breast-feeding mothers showed that the incidence of children's food allergy up to 2 years of age was increased [26]. Another recent German prospective cohort study, including 378 mother–child pairs showed that high vitamin D levels in pregnancy and at birth may contribute to a higher risk for food allergy up to 2 years of age [27].

Studies for a Link between Low Vitamin D and Food Allergy

Pregnant women taking vitamin D supplements and infants exposed early to vitamin D have fewer allergic diseases [28]. A rising prevalence of vitamin D insufficiency over the last 20 years, with up to 30% of Melbourne pregnant women now vitamin D insufficient, has paralleled the rise in children's food allergy [13]. Australia is one of the few developed countries where routine fortification of the food chain supply with vitamin D does not occur [26]. Another study conducted with African American children in the U.S revealed that children who had very low vitamin D status at birth but sufficient vitamin D during their early life had no or a lower risk of food allergy; while children who were exposed to persistently low vitamin D both pre- and post-natally had the highest risk of food allergy [29]. A recent systematic review revealed that maternal dietary patterns associated with less risk for allergic disease in children included Mediterranean dietary patterns, diets rich in fruits and vegetables, fish, and vitamin D-containing foods [30].

Reconciling the Conflicting Data

To reconcile these conflicting data regarding vitamin D and food allergy, it has been proposed that both high and low vitamin D may predispose to allergic disease – a so called 'U-shaped' association [11]. 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 [31], 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 vitamin D and allergy. While the potential association between elevated vitamin D and allergic outcomes are insufficient to dismiss the hypothesis that low vitamin D is a risk factor for food allergy, it is certainly highlighted the need for improved data before proceeding with interventional trials or changes in public health policy.

CONCLUDING REMARKS

Breast milk seems to be implicated in the development of the infant's immune system. Breast-fed infants are usually given vitamin D supplementation to overcome the low concentrations of human milk in vitamin D. Prospective analytical studies will be required to unravel whether emerging risk factors for food allergy exert their effect partially through vitamin D-dependent pathways or whether these factors are associated with food allergy through different pathways and merely also linked to vitamin D. Future research will be required to estimate judicious correction of vitamin D deficiency during pregnancy, lactation and early childhood in order to promote tolerance, improve mucosal immunity and thereby blunt the food allergy epidemic in children.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

