to determine efficacy in preventing sensitization and progression to clinical disease.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2017–2475T

Lisa Martorano, DO
David R. Stukus, MD
Columbus, OH

Serum 25-Hydroxyvitamin D in Early Childhood Is Nonlinearly Associated With Allergy

Savilahti EM, Mäkitie O, Kukkonen AK, et al. *Int Arch Allergy Immunol*. 2016;170(3):141–148

PURPOSE OF THE STUDY. To assess for an association between serum 25-hydroxyvitamin D (25-OHD) levels at birth and at 2 years of age and the development of allergic sensitization and disorders in early childhood.

STUDY POPULATION. Subjects were part of a randomized, double-blinded, placebo-controlled trial designed to evaluate the effect of probiotics on allergy development. Infants with family history of atopy (1 or both parents had doctor-diagnosed allergic disease) were managed from birth until 5 years of age (n = 819).

METHODS. Subjects were examined at 3 months, 6 months, 2 years, and 5 years of age. The primary outcome was the cumulative incidence of any allergic disease and any immunoglobulin E (IgE)–mediated allergic disease until the age of 2 or 5 years. Skin prick tests and serum-specific IgE to a panel of foods and environmental aeroallergens were completed at 2 and 5 years. Sensitization was defined as at least 1 or more positive skin prick test (≥3 mm larger than negative control) results or positive serum-specific IgE (>0.7 kU/L) results. IgE-mediated allergy was defined as sensitization that matched the allergic disorder. 25-OHD levels were measured from cord blood at birth (divided into tertiles) and serum at 2 years of age (divided into quartiles). The following variables were included in the multivariate logistic regression if they met the criteria for confounding: sex, dual parental allergy, mode of delivery, season of birth, season when 2-year serum sample was drawn, months of exclusive breastfeeding, household smoking (at age 0–2 years), and having a cat or dog in the household (at age 0–2 years). Probiotic treatment group was included in all regression models.

RESULTS. Cord blood 25-OHD levels in the second tertile (21.5–29.5 nmol/L) were significantly associated with increased allergic sensitization by 2 years of age (odds ratio [OR] 1.59; 95% confidence interval [CI]: 1.06–2.39) and allergic disorders by 5 years (OR 1.85; 95% CI: 1.25–2.73). 25-OHD levels measured at 2 years of age in the third quartile (51.7–62.6 nmol/L) were significantly associated with increased allergic sensitization by 5 years (OR 2.23; 95% CI: 1.21–4.12), increased diagnosis of IgE-associated allergic disorder by 5 years (OR 2.35; 95% CI: 1.22–4.52), and increased IgE-associated eczema by 5 years (OR 2.06; 95% CI: 1.02–4.17). A change in 25-OHD levels between birth and 2 years was not associated with allergic outcomes.

CONCLUSIONS. Significantly increased odds of allergic sensitization and/or physician-diagnosed, IgE-mediated allergic disorder or eczema in early childhood were found at the following 25-OHD levels: 21.5 to 29.5 nmol/L from cord blood at birth and 51.7 to 62.6 nmol/L at 2 years of age. 25-OHD levels measured at birth and 2 years of age were nonlinearly associated with allergic sensitization and disease.

REVIEWER COMMENTS. The authors of few studies have evaluated the effect of 25-OHD in early childhood through a prospective study by using measurements of vitamin D at 2 time points. Conflicting results have been published in the literature on the effect of 25-OHD on allergic outcomes. The authors of this study highlight that the relationship between vitamin D and allergy could be nonlinear and warrants further study.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2017–2475U

Angela Tsuang, MD, MSc
Julie Wang, MD
New York, NY

Vitamin D Supplementation During Pregnancy and Infancy Reduces Aeroallergen Sensitization: A Randomized Controlled Trial

Grant ML, Crane J, Mitchell EA, et al. *Allergy*. 2016;71(9):1325–1334

PURPOSE OF THE STUDY. To determine whether vitamin D supplementation during pregnancy and infancy prevents aeroallergen sensitization and respiratory illness identified by primary care providers.

STUDY POPULATION. Two hundred and sixty women were recruited from an urban primary care maternity clinic in New Zealand from April 2010 to July 2011. The women were managed from 27 weeks' gestation to delivery, and their infants were managed from birth to 18 months of age. Participants were not taking vitamin D supplementation before enrollment.

METHODS. This was a randomized, double-blind, placebo-controlled, parallel-group trial. The mother and infant pairs were randomly assigned to daily placebo and placebo, lower-dose vitamin D (1000 IU/day for mother; 400 IU/day for infant), or higher-dose vitamin D (2000 IU/day; 800 IU/day). When the children were 18 months of age, skin prick testing and specific immunoglobulin E (IgE) antibodies were measured to common aeroallergens including house dust mites (such as *Dermatophagoides farinae* and *Dermatophagoides*

pteronyssinus), cats, and grass pollen. In addition, serum 25-hydroxyvitamin D concentration was measured, and primary care visits were reviewed to assess the incidence of acute respiratory illnesses among the treatment groups.

