Vitamin D Earns More than a Passing Grade

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(Vitamin D has a long and colorful history in medicine and infectious diseases. We are taught that the early European explorers experienced rickets due to vitamin D deficiency and that generations of children were coaxed to take cod liver oil to escape the ravages of insufficient vitamin D. In the mid-19th century, cod liver oil was reported by Williams [1] to provide improvement to patients with pulmonary tuberculosis [2], and it was subsequently found to contain high quantities of vitamin D. In the preantibiotic era, Charpy synthesized vitamin D, and devised treatment strategies involving the use of vitamin D for cutaneous tuberculosis [1]. More recently, vitamin D deficiency has been associated with a broad range of diseases in humans, including osteoporosis, periodontal disease, type 1 diabetes, cancer (particularly colorectal and prostate cancer), myopathy, and depression [3]. Vitamin D deficiency has also been associated with a wide range of infectious diseases in childhood, including acute respiratory tract infections and pneumonia [4].

In this issue of the Journal, Mehta and colleagues [5] present data suggesting that infants born to human immunodeficiency virus (HIV)–infected women with low vitamin D levels have an increased risk of acquiring HIV infection at each of the following stages: in utero, intrapartum, and during breast-feeding. In addition, HIV-infected mothers with low vitamin D levels and their infants, regardless of HIV status, are more likely to die than are those with adequate levels of vitamin D. At first glance, these data might be dismissed. Previous studies by this group of investigators were predominantly designed to investigate the benefits of multivitamin supplements and vitamin A on mother-to-child transmission (MTCT) of HIV as well as on maternal and child outcomes in Tanzania [6, 7]. The assessment of vitamin D levels was part of a secondary study and surely will need to be confirmed by other investigators. However, are these results biologically plausible? Having become a recent convert to believing in the benefits of vitamin D, I would argue that the data presented are not only plausible but provide insight into a potential approach to improving the outcomes of children born to HIV-infected women.

How might vitamin D decrease MTCT of HIV and improve overall survival? Much can be learned from the elegant research on Mycobacterium tuberculosis conducted by a number of groups [8]. Several mechanisms of action have been proposed for the antimycobacterial activity of the active metabolite of vitamin D (1,25-dihydroxyvitamin D3) in macrophages, including induction of superoxide burst and enhancement of autophagy in M. tuberculosis–infected cells [1]. Both of these responses are mediated by phosphatidylinositol 3–kinase, suggesting that this response is initiated through the vitamin D receptor. Recent studies have further indicated that Toll-like receptor activation of macrophages enhances the expression of the vitamin D receptor and the vitamin D–1–hydroxylase genes, leading to induction of the antimicrobial peptide cathelicin with killing of M. tuberculosis [9, 10].

From the research on M. tuberculosis, it is reasonable to hypothesize that the beneficial effects of vitamin D observed by Mehta and colleagues might be associated in part with enhanced autophagy and cathelicidin levels in mothers and infants with higher levels of vitamin D. Autophagy is of particular interest in this respect. Autophagy is evolutionarily conserved in eukaryotes from yeast to mammals and enables cells to digest their own cytosol during starvation, remove large protein aggregates, eliminate defective organelles, and kill intracellular microbes [11]. Three types of autophagy have been described: chaperone-mediated autophagy, microautophagy, and macroautophagy (ie, autophagy), representing the typical autophagic process. The hallmark of autophagy is a double-membrane-bound autophagosome, which fuses with a lysosome to form an autolysosome, releasing its contents into the cytosol for degradation. The process involves the formation of autophagophores, which sequester cytoplasmic components into double-membrane-bound autophagosomes. The autophagosomes then fuse with lysosomes and deliver their contents to the lysosomal compartment for degradation. This process is evolutionarily conserved across a wide range of organisms and is essential for cellular homeostasis and survival. In the context of this article, the findings from Mehta and colleagues are consistent with a role for vitamin D in enhancing autophagy and potentially reducing the risk of HIV transmission. Further research is needed to fully understand the mechanisms by which vitamin D modulates autophagy and its impact on HIV transmission and overall survival.

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branched autophagosome that engulfs bulk cytoplasm and cytoplasmic organelles, such as mitochondria and endoplasmic reticulum [12, 13]. Autophagosomes ultimately fuse with lysosomes, thereby generating single-membraned autophagolysosomes (ie, autolysosomes) that are capable of degrading the contents, which can then be recycled by the cell. It is important to note that the major role of autophagy is cell survival and maintenance cellular homeostasis [14]. Autophagy has been found to be critical in the cellular control of microorganisms from bacteria (including group A streptococcus and Listeria monocytogenes) to protozoa (including Toxoplasma gondii) to viruses (including picornaviruses, flaviviruses, and lentiviruses, among many others) [15]. In fact, it would appear that a common requirement for all intracellular microbes is to develop mechanisms designed to deal with autophagy. Recently, we found that HIV infection of CD4+ lymphocytes and macrophages results in a down-regulation of autophagy, whereas inducers of autophagy, such as rapamycin and the active form of vitamin D3 (calcitriol), inhibit HIV replication [16, 17]. Additional support for vitamin D contributing to the immune control of HIV comes from Fibla and colleagues [18, 19], who have found that genetic variants in the vitamin D receptor alter both the risk for HIV infection and the rate of disease progression. Moreover, we and others have identified that cathelicidin appears to inhibit early events in HIV infection [20, 21]. Estimates are that as many as 1 billion people worldwide are deficient in vitamin D [22]. In developing countries, much of the population has suboptimal calcium intake and insufficient levels of vitamin D. Although the optimal levels of vitamin D are unknown, a level of ≥30 ng/mL (similar to the level of 32 ng/mL used by Mehta et al) is generally considered to be sufficient [23]. Although considerable research has attempted to define the optimal levels of vitamin D needed to prevent bone disease, there is little information on the vitamin D levels needed to generate an optimal immunologic response. Liu et al [9] identified that activation of macrophages by Toll-like receptor-2 and Toll-like receptor-1 enhances the expression of the vitamin D receptor and the vitamin D−1−hydroxylase genes, which, in turn, induce cathelicidin and improve killing of M. tuberculosis. As a corollary, they also found that African Americans, who are known to have increased susceptibility to tuberculosis, more often had vitamin D levels of <20 ng/mL, levels that they demonstrated were associated with impaired induction of cathelicidin from monocytes. In addition, numerous investigators have identified human breast milk as generally a poor source of vitamin D [4]. It is not a stretch to suggest that breast-feeding infants of mothers with low vitamin D levels will also have insufficient levels of vitamin D and will be more susceptible to a wide range of infectious diseases. Whether supplementation of infants with vitamin D would improve the overall health of these children could be answered through a controlled clinical trial.

In sum, considerable information suggests that the beneficial effects observed for MTCT of HIV and for overall survival of HIV-exposed and HIV-infected children and their mothers with adequate levels of vitamin D are associated with the inhibitory effects of vitamin D on HIV infection, as well as with a decrease in the number and severity of other infectious diseases. Moreover, the findings of Mehta and colleagues suggest that vitamin D provides considerable benefits to HIV-infected pregnant women and their offspring. A clinical trial to systematically assess these findings seems to be warranted.

References

