Is Vitamin D Inadequacy in Early Life an Instance of the "Barker Hypothesis"?

Robert P. Heaney, MD

In 1986, David Barker, a British epidemiologist, noted a connection between small infant birth size and risk of heart disease later in adult life.[1] The theory that certain adult-onset diseases might have their roots in nutritional insults sustained in the perinatal period (either in utero or in the early months of infancy—or perhaps both) has since been known as "the Barker hypothesis" or sometimes "The Fetal Origins Hypothesis." The original association between undernutrition in utero and late-life heart disease has been difficult to confirm, but the idea that early-life influences can have important downstream consequences is intuitively attractive and is supported by such concrete instances as perinatal thyroid function (and, its cognate, adequate dietary iodine), which is absolutely essential for early-life brain development and maturation. Perinatal iodine deficiency and hypothyroidism from any cause are recognized as important contributors worldwide to mental retardation and learning disabilities during childhood and adult life. In this example, iodine deficiency and its consequences certainly qualify as an outspoken instance of the Barker hypothesis in operation. A critical feature of diseases occurring by way of the Barker hypothesis is the nutritional irreversibility of the long-latency disorders that result. Beyond certain critical points in development, full nutrient repletion is not able to offset or reverse the early inadequacy. This irreversibility is the major stimulus for the better elucidation of these disorders, leading to emphasis on the imperative of early-life preventive nutrition.

The Barker hypothesis has been elaborated and evaluated in several reviews,[2–4] but to the best of my knowledge, there has been no attempt to evaluate the hypothesis specifically for vitamin D. Thus, what I propose to explore in this very brief review is the evidence relating unrecognized, perinatal vitamin D inadequacy to increased risk of certain chronic diseases later in life, that is, to ascertain whether any such effects might be an instance of the "Barker hypothesis."

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I deliberately avoid use of labels such as "deficient" or "insufficient" in characterizing vitamin D status, as these terms are often linked to specific values for serum 25-hydroxyvitamin D [25(OH)D], about which there is considerable controversy. Instead, I use terms such as "low" or "inadequate," referencing in each such use prevailing values for vitamin D status or input relative to values found in those individuals who do not manifest the disorders concerned. I defer until the end of this review consideration of the actual, numerical range of vitamin D status values that appears to permit avoidance of the Barker effect if it is present. Also, it is important to be clear that I am not including in this exploration the well-known downstream skeletal effects of classic rickets, for example, the pelvic deformation that is considered to have been a major factor in the evolution of pale skin for populations living in, or migrating to, high latitudes. Rickets in childhood is a serious disorder and fortunately is evident and both preventable and treatable. Instead, where I focus here is on the nonskeletal consequences both of untreated rickets and of lesser degrees of vitamin D inadequacy, often not clinically apparent and occurring at critical periods during maturation, in some instances well before the life stages when rickets is typically manifest.

For most of the disorders concerned, etiology is almost always multi-factorial. The relation to vitamin D inadequacy should be understood simply as just one of the conditions that, when met, together lead to expression of the diseases concerned. Removing that single factor will not usually be expected completely to eradicate the disease of interest, but will reduce its expression at a population level. For the handful of diseases discussed in what follows, the extent of that risk reduction appears to be large enough to demand serious attention, including more research.

AUTOIMMUNE DISORDERS

Two serious autoimmune diseases have been linked to low vitamin D status in early life, type 1 diabetes mellitus (DM1) and multiple sclerosis (MS). The EURODIAB study[5] showed that 7 European centers that practiced regular vitamin D supplementation during infancy had a 33% lower incidence of juvenile diabetes prior to age 15 years than centers that did not encourage regular supplementation. A few years after the publication of that work, Hyppönen et al[6] reported

an 88% reduction in incidence of DM1 developing prior to age 31 years in a 1967 Finnish birth cohort, for infants receiving 2000 IU vitamin D_3 per day, relative to members of the same birth cohort receiving no vitamin D. In addition, infants in the same study clinically suspected of having rickets exhibited a 3-fold increase in incidence of DM1 relative to nonrachitic infants. This latter finding is an instance of a nonskeletal consequence occurring in individuals with untreated (or inadequately treated) rickets.

Multiple sclerosis has long been recognized to be more common above the 37th parallel (the upper border of Tennessee in the United States). That association is not, in itself, an indication of an early-life origin. However, it is known that the increased incidence of MS in the northern tier of states in the United States is enhanced, when, instead of state of residence, epidemiologists evaluate the data on the basis of state of birth. The underlying presumption is that latitude of birth state influences the 25(OH)D concentration of the intrauterine environment, in which fetuses grow and mature. Birth month, in itself, exhibits precisely that relationship.[7] The underlying presumption is that the intrauterine environment would have been relatively deprived of vitamin D for births occurring in late spring, and the same environment would have been richer in vitamin D for births occurring in late fall. This is shown forcefully in a study of more than 44 000 adult patients with MS from Canada, the United Kingdom, Denmark, and Sweden.[7] Figure 1 presents the ratio of the observed to expected cases for each of the 12 months of the year from that study. (Note that, if there were no seasonal variation, the observed cases in a given month would be approximately 1/12 of the annual total; ie, 1.0 would be the expected value of the ratio. Thus, ratios greater than a value of 1.0 indicate a higher than expected incidence, and ratios less than 1.0, a lower-than-expected incidence.) Note, in the figure, that the data points nicely fit a sine curve, matched to season. The highest risk of MS is observed in individuals born in May, and the lowest risk in individuals born in November. Once again, May births would have followed a winter-long, vitamin D–deprived pregnancy, whereas November births would have followed a summer-long pregnancy with presumably higher vitamin D status values.

