Editorial

Vitamin D and Atopy

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Vitamin D is primarily found in vertebrates and it is mostly responsible for calcium homeostasis and maintenance of healthy bones.[1,2] Natural vitamin D is obtained from intake of fish oils and other animal sources. Interestingly, microalgae contain both pre−vitamin D and active vitamin D3.[3] In humans, vitamin D synthesis is initiated in the skin by a photochemical conversion of pre−vitamin D3 by ultraviolet B rays, followed by isomerization to vitamin D3 (cholecalciferol).[1] Vitamin D then undergoes the first hydroxylation in the liver to 25-hydroxyvitamin D3 [25(OH)D3], the circulating metabolite, which is what is meant when the term *vitamin D* is used in this Editorial. The active form of vitamin D is 1,25-dihydroxyvitamin D3 [1,25$(OH)_2$D3] (calcitriol) and is synthesized primarily in the kidneys.[1]

Vitamin D exerts its actions by binding to a vitamin D receptor (VDR), which has been found in many cells, including T and B lymphocytes, macrophages, and mast cells (MCs). VDR activation by vitamin D results in transcription of numerous genes. Vitamin D status is assessed by serum 25(OH)D3 levels; unfortunately, there is no accepted standardization of serum vitamin D measurements, which makes comparisons of clinical studies difficult.[4]

Immunologic studies and epidemiologic investigations have suggested a link between vitamin D deficiency and allergic skin diseases, especially skin inflammation.[5] Vitamin D deficiency was significantly associated with increased susceptibility to chronic idiopathic urticaria[6] and atopic dermatitis (AD).[7] The ability of vitamin D to induce terminal differentiation and inhibit proliferation of keratinocytes has resulted in its use for treatment of psoriasis.[8,9] Moreover, vitamin D−deficient mice have an increased contact hypersensitivity response compared with those with normal vitamin D levels.[10,11] Immune cells express VDRs, activation of which decreases inflammation,[12–14] and vitamin D deficiency has been implicated in autoimmunity.[15]

MCs are important in the pathogenesis of allergies and mastocytosis[16] and related diseases,[17] as well as in inflammation.[18,19] MC-derived tumor necrosis factor can promote T helper 17 cell−dependent neutrophil recruitment.[20] Vitamin D has been shown to suppress immunoglobulin E antibody class switch.[21] Vitamin D also appears to have inhibitory actions on MCs.[22,23] In fact, human MCs convert vitamin D through CYP27B1 to metabolites that inhibit immunoglobulin E−induced MC inflammatory mediator release.[24] A recent paper reported that the human leukemic MC line, human mast cell-1, and the rat leukemic MC RBL-2H3 have higher basal reactivity in the absence of vitamin D, while exposure to the vitamin increased expression of VDR, which complexed with signaling molecules downstream from the surface immunoglobulin E receptor FcεRI and prevented MC degranulation; VDR also bound to the promoter for tumor necrosis factor and inhibited its expression.[25] Vitamin D also enhances production of the soluble interleukin-33 receptor, ST2, and inhibits interleukin-33 action.[26] This is critical because interleukin-33 is considered a "danger signal"[27] and has been implicated in allergic inflammation.[28–30] We have found that IL-33 acts synergistically with the neuropeptide substance P to stimulate skin MCs and induce skin inflammation.[31]

A systematic review found a significant relationship between low vitamin D levels and severity of polypoid rhinosinusitis.[32] Low cord serum vitamin D levels also were associated with increased childhood AD, but not asthma.[33,34] In addition, low vitamin D levels were associated with atopy[35,36] and food allergy.[37,38] We and others have reported that allergies, AD, and psoriasis contribute to an increased risk of autism spectrum disorder (ASD)[39,40] through activation of MCs.[41]

It is, therefore, of great interest that a number of papers reported that low serum vitamin D levels may be associated with neuropsychiatric diseases[42] and neurocognitive dysfunction,[43,44] as well as with increased risk for ASD.[45–50] In fact, vitamin D supplementation (300 IU/kg/d not to exceed 5,000 IU/d for 3 months) significantly improved clinical outcomes in 80% of children (n = 106) with ASD.[51]

High oral doses of vitamin D and its analogs are required for systemic anti-inflammatory effects, with possible risk for adverse calcemic effects.[52] However, doses of 10,000 to 60,000 IU of $1,25(OH)_2D3$ were apparently well tolerated by adult males.[53] A systematic review found that a topical combination of calcipotriol and betamethasone diproprionate used for psoriasis vulgaris was tolerable.[54]

A topical formulation developed by the author combines microalgae-derived vitamin D with the natural flavonoid tetramethoxyluteolin; a pilot study of a skin lotion containing only tetramethoxyluteoilin recently reported benefits in AD and psoriasis.[55] Tetramethoxyluteolin (tetramethoxyflavone) is a naturally occurring flavonoid, structurally related to luteolin (tetrahydroxyflavone), which has anti-inflammatory activity[56] but also inhibits keratinocytes[57] and MCs.[58] In fact, a luteolin-containing dietary supplement significantly improved symptoms of ASD in 2 pilot clinical trials.[59,60] We recently reported that tetramethoxyluteolin is a better inhibitor than luteolin of MCs[58] and microglia,[61] which are increasingly invoked in the pathogenesis of ASD.[40,62–64]

In conclusion, vitamin D deficiency has been associated with increased risk of atopic diseases and ASD, possibly through reduced ability to inhibit MCs and other inflammatory cells. Vitamin D supplementation alone, or together with other natural immunomodulatory agents, might prove useful in atopic and inflammatory diseases. In this issue, 5 expert groups address additional aspects of vitamin D in immunity, asthma, tuberculosis, and cancer.[65–69]

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