

Editorial

Vitamin D and Atopy

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)₂D3] (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



Theoharis C. Theoharides, MS, MPhil, PhD, MD, FAAAAI

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 urticaria⁶ 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 mastocytosis¹⁶ 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 diseases⁴² 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 dipropionate 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 tetramethoxyluteolin recently reported benefits in AD and psoriasis.⁵⁵ Tetramethoxyluteolin (tetramethoxyflavone) is a naturally occurring flavonoid, structurally related to luteolin (tetrahydroxyflavone), which has anti-inflammatory activity⁵⁶ but also inhibits keratinocytes⁵⁷ 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 MCs⁵⁸ 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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Theoharis C. Theoharides, MS, MPhil, PhD, MD
Molecular Immunopharmacology and Drug Discovery Laboratory,
Departments of Integrative Physiology and Pathobiology,
Internal Medicine and Psychiatry,
Tufts University School of Medicine and Tufts Medical Center,
Boston, Massachusetts

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