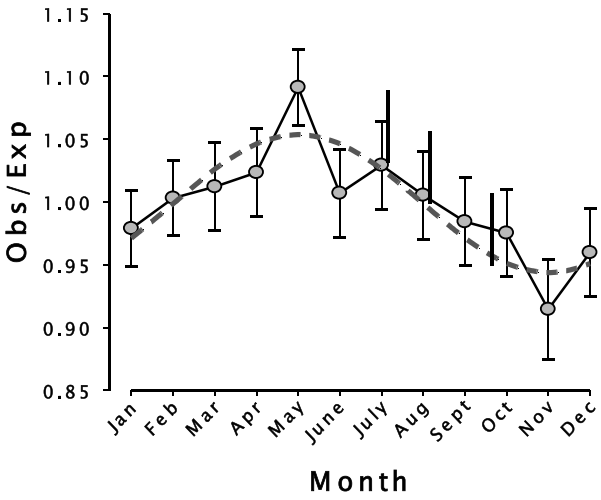

FIGURE 1. Plot of the ratio of observed to expected cases of multiple sclerosis by birth month, redrawn from the work of Willer et al.[7] Data points are means ± 2 SEM. The dashed line is the sine-curve fit to the data, showing the seasonal variation predicted for a phenomenon exhibiting a 12-month cycle of expression. (Copyright Robert P. Heaney, MD, 2015. Used with permission.)

PREGNANCY COMPLICATIONS

One of the most striking and surprising findings to emerge from the Finnish birth cohort study described previously was the fact that 20+ years after their infancy exposure to vitamin D, women in the cohort who, as adults, became pregnant exhibited an approximate 50% reduction in risk of preeclampsia in their own first pregnancies,[8] once again, relative to women who had not received the then recommended 2000 IU/d of vitamin D in infancy.

SCHIZOPHRENIA

McGrath et al[9] have evaluated the association between vitamin D status at birth and the development of schizophrenia later in life. Denmark has a long-standing practice of storing cord blood samples on all newborns, making it possible to explore associations between late-life–onset diseases and vitamin D status at birth. The observed association is so strong that McGrath et al estimated that 50% of the burden of schizophrenia in the entire country of Denmark could perhaps be attributed to problems produced by low perinatal vitamin D status. While this association might initially seem far-fetched, it is important to note that the great famine in China in 1958 to 1961 was associated with a subsequent rise in the incidence of schizophrenia in famine victims.[2] Measured vitamin D status values in these individuals are not available, but it has long been known that rickets was endemic in China and certainly was so at the time of the famine. Hence, it is likely that the malnutrition of the famine would have included vitamin D deficiency as well as other inadequacies. McGrath et al also point out that rats reared on vitamin D–deficient diets produce pups that have morphologically abnormal brain structures.[9–11] Schizophrenia is usually considered more a functional disorder with morphological alterations than a primarily morphologic one, and the rat data indicate that vitamin D is essential for normal brain development and hence plausibly for normal brain function.

COGNITIVE FUNCTION AND LEARNING DISABILITIES

Whitehouse et al[12] report on the prevalence of learning disabilities in school-age children as a function of maternal

vitamin D status at the time when the children concerned were born. Briefly, at age 5 years, 13% of children born of mothers in the lowest quartile of vitamin D status [25(OH)D <18 ng/mL] exhibited learning disability, as contrasted with only 4% of children born of mothers in the highest 25(OH)D quartile (>29 ng/mL), that is, a better than 3-fold increase in risk of the lowest quartile. Because other factors, such as socioeconomic status and ethnic background, could explain both the low vitamin D status and the poor performance in school in this group of children, this association cannot be considered causal. The authors, making that point, went further and asserted that randomized controlled trials (RCTs) must be performed in order to establish a causal connection, if any. The problem with that recommendation is that such trials cannot be performed. In the first place, they are not feasible, and even if they were, they would fail to meet ethical standards. This is because, even if there were no connection between the vitamin D status and the observed learning difficulty, the group of pregnant women to be studied would have to be placed and maintained on a vitamin D status, which is recognized to be inadequate on other grounds (ie, <18 ng/mL) and therefore productive of harmful outcomes.

