

Letter to the Editor

Vitamin D and atopic disorders in an obese population screened for vitamin D deficiency

To the Editor:

Vitamin D is a secosteroid that can be synthesized in the skin under the influence of ultraviolet light or obtained from dietary intake.¹ Vitamin D exerts many of its effects through interaction with the vitamin D receptor.² The importance of vitamin D in bone metabolism was established in the early 1900s with the diseases rickets and osteomalacia. In recent years, the vitamin D receptor has been found in a variety of cells, including keratinocytes and numerous cells of the immune system (eg, dendritic cells, natural killer cells, and T and B cells).² A number of studies have explored the effects of vitamin D on autoimmune diseases (eg, multiple sclerosis, type I diabetes, and inflammatory bowel disease), inflammatory skin diseases (psoriasis), and malignancies (eg, prostate, breast, and colon).^{1,2} The role of vitamin D in traditional atopic disorders (ie, asthma, allergic rhinitis, and atopic dermatitis [AD]) is uncertain.

A recent genome study by Poon et al³ found an association between genetic variants of the vitamin D receptor and susceptibility to asthma and atopy. At the 2006 American Academy of Allergy, Asthma & Immunology Annual Meeting, Camargo et al⁴ first presented results of a birth cohort study showing that maternal intake of vitamin D during pregnancy increased the risk of early childhood wheezing; the explanation for this strong inverse association remains unclear but could involve favorable effects of vitamin D on atopy risk, innate immunity, or both. In the present study we sought to examine the association between vitamin D status and the prevalence of atopic disorders in a population routinely screened for vitamin D deficiency.

The Massachusetts General Hospital Weight Center offered a unique opportunity to examine these issues because all patients are screened at their initial visit with a serum 1,25-dihydroxy vitamin D3 (25[OH]D) level. All patients undergo a comprehensive history and physical examination, including detailed questions about current medical problems (eg, asthma, allergic rhinitis, and AD), current medications, and a thorough review of systems.

Two investigators (E.O. and A.B.) reviewed 717 charts from the Weight Center to identify 100 patients who were vitamin D deficient (defined as a serum 25(OH)D level of <25 nmol/L) and 190 patients who were vitamin D replete (defined as a serum 25(OH)D level of ≥ 75 nmol/L). The study was powered to detect prevalence ratios of approximately 1.8 or higher. Electronic chart records were obtained after receiving approval from the institutional review board of the Massachusetts General Hospital. Inclusion criteria were presentation to the Weight Center for initial evaluation between the years 2004 and 2007, age 10 years or older, and no prior history of bariatric surgery. Subjects in the replete group could not have any prior serum 25(OH)D level of less than 75 nmol/L or a history of vitamin D deficiency as obtained by the physician at the time of initial evaluation to minimize misclassification of vitamin D status (eg, an only recent correction of longstanding vitamin D deficiency). For methodologic consistency, subjects in the deficient group could not have any prior serum 25(OH)D level of 25 nmol/L or greater. A total of 427 subjects were excluded because of prior vitamin D levels that

were not consistently in the deficient or replete categories or because of a history of prior bariatric surgery. Charts were reviewed for demographic characteristics (age, sex, and race), body mass index (BMI), vitamin D status (including date of serum 25(OH)D level and potential use of vitamin D supplements), and history of asthma, allergic rhinitis, and AD, including medications currently used for these conditions by affected individuals.

The mean age of our 290 subjects was 43 ± 15 years (range, 10-73 years), and 74% were female. Consistent with hospital statistics, the racial mix was 77% white, 11% black, and 12% other. The mean BMI was 44.8 ± 9.7 kg/m² (range, 25.9-88 kg/m²). Vitamin D status was not associated with the prevalence of asthma (37% of the deficient group vs 30% of the replete group, $P = .23$) or allergic rhinitis (22% vs 19%, respectively; $P = .54$). There was no significant association between vitamin D and either condition in the unadjusted or fully adjusted logistic regression models (data not shown). Consistent with prior studies,⁵ asthma was more common in women (adjusted odds ratio [OR], 1.9; 95% CI, 1.1-3.6). Age, race, and BMI were not significantly associated with asthma (all $P > .05$). None of these factors was associated with allergic rhinitis (data not shown).

By contrast, patients with vitamin D deficiency were more likely to report AD than their vitamin D-replete counterparts (5% vs 1%, respectively; $P = .05$, Fisher exact test). Although small numbers precluded detailed analysis, serial adjustment for age, sex, white race, and BMI did not alter the OR of approximately 5 (unadjusted OR, 4.9; 95% CI, 0.9-26; $P = .06$). None of these potential confounders was associated with AD (data not shown).

Thus we found an increased risk of AD among obese individuals with vitamin D deficiency compared with their vitamin D-replete counterparts. By contrast, vitamin D did not appear to have a significant association with the prevalence of either asthma or allergic rhinitis.

