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Vitamin D status through the first 10 years of life: A vital piece of the puzzle in asthma inception

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In the 19th century through the early 20th century, an adequate diet was thought to be composed of proteins, minerals, fats, and carbohydrates. However, experiments in the early 20th century showed that animals fed these purified components alone did not survive. Hence the search was on for ''vital amines,'' elements present in foods that were required for health and survival and later termed vitamins,[1] of which vitamin D was the fourth to be discovered. We now know that human subjects get vitamin D not only from the diet but also from sun exposure.

The investigation of the role of vitamin D as a treatment for asthma and allergies dates back to the 1930s, soon after the isolation of vitamin D, when viosterol (activated ergosterol) in large doses (at least 120,000 IU daily) was compared with corn oil in adults with asthma and hay fever.[2] Because the mechanism of vitamin D in asthma and allergies could not be determined, this avenue of investigation in human subjects was largely abandoned. Investigations in animal models continued, showing that exposure to vitamin D by the developing lung *in utero* led to improved lung maturation and surfactant production and diminished airway inflammation after a viral infection and led to decreased airway smooth muscle mass (reviewed by Litonjua[3]). In addition, studies in immune cells showed that vitamin D is important in the immune response.[4]

Based on our epidemiologic studies and review of animal experiments of the developing lung, we hypothesized in 2007[5] that vitamin D deficiency could have a role in the increase in asthma and allergies, and the number of reports in the literature dramatically increased. The

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observational human studies investigating vitamin D in the development of asthma were understandably mixed, with studies using estimates of maternal intake of vitamin D generally showing a protective effect of higher vitamin D levels during pregnancy and studies using one measure of vitamin D status (25-hydroxyvitamin D [25OHD]) generally showing no effects,[6] likely because the intake estimates were reflective of longer-term intakes, whereas the 25OHD level was reflective of shorter-term exposures. Clinical trials were supposed to clarify the role of vitamin D in the prevention of asthma and allergies in young children.

The Vitamin D Antenatal Asthma Reduction Trial (VDAART)[7] and the Copenhagen Prospective Studies on Asthma in Childhood 2010[8] trial, both trials of prenatal supplementation of vitamin D to prevent asthma, wheezing, and allergies in young children, were recently published. Although strict statistical significance was not met in either trial, suggesting that power was an issue, there were strikingly identical effects of vitamin D supplementation on asthma and recurrent wheeze in the offspring: about a 20% reduction in the risk for these disorders by 3 years of age. However, it turns out that statistical power was likely not the main problem in the design of these clinical trials.

Heaney[9] recently showed that nutrient trials, such as for vitamin D, are different than drug trials in many ways. Primary among these are that unlike drug trials, nutrient trials do not have a real placebo arm because of the fact that all subjects are exposed to some level of the nutrient and thus have some circulating level of the nutrient, leading to different starting points at the time of supplementation. We have shown this to be the case in VDAART and have shown potentially different effects of supplementation depending on the initial level of 25OHD on entry into the trial.[10] Other factors influencing the results of VDAART have been summarized previously.[11]

In this issue, Hollams et al[12] add another piece of information to our growing understanding about the effects of vitamin D on asthma occurrence. The investigators followed a birth cohort at high risk for asthma and allergies through the first 10 years of life, with assessment of vitamin D status at birth (cord blood), 6 months, and 1, 2, 3, 4, 5, and 10 years of age. They found that there were consistent inverse associations of 25OHD levels with allergic sensitization in early life, whereas there were no cross-sectional associations of 25OHD levels with asthma. However, they also found that over the 10-year period, the number of times a child was found to be deficient in vitamin D (defined as a level of <50 nmol/L, which is equivalent to <20 ng/mL) was positively associated with the risk for asthma and wheeze at age 10 years, suggesting that prevention of vitamin D deficiency throughout childhood was necessary to prevent asthma. These findings are consistent with the results of null cross-sectional reports of the association between vitamin D and asthma and reports in which only 1 measurement of vitamin D status was used. These findings also make sense because the many mechanisms of vitamin D that might prevent asthma (eg, effect on gene expression, effect on postviral inflammatory state, balance of T_H1 and T_H2 responses, and effect on smooth muscle inflammation and remodeling) are dynamic processes responsive to changes in the environment. Thus maintenance of adequate vitamin D status would logically lead to these beneficial effects.

Other important findings in this study need to be highlighted. First, the authors found that vitamin D status in early life was inversely associated with nasopharyngeal colonization with *Streptococcus* species and age of first febrile lower respiratory illness. The authors' findings suggest that vitamin D might be important in helping to establish a beneficial airway microbiome and might have effects on early-life respiratory tract infections. This is consistent with the experimental findings that vitamin D is an important player in stabilization of the intestinal mucosa,[13] and our group has also found that vitamin D status at birth is a determinant of the early-life intestinal microbiome.[14] Although clinical trials of vitamin D to prevent respiratory tract infections have been disappointing, this might again be due to the initial levels of 25OHD and the low doses of vitamin D used.[15] A longitudinal observation study suggested that maintenance of 25OHD levels of at least 95 nmol/L (38 ng/mL)[16] was necessary for prevention of viral respiratory illnesses.

Second, the authors found that the majority of children could be defined as having vitamin D deficiency at birth, suggesting that pregnant mothers were also likely to be deficient. As suggested by results of recent trials, improving vitamin D status in pregnancy might have provided additional benefits.