COMMENT

The foregoing associations are both far-ranging and challenging. Can it be that vitamin D inadequacy contributes to the disease burden of so many otherwise unrelated disorders? The answer is yes. Well over 1000 human genes (and perhaps as many as 3000) have vitamin D response elements. These genes cover a broad range of functions ranging from cell-to-cell adhesion, to macrophage production of defensins in response to mycobacterial infection, to intestinal calcium absorption, and many others.[13] In essentially all such actions, vitamin D, in its active form as $1,25(OH)_2D_3$, functions as a part of the molecular apparatus opening the genome, permitting expression of the genes concerned. Thus, the effects of vitamin D inadequacy are as far-ranging as the tissues concerned, all of which require vitamin D to gain access to information stored in their genes.

At this stage of the discussion, it is generally *de rigueur* to stress that association is not causation. Unfortunately, as just noted, the generally preferred means of establishing causation, the RCT, is not easily applicable to problems of this sort. Aside from the logistics problems created by trials extending over decades of their subjects' lives, there are also, as just noted, formidable ethical problems with trials directly addressing many of these associations. In the final analysis, the underlying hypothesis is not that vitamin D supplementation will reduce the disease burden of DM1, preeclampsia, MS, schizophrenia, or the other disorders listed, rather, the relevant hypothesis is, instead, that it is precisely vitamin D inadequacy that increases or aggravates the disease burden of these varied outcomes. A clinical trial in humans to test a hypothesis of harm (ie, disease causation) is precluded by standard ethical norms. The potential benefits of nutrient supplementation follow logically only after it is accepted that inadequacy results in the preceding set of harms. This is an absolutely central consideration. Once a condition of deficiency is established, repair becomes imperative and needs no further justification. Once it is established that nutrient deficiency is the basis for a particular clinical situation, about the only need or room for an RCT is to test whether a particular regimen of nutrient replacement is better than some alternative approach. But there is no evident need for an RCT to test whether replacing a demonstrably deficient nutrient is appropriate.

BIOLOGICAL PLAUSIBILITY

In fact, the inability to perform RCTs for most of the previous end points necessarily shifts the focus of the argument to the issue of biological plausibility. Are there recognized mechanisms whereby vitamin D status may influence late-life outcomes? It turns out there are. As organisms develop both in utero and perinatally, the vast array of their genes opens up in a controlled sequence, thereby programming how the adult organism will look and function. During that process, many of the relevant genes are "capped"—temporarily or permanently—so that their expression is delayed or even blocked, a phenomenon termed *epigenetics*. The enzymes responsible for doing this are themselves encoded in the genome,[14] and at least some have vitamin D response elements of their own. That means that vitamin D status can influence not so much the content of our genetic heritage as when and to what extent it gets expressed. An example would be the programming of the immune system so as to recognize self and nonself. The process is vastly more complex than can be even roughly outlined here. But the fact is that how we function after birth does appear to be susceptible to influence by perinatal vitamin D status. Hence, the Barker hypothesis, or something closely approximating it, is very likely to be operative in the functioning of the vitamin D economy during human development. That operation can be schematically summarized in Figure 2, which illustrates not merely 1 specific set of outcomes, but the time lines (latency periods[15]) over which manifestation of the epigenetic effects is delayed.

In closing, it would seem important to emphasize that the likely vitamin D status values (and the corresponding daily intakes) associated with protection from the delayed outcomes discussed here are entirely physiological, not pharmacological (ie, in the range of 40–60 ng/mL). African nationals living under ancestral conditions exhibit vitamin D status values in the middle of this range (ie, approximately 46 ng/mL).[16]

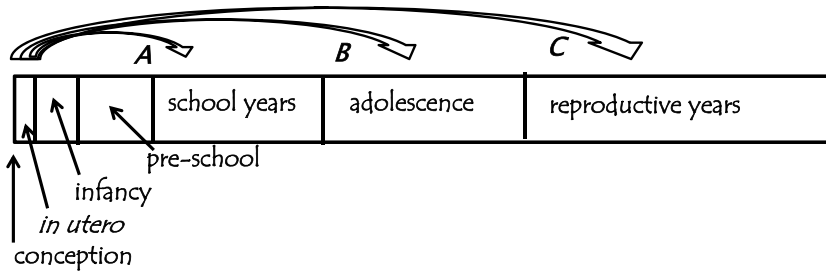

FIGURE 2. Schematic diagram delineating the multiyear gap from perinatal exposure to later-life expression of the several adult-onset disorders described in this review. A denotes the group of earlier-onset disorders, for example, learning disabilities; B denotes those with a more delayed onset, for example, multiple sclerosis, schizophrenia, and juvenile diabetes; and C, the later-onset disorders, for example, preeclampsia and DM1. (Copyright Robert P. Heaney, M.D., 2015. Used with permission.)

In conclusion, while one cannot say that the Barker hypothesis has been definitively established for each of the delayed vitamin D inadequacy outcomes described here, it would seem that the prudent course, both for oneself as an individual and for one's patients and clients, is to assume the applicability of the hypothesis and, accordingly, to ensure a vitamin D status approximating that of ancestral humans.

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