To date, there is sparse information on vitamin D status and AD. Although our earlier birth cohort study⁴ did not find an association between maternal intake of vitamin D during pregnancy and parent-reported eczema in their offspring, we believe that these null findings probably reflect misclassification of true AD status. In support of this belief, we note a recent randomized trial that demonstrated improved AD among children who were randomized to live in a subtropical (sunny) climate for 4 weeks compared with staying in Norway.⁶ Moreover, we recently completed a small, randomized, double-blind, placebo-controlled trial and found that vitamin D supplementation significantly improved skin symptoms in 11 children with winter-related AD.⁷

These results raise interesting questions about the potential role of vitamin D in the pathogenesis of AD. Adorini et al⁸ have shown that vitamin D can induce tolerogenic dendritic cells exhibiting decreased expression of CD40, CD80, and CD86, as well as having enhanced IL-10 secretion, and that this has an effect on allograft rejection and autoimmune diseases, such as type 1 diabetes and psoriasis. It is possible that this same dendritic cell profile could have an ameliorating effect on AD activity. Another potential role for vitamin D is suggested by the work of Schaubert et al,⁹ who found that 1,25(OH)D3 enables keratinocytes to recognize and respond to microbes through action on the Toll-like receptor 2 and leads to upregulation of cathelicidin. This work suggests that vitamin D deficiency might be important in the predisposition

of skin from patients with AD to superinfection by *Staphylococcus aureus*.

Our case-control study does have several limitations. The atopic disorders were self-reported to physicians during their initial evaluation at the Weight Center. The prevalence of asthma might appear to be high, but this result is in agreement with prior studies on the prevalence of self-reported asthma in the morbidly obese.¹⁰ This does not remove the possibility that asthma, as reported in this obese population, is of a different phenotype than that found in normal-weight individuals. Although we found that patients' medication records corroborated their reported diagnoses, the possibility of recall bias is inherent to this type of study. Furthermore, because this is a population seeking care for their obesity, there is a chance for selection bias as well. The interrelations between vitamin D, obesity, and atopic disorders are likely to be complex. We encourage further work on these issues in diverse populations.

The absence of a significant difference for asthma in the vitamin D-deficient and vitamin D-replete groups might, at first glance, appear to contradict the prior finding by Camargo et al.⁴ However, that earlier study examined early childhood wheeze, an outcome that likely represents a different phenotype from this group of obese adults with asthma. The role of vitamin D in respiratory infections, atopy, and the various asthma phenotypes will likely prove a rich field of study.

A final limitation relates to the study design. Because all data come from a single point in time (the initial clinical evaluation), we cannot determine the temporal nature of the association between vitamin D deficiency and AD: Which came first? Longitudinal studies with baseline serum 25(OH)D levels would be better suited to address this important issue.

In summary, we found an increased likelihood of AD in obese patients with vitamin D deficiency and no apparent association between vitamin D status and either asthma or allergic rhinitis. The AD finding raises the possibility that small amounts of intentional sunlight exposure (eg, 15 minutes per day for 2-3 days per week) or vitamin D supplements (eg, 1000 IU/d) could decrease the risk of AD, ameliorate symptoms in those already

with AD, or both. Large cohort studies and clinical trials are warranted to assess the role of vitamin D in the prevention and treatment of AD.

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REFERENCES

1. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007;357:266-81.
2. Nagpal S, Na S, Rathnachalam R. Noncalcemic actions of vitamin D receptor ligands. *Endocr Rev* 2005;26:662-87.
3. Poon AH, Laprise C, Lemire M, Montpetit A, Sinnett D, Schurr E, et al. Association of vitamin D receptor genetic variants with susceptibility to asthma and atopy. *Am J Respir Crit Care Med* 2004;170:967-73.
4. Camargo CA Jr, Rifas-Shiman SL, Litonjua AA, Rich-Edwards JW, Weiss ST, Gold DR, et al. Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3 y of age. *Am J Clin Nutr* 2007;85:788-95.
5. Schatz M, Camargo CA Jr. The relationship of sex to asthma prevalence, health care utilization, and medications in a large managed care organization. *Ann Allergy Asthma Immunol* 2003;91:553-8.
6. Byremo G, Rod G, Carlsen KH. Effect of climatic change in children with atopic eczema. *Allergy* 2006;61:1403-10.
7. Sidbury R, Sullivan AF, Thadhani RI, Camargo CA Jr. Randomized trial of vitamin D supplementation for winter-related atopic dermatitis in Boston: a pilot study. *Br J Dermatol* 2008. In press.
8. Adorini L, Penna G, Giarratana N, Uskokovic M. Tolerogenic dendritic cells induced by vitamin D receptor ligands enhance regulatory T cells inhibiting allograft rejection and autoimmune diseases. *J Cell Biochem* 2003;88:227-33.
9. Schaubert J, Dorschner RA, Coda AB, Buchau AS, Liu PT, Kiken D, et al. Injury enhances TLR2 function and antimicrobial peptide expression through a vitamin D-dependent mechanism. *J Clin Invest* 2007;117:803-11.
10. Simard B, Turcotte H, Marceau P, Biron S, Hould FS, Lebel S, et al. Asthma and sleep apnea in patients with morbid obesity: outcome after bariatric surgery. *Obes Surg* 2004;14:1381-8.

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