RESULTS. Skin prick tests for the selected aeroallergens were available for 184 out of 186 children from whom serum was also collected at 18 months of age. Less than 5% of children had measurable specific IgE to aeroallergens other than dust mites. As a result, group comparisons were made for the mite antigen groups only. For the skin prick testing, children who received higher-dose vitamin D supplementation had a reduced risk of mite antigen sensitization ($P = .03$). The proportion of children with serum-specific IgE positivity to dust mites was significantly decreased for both low-dose and high-dose vitamin D supplementation. In regard to primary care visits, the number of children presenting with asthma and in whom asthma was listed as a diagnosis was significantly smaller in the groups receiving vitamin D supplementation.

CONCLUSIONS. Vitamin D supplementation during the third trimester and first 6 months of life decreases sensitization to house dust mites and the number of primary care visits for asthma at the age of 18 months.

REVIEWER COMMENTS. Vitamin D has immune-modulating effects, and it is known that atopic sensitization can start before birth. The authors of this study suggest that early vitamin D supplementation in utero and in early infancy can decrease the sensitization to dust mites later in life. These results are especially important for populations at risk for vitamin D deficiency, such as in breastfed infants. Current guidelines recommend supplementation with 400 IU per day, yet the authors of this study suggest that a higher dose of 800 IU per day may decrease infants' sensitization to house dust mites. Further studies are needed to determine optimum doses and durations of vitamin D supplementation as a possible allergy prevention measure.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2017–2475V

Elizabeth Smith, MD
Elizabeth Wisner, MD
Ricardo Sorensen, MD
New Orleans, LA

Variation in Microbiome LPS Immunogenicity Contributes to Autoimmunity in Humans

Vatanen T, Kostic AD, d'Hennezel E, et al. *Cell*. 2016; 165(4):842–853

PURPOSE OF THE STUDY. Characterize the gut microbiota during the first 3 years of life and elucidate a mechanism by which it can shape the immune system and impact the incidence of autoimmune diseases such as type 1 diabetes (T1D).

STUDY POPULATION. A subcohort from the DIABIMMUNE (http://www.diabimmune.org) study of 1000 infants from Finland, Estonia, and Russia matched by sex, age, and human leukocyte antigen–associated risk factors. In Finland and Estonia, autoimmunity is more common than in Russia.

METHODS. Stool and serum samples were collected periodically from birth up to 3 years of age. Stool samples were sequenced and their functional potential was compared by HUMAn2 software (http://huttenhower.sph.harvard.edu/humann2). NF-κB–dependent cytokines were determined in peripheral blood mononuclear cells after *Escherichia coli* or *Bacteroides dorei* lipopolysaccharide (LPS) stimulation. A nonobese-diabetic mouse model was used to evaluate effects of these 2 types of LPSs in the development of autoimmunity.

RESULTS. Sequencing of stool samples revealed a substantially different composition between Russian and Finnish or Estonian microbiota. Finns and Estonians had a greater abundance of *B dorei*, and the amount of *B dorei* correlated directly with insulin autoantibody levels. In terms of functional potential, glycolytic functions associated to milk oligosaccharide metabolism were increased in Russian samples, whereas LPS and lipid A biosynthetic processes were increased in the Finnish infants. Lipid A was mainly derived from *E coli*, but in Finland and Estonia it was also derived from *B dorei*. The authors show that *E coli* and *B dorei* LPSs are structurally and functionally different and that *B dorei* LPS inhibits NF-κB–dependent cytokine production induced by *E coli* LPS in a dose-dependent manner. Thus, in peripheral blood mononuclear cells, *B dorei* dampens the immunomodulatory effect of *E coli*. This was translated into an in vivo model because mice injected with *E coli* LPS had a lower incidence and later onset of T1D than mice injected with *B dorei* LPS. In these latter mice, their splenocytes were hyporesponsive 24 hours after *E coli* LPS injection.

CONCLUSIONS. Despite their geographical proximity, there is a significant difference in the composition and function of gut microbiota in infants from 3 different countries with distinct prevalence of autoimmune and allergic diseases. The presence of *B dorei* during early infancy could inhibit endotoxin tolerance induced by *E coli* LPS and predispose for autoimmunity.

REVIEWER COMMENTS. The incidence of T1D is increasing worldwide, with an exponential increase in prevalence over the last 40 years. Despite extensive research, the specific causes of this rise are unknown, and primary prevention strategies are lacking. Recent evidence highlights the relevance of gut microbes and its impact on immunity and immunopathology. However, the definition of a protective microbiota is poorly defined. The authors of this study identify *E coli* as a protective element in microbiota and *B dorei* as a deleterious

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Pediatrics 2017;140;S183
DOI: 10.1542/peds.2017-2475V

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