Vitamin D, A Pluripotent Hormone of Antiquity That Challenges Modern Day Thinking: Focusing On the Breastfeeding Mother-Infant Dyad

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SHORT COMMENTARY

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In the past three decades, the number of peer reviewed articles concerning vitamin D has gone from under a hundred per year to thousands. With the increase in published articles has come an increase in controversy. Some suggest that vitamin D as the preprohormone of the active form—calcitriol or 1,25-dihydroxy-vitamin D ($1,25(OH)_2D$)—is an enabler of various processes in the body (1), that include both innate and adaptive immune functions and explain vitamin D's link with long latency diseases such as multiple sclerosis (2, 3), diabetes (4-7), rheumatoid arthritis (8, 9), certain cancers (prostate (10) and colon (11, 12) cancers), autism (13-16), and infections such as tuberculosis (17), and derangement in placental function that manifests as preeclampsia and premature birth, and later childhood asthma (18-22). There are as many articles showing benefit as there are negative studies. It is confusing and problematic for health care providers and policy makers. While no one would dispute vitamin D's endocrine function in helping maintain calcium and phosphate metabolism (23), the confusion surrounds whether vitamin D has the capacity to change an individual's health trajectory.

We have become a bit more sophisticated in our understanding of vitamin D and realize that there are genetic variations in the way vitamin D is processed, whether made in the epidermis through UVB exposure or through diet or dietary supplementation, where vitamin D is absorbed from the intestines. The vitamin D binding protein is the controller of how vitamin D and its metabolites—25-hyroxy-vitamin D or 25(OH)D and $1,25(OH)_2D$—are carried around the body—how tightly bound and how easily or not vitamin D and its metabolites are delivered to cells throughout the body. It is the vitamin D receptor that is found in the nucleus of cells that binds to $1,25(OH)_2D$. Genetic variations impact the carrying of vitamin D and its delivery. Once bound to calcitriol, the VDR partners with another protein called retinoid X receptor (RXR), forming a complex that then binds to the vitamin D response elements on DNA, and thereby regulates the activity of vitamin D-responsive genes. The vitamin D responsive genes are enabled by calcitriol and the complex, and in turning these downstream genes on or off, the complex help control calcium and phosphate absorption and other processes. It is the "other processes" that has been an area of contention, with variable effects in demonstrating health effects of vitamin D.

Part of the problem has been that there is little agreement on how much vitamin D is needed by the body to maintain the various non-calcium related functions. How does one assess the effect of vitamin D on long-latency

diseases that may take months to years to manifest? Focusing on observational or epidemiological studies has shown association between vitamin D deficiency and as described earlier, diseases such as multiple sclerosis, cancers, autism, and pregnancy complications. Randomized controlled trials using various dosing regimens has provided mixed results—those study populations with the greatest vitamin D deficiency appear to have the greatest improvement (24), and in contrast, those study populations without frank deficiency and who are prescribed—what some consider minimal dosing—have shown minimal effects. When vitamin D supplementation is initiated also appears to impact results; for example, if dosing of higher dose vitamin D occurs early during pregnancy affecting placentation appears to impact maternal and fetal health differently than if supplementation occurs later in pregnancy (25-28). There have been numerous meta-analyses performed on the various topics—vitamin D and cardiovascular health, all-cause mortality risk, pregnancy complications and other long latency diseases such as cancers, multiple sclerosis, and autism with variable results (15, 29-33). Most meta-analyses do not consider VDBP or VDR genotype differences, and so the conclusions are based on a combined reference group of people without such knowledge. In such meta-analyses, there is a wide range of dosing—from no vitamin D given—true placebo to minimal doses given—400 international units (IU), the amount that is prescribed for a neonate in the US that is also prescribed for pregnant and lactating women and is the typical amount found in prenatal vitamins (34). Other studies have included a randomization schedule with higher doses given up to 10,000 IU/day in healthy males during winter months (35, 36); but there are also differential dosing schedules—weekly, biweekly, monthly, quarterly, and even high dose yearly dosing—all with variable results (34). The tests themselves to measure the metabolite 25(OH)D, which is considered the gold standard for assessing vitamin D status given its 2-3-week half-life, can be measured a number of ways and not all methods are equivalent or accurate (37, 38).

Another area of controversy in the vitamin D realm is the vitamin D requirements of the lactating woman and her breastfeeding infant. The *status quo* is that all breastfeeding infants should receive 400 IU vitamin D/day. This seems like an easy prescription yet adherence or compliance of giving infant daily drops of vitamin D is quite low in certain areas of the world, including the US (39, 40). It begs the question of why does one really have to supplement a breastfeeding infant when all other nutrients and bioactive substances are well provided; mothers who are exclusively breastfeeding mention this inconsistency frequently. The data from the 1980's was that breast milk provided minimally sufficient vitamin D (41), but what was the vitamin D status of those mothers? Data from our laboratory suggests that breast milk is marginally sufficient in vitamin D when mother herself has marginal sufficiency (42-45). When we provide a vitamin D supplement to mother in the amount that increases the vitamin D content in her milk (and remember, it is the parent compound—vitamin D itself—cholecalciferol or ergocalciferol—that gets into the breast milk—with minimal amounts of 25(OH)D), then mother is safely sufficient, her milk is enriched, and her infant receives at least 400 IU/L breast milk and has vitamin D status comparable to an infant who receives daily 400 IU/day vitamin D supplementation and whose mother is taking 400 IU/day herself (43-45).

Despite the findings of two earlier pilot studies and a larger, National Institutes of Health (NIH)-sponsored study (43-45), the recommendations put forth by various agencies have not been changed. Why should we care? Does it matter if mother herself is vitamin D sufficient or not, if her baby is receiving daily vitamin D supplementation? Some would argue no, as long as the baby is sufficient. Yet, if we look at breast milk not only as a nutritive medium but as a bioactive substance that continues what began in utero as an ex-utero extension of processes impacting life-long immune function (46), we would answer yes: that through the actions of vitamin D on the mother herself and the refinement of her immune function and the immune signalling that then occurs through her milk become vital processes to her recipient infant. We know that maternal

vitamin D status during pregnancy impacts neonatal immune function (47); why not maternal vitamin D status and its resulting effect on maternal immune status being a specific delivery/signalling system to the recipient infant? When we make mother vitamin D replete, we no longer have to supplement her breastfeeding infant, and quite possibly we are insuring an immune signalling process that will have life-long impact. It is certainly something worth studying.

Disclosures

Drs. Wagner and Hollis serve as scientific consultants for Church & Dwight, Inc, Princeton, NJ, and Dr. Wagner was an invited speaker at the Mead Johnson Pediatric Nutrition Institute seminar on September 27, 2018.

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