

to evaluate appropriate immune function. Serum 25D3 is only one variable in vitamin D regulated systems. Hydroxylation and subsequent activation of 25D3 to 1,25-dihydroxy vitamin D3 (1,25D3) are crucial for vitamin D3 function. Recent studies demonstrate that this activation step in the extrarenal circulation is more important than previously estimated and that regulation of 1,25D3 at the target tissue will occur independently of serum 25D3 levels.^{3,6}

Further experimental and clinical studies are needed to establish a firm link between vitamin D deficiency and asthma. Adverse effects of increased vitamin D intake must be considered. Cells treated with 1,25D3 will increase the expression of cathelicidin, an antimicrobial peptide, and TLR2 and CD14, important microbial recognition molecules.⁶ This is beneficial in a setting of infection or injury, where increased innate immunity is essential for protection. However, inappropriate increase in constitutive antimicrobial activity might lead to changes in the resident flora and can be proinflammatory.⁷ Furthermore, because the commensal flora is important for effective barrier function at epithelial surfaces and defense against colonisation by pathogens, disturbances in this fragile balance might be disadvantageous.

In summary, the article by Drs Litonjua and Weiss¹ adds to the growing evidence to suggest that vitamin D plays an important role in inflammation. Current dietary recommendations established before knowledge of these events did not consider the need for vitamin D to regulate immune function. Careful oral supplementation might improve some elements of diseases associated with dysregulation of inflammation such as asthma and atopic dermatitis. There is also mounting evidence that vitamin D plays a role in the prevention of breast, colorectal, and prostate cancer. Further prospective clinical trials and additional work to uncover the full range of functions of vitamin D are needed.

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Reply

To the Editor:

We thank Drs Schaubert and Gallo¹ for their interest in our recent article, in which we proposed a hypothesis to explain the asthma epidemic, namely that vitamin D deficiency may be partly to blame for the rise in asthma prevalence. We agree with the points that they raise, and although this link is not yet established, we feel that there is sufficient evidence for vitamin D as an immune modulator to propose this hypothesis. Indeed, the main reason for writing this article was to stimulate research into this potential link. We would now like to expound on the main points raised in the letter.

Although we have focused on vitamin D, we are aware that UV light has effects on immune cells via mechanisms that may be independent of the effects of vitamin D.^{2,3} However, because of the known risks of UV light exposure, the best approach to prevention will ultimately be through oral supplementation, if indeed the effects are mediated through the active forms of vitamin D.

As alluded to by Drs Schaubert and Gallo,¹ the appropriate dose and circulating level (as measured by 25-hydroxyvitamin D₃, 25[OH]D) of vitamin D for beneficial immune effects are unknown. This dose is likely to be different from that for bone health and may be different at various stages of the life cycle (ie, prenatal vs postnatal). After acute exposure to sunlight, humans can produce between 10,000 and 20,000 IU vitamin D₃, depending on the intensity of exposure and skin pigmentation.⁴ However, because levels can fluctuate depending on season and behavior,⁵ future epidemiologic research will need to collect information not only on circulating levels of 25(OH)D but also on diet (including supplement use) and on sun exposure behaviors as indices of more chronic exposure. With regard to toxicity, to date, ongoing clinical trials of vitamin D supplementation in pregnant and lactating women have not reported any clinical toxicity with doses as high as 6000 IU/d.⁶ Continued monitoring for potential toxicity in clinical trials will be both prudent and responsible conduct for research. We also agree that extrarenal and tissue-specific activation of vitamin D is important, and studies using animal models and cell systems will be necessary. A corollary is that genetic polymorphisms in the genes encoding the receptor and the enzymes will be important modifiers of the effect of vitamin D, given a particular dose.

Finally, the human microbiota (particularly the gut microbiota)⁷ has important effects on both the innate and adaptive immune system. How vitamin D intersects and interacts with the microbiota is a very important area of future research. We are in agreement with Drs Schaubert and Gallo that well designed multidisciplinary studies are needed to shed light on the role of vitamin D in both asthma pathogenesis and treatment.