- [1] Karatekin, G.; Kaya, A.; Salihoglu, O.; Balci, H.; Nuhoglu, A. Association of subclinical vitamin D deficiency in newborns with acute lower respiratory infection and their mothers. *Eur J Clin Nutr.*, **2009**, 63(4),473-477.
- [2] Peroni, D.G.; Piacentini, G.L.; Cametti, E.; Chinellato, I.; Boner, A.L. Correlation between serum 25-hydroxyvitamin D levels and severity of atopic dermatitis in children. *Br J Dermatol.*, **2011**, 164(5), 1078-1082.
- [3] Akbar, N.A.; Zacharek, M.A. Vitamin D: immunomodulation of asthma, allergic rhinitis, and chronic rhinosinusitis. *Curr Opin Otolaryngol Head Neck Surg.*, **2011**, 19(3), 224-228.
- [4] Liew, W.K.; Williamson, E.; Tang, M.L. Anaphylaxis fatalities and admissions in Australia. *J Allergy Clin Immunol* 2009; **123**(2):434-432.
- [5] Mullins, R.J. Paediatric food allergy trends in a community-based specialist allergy practice, 1995-2006. *Med J Aust.*, **2007**, 186 (12), 618-621.
- [6] Osborne, N.J.; Koplin, J.J.; Martin, P.E.; Gurrin, L.C.; Lowe, A.J.; Matheson, M.C.; Ponsonby, A.L.; Wake, M.; Tang, M.L.; Dharmage, S.C.; Allen, K.J. Health Nuts Investigators. Prevalence of challenge-proven IgE mediated food allergy using population-based sampling and predetermined challenge criteria in infants. *J Allergy Clin Immunol.*, **2011**, 127(3): 668-676.
- [7] Prescott, S.; Allen, K.J. Food allergy: riding the second wave of the allergy epidemic. *Pediatr Allergy Immunol.*, **2011**, 22 (2):155-160.
- [8] Allen, K. J.; Martin, P.E. Clinical aspects of pediatric food allergy and failed oral immune tolerance. *J Clin Gastroenterol.*, **2008**, 44 (6), 391-401.
- [9] Lack, G. Update on risk factors for food allergy. *J Allergy Clin Immunol.*, **2012**, 129 (5):1187-1197.
- [10] Holick, M.F. Vitamin D deficiency. *N Engl J Med.*, **2007**, 357 (3), 266-281.
- [11] Vuillermin, P.J.; Ponsonby, A.L.; Kemp, A.S.; Allen, K.J. Potential links between the emerging risk factors for food allergy and vitamin D status. *Clin Exp Allergy* **2013**, 43 (6), 599-607.
- [12] Hollis, B.W.; Wagner, C.L. Assessment of dietary vitamin D requirements during pregnancy and lactation. *Am J Clin Nutr.*, **2004a**, 79(5), 717-726.
- [13] Hoogenboezem, T.; Degenhart, H.J.; de Muinck Keizer-Schrama, S.M.; Bouillon, R.; Grose, W.F.; Hackeng, W.H.; Visser, H.K. Vitamin D metabolism in breast-fed infants and their mothers. *Pediatr Res.*, **1989**, 25 (6), 623-638.
- [14] Hollis, B.W.; Wagner, C.L. Vitamin D requirements during lactation: high dose maternal supplementation as therapy to prevent hypovitaminosis D for both the mother and the nursing infant. *Am J Clin Nutr.*, **2004b**, 80 (6, Suppl), 1752S-8S.
- [15] Wagner, C.L.; Hulsey, T.C.; Fanning, D.; Ebeling, M.; Hollis, B.W. High-dose vitamin D3 supplementation in a cohort of breastfeeding mothers and their infants: a 6-month follow-up pilot study. *Breastfeed Med.*, **2006**, 1(2), 59-70.
- [16] Powers, H.J. Vitamin requirements for term infants: considerations for infant formula. *Nutr Res Revs.*, **1997**, 10 (1):1-33.
- [17] Ala-Houhala, M.; Koskinen, T.; Parviainen, M.T.; Visakorpi, J.K. 25- Hydroxyvitamin D and vitamin D in human milk: effects of supplementation and season. *Am J Clin Nutr.*, **1988**, 48, 1057-1060.
- [18] Dawodu, A.; Zalla, L.; Woo, J.G.; Herbers, P.M.; Davidson, B.S.; Heubi, J.E.; Morrow, A.L.; Heightened attention to supplementation is needed to improve the vitamin D status of breastfeeding mothers and infants when sunshine exposure is restricted. *Maternal & Child Nutr.*, **2014**, 10, <http://onlinelibrary.wiley.com/doi/10.1111/mcn.2014.10.issue-3/issuetoc383-397>.
- [19] Cancela, L.; LeBoulch, N.; Miravet, L. Relationship between the vitamin D content of maternal milk and the vitamin D status of nursing women and breastfed infants. *J Endocrinol.*, **1986**, 110 (1),43-50.
- [20] Vieth, R. Vitamin D supplementation, 25-hydroxy-vitamin D concentrations, and safety. *Am J Clin Nutr.*, **1999**, 69 (5),842-856.
- [21] Kovacs, C.S. Vitamin D in pregnancy and lactation: maternal, fetal, and neonatal outcomes from human and animal studies. *Am J Clin Nutr.*, **2008**, 88, 520S-528S.
- [22] Oberhelman, SS.; Meekins, M.E.; Fischer, .PR.; Lee, B.R.; Singh, R.J.; Cha, S.S.; Brian, M.; Gardner, B.M.; Pettifor, J.M.; Croghan, I.T.; Thacher, T.D. Improve the vitamin D status of breast-fed infants: A randomized controlled trial. *Mayo Clin Proc.*; **2013**, 88 (12), 1378-1387.
- [23] Klemens, C.M.; Berman, D.R.; Mozurkewich, E.L. The effect of perinatal omega-3 fatty acid supplementation on inflammatory markers and allergic diseases: a systematic review. *BJOG.*, **2011**, 118 (8), 916-925.
- [24] Kull, I.; Bergstrom, A.; Melen, E.; Lilja, G.; van Hage, M.; Pershagen, G.; Wickman, M. Early-life supplementation of vitamins A and D, in water-soluble form or in peanut oil, and allergic diseases during childhood. *J Allergy Clin Immunol.*, **2006**, 118 (16), 1299-1304.
- [25] Wjst, M. Introduction of oral vitamin D supplementation and the rise of the allergy pandemic. *Allergy Asthma Clin Immunol.*, **2009**, 5 (1), 8.
- [26] Norioze, C.; Akiyama, N.; Segawa, T.; Tachimoto, H.; Mezawa, H.; Ida, H.; Urashima, M. Increased food allergy and vitamin D: randomized, double-blind, placebo-controlled trial. *Pediatr Int.*, **2014**, 56 (1),6-12.
- [27] Weisse, K.; Winkler, S.; Hirche, F.; Herberth, G.; Hinz D.; Bauer, M.; Röder, S.; Rolle-Kampczyk, U.; von Bergen, M.; Olek, S.; Sack, U.; Richter, T.; Diez, U.; Borte, M.; Stangl, G.I.; Lehmann, I. Maternal and newborn vitamin D status and its impact on food allergy development in the German LINA cohort study. *Allergy*, **2013**, 68 (2), 220-228.
- [28] Brehm, J.M.; Celedón, J.C.; Soto-Quiros, M.E.; Avila, L.; Hunninghake, G.M.; Forno, E.; Laskey, D.; Sylvia, J.S.; Hollis, B.W.; Weiss, S.T.; Litonjua, A.A. Serum vitamin D levels and markers of severity of childhood asthma in Costa Rica. *Am J Respir Crit Care Med.*, **2009**, 179 (9), 765-771.
- [29] Liu, X.; Arguelles, L.; Zhou, Y.; Wang, G.; Chen, Q.; Tsai, H.J.; Hong, X.; Liu, R.; Price, H.E.; Pearson, C.; Apollon, S.; Cruz, N.; Schleimer, R.; Langman, C.B.; Pongracic, J.A.; Wang, X.

- Longitudinal trajectory of vitamin D status from birth to early childhood in the development of food sensitization. *Pediatr Res.*, **2013**, 74 (3), 321-326.
- [30] Merryn, J.; Netting, M.J.; Middleton, P.F.; Makrides, M. Does maternal diet during pregnancy and lactation affect outcomes in offspring? A systematic review of food-based approaches. *Nutrition*, **2014**, 30 (11-12), 1225-1241.
- [31] Matheu, V.; Back, O.; Mondoc, E.; Issazadeh-Navikas, S. Dual effects of vitamin D-induced alteration of TH1/TH2 cytokine expression: enhancing IgE production and decreasing airway eosinophilia in murine allergic airway disease. *J Allergy Clin Immunol.*, **2003**, 112 (3), 585-592.

Received: ???????, 2015

Revised: ???????, 2015

Accepted: ?????????, 2015