Third, there was marked variability in 25OHD levels over time (intraclass correlation, 0.31), which is consistent with previous studies,[17] emphasizing the fact that one measurement is not sufficient as a measure of long-term exposure and that longitudinal studies with multiple measures of exposure are more informative than cross-sectional studies.

The biology of vitamin D is complex, and we are learning more about it every day. Interpretation of data from this and other studies suggests a dynamic process of asthma and allergy inception that begins in the womb and continues throughout childhood and likely through adulthood (Fig 1). Because of flaws in the design of current human studies that have led to conflicting results or inadequate statistical significance, some have called for tempering the enthusiasm for vitamin D. On the contrary, we believe that there is much more to uncover, such as the dose and timing of supplementation and the level that maximizes protection. Although we have surmised that adequate vitamin D status from birth throughout life is necessary, the article by Hollams et al[12] has finally given us a part of the answer: we at least need to eliminate vitamin D deficiency in childhood to prevent asthma. Rather than tempering the enthusiasm, we need to redouble our efforts to continue to define the role of vitamin D in the inception of asthma. Only then will we be able to make inroads in solving the asthma puzzle and ultimately achieve the holy grail of preventing the disorder.

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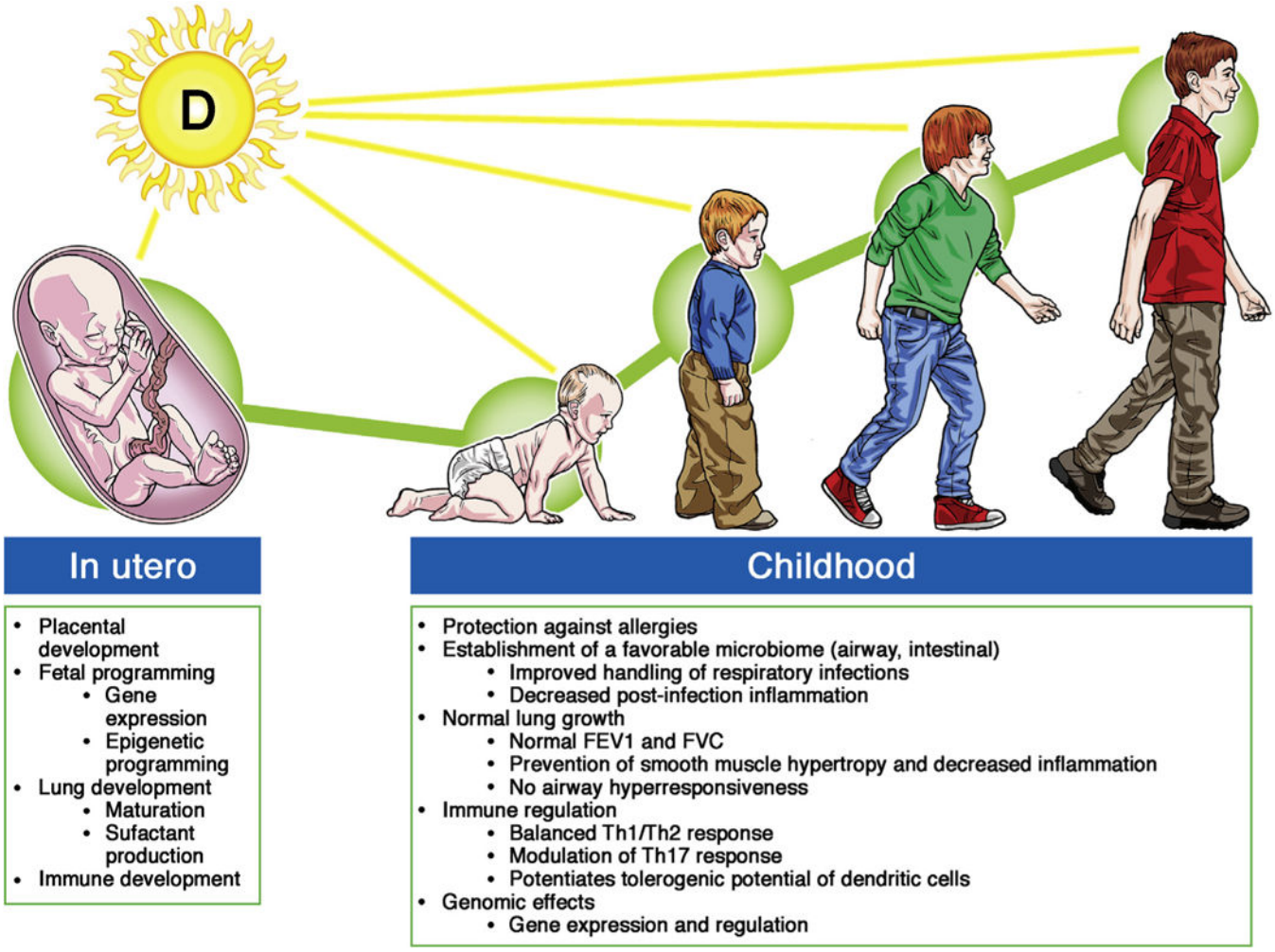

FIG 1.

Adequate vitamin D status prenatally and throughout childhood in the prevention of asthma and allergies. *FVC*, Forced vital capacity.