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Omalizumab also successful in chronic urticaria

To the Editor:

We read with interest "Successful treatment of 3 patients with recurrent idiopathic angioedema with omalizumab."¹

We recently reported on 3 patients with refractory chronic urticaria who had marked improvement with omalizumab.² Two of the patients showed evidence of elevated anti-FcεRI antibodies, whereas 1 did not. We postulated that the possible mechanisms included the downregulation of IgE receptors providing fewer targets for IgE or anti-FcεRI antibodies.

In discussion of possible mechanisms, the authors indicate that the cases "do not appear to be IgE-mediated events." However, patients 1 and 2 had elevated IgE (244 and 510, respectively). The assay used to detect anti-FcεRI antibodies was not mentioned, but current commercial assays can be associated with false-negatives. The autologous serum skin test can similarly be false-negative. A basophil histamine release test, in which patient serum is incubated with donor basophils, was not performed but would be a useful indication of the presence of autoantibodies if positive.

It is also suggested by the authors that the apparent rapid improvement suggests a non-IgE-mediated mechanism because "omalizumab effects in asthma and allergic rhinitis occur in 8 to 10 weeks concomitant with reduction of bound IgE and IgE receptors and not with the initial reduction in free IgE levels." On the contrary, many omalizumab studies have correlated clinical improvement with reduction in free IgE levels within 4 weeks.^{3,4} In our report, 2 patients responded with clearing of urticaria within 1 week and 1 patient within 6 weeks. Aside from the mechanisms of binding of free IgE and downregulation of IgE receptors attributed to omalizumab, an effect on mast cell and basophil survival may be involved.⁵

It is not mentioned how long after stopping lisinopril omalizumab was started. Angiotensin-converting enzyme inhibitor-induced angioedema can persist for a period after cessation of the drug, making it possible for spontaneous resolution to have occurred after omalizumab was initiated.

Finally, one of our patients had low serum IgE level (<9 IU/mL), so we agree with the possibility of a non-IgE-mediated mechanism of action for omalizumab brought up by the authors.

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Reply

To the Editor:

We appreciate the correspondence from Spector and Tan¹ regarding our article on treatment of recurrent idiopathic angioedema with omalizumab.² We note their report on omalizumab use in chronic refractory urticaria.³

There are several common threads in both articles. The mechanisms driving neither idiopathic urticaria nor idiopathic angioedema are fully elucidated. Omalizumab, having apparent efficacy in both short series, demonstrates potential as a new therapeutic agent pending results of controlled trials. One might infer, therefore, that these partially overlapping syndromes, responding to similar treatment, might share underlying mechanisms. However, neither case series is designed to address mechanisms, so comments about mechanism in either group of patients remain highly speculative. Stated differently, some or none of the 6 patients described in either study might have responded to omalizumab because of IgE-mediated mechanisms.

We take issue with the implication by Spector and Tan¹ that the presence of elevated serum IgE levels in 2 of 3 patients with angioedema carries much predictive weight mechanistically. Total serum IgE levels have limited diagnostic utility because of considerable overlap in normal and atopic populations.⁴ Even in the urticaria series by Spector and Tan,³ 1 of 3 patients had a normal IgE level. We agree that for prospective studies, a panel of tests for antibodies directed against FcεRI, *in vitro* basophil histamine release, and possibly the autologous serum skin test would be appropriate, fully recognizing that the sensitivity and specificity of these tests are less than ideal in urticaria, let alone angioedema.^{5,6} We used a commercially available functional FcεRI antibody assay.

We concede that some asthma and rhinitis studies of omalizumab demonstrated efficacy as early as 4 weeks after initial dosing.^{7,8} We reiterate that IgE and downregulation of its cellular receptors have in no way been excluded as mechanisms for improvement in our series. However, the fact that this mechanism was linked to improvement in nonangioedema populations does not prove that it is operative in our series. It is intriguing that the patients of Spector and Tan,¹ like ours, had rapid improvement within weeks of initiating omalizumab. This might improve the chances of identifying the mechanisms involved.

Regarding their query that lisinopril (in 1 case) may have been a confounder, it was discontinued more than 1 year before instituting omalizumab.

Angioedema and urticaria may occur independently or in combination. Nevertheless, idiopathic angioedema and urticaria,