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A Review of the Relationship Between Inflammatory Bowel Disease and Vitamin D

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A wide range of evidence exists linking vitamin D and the immune system suggesting that lower levels maybe associated with autoimmune diseases. The main driver of vitamin D levels, UV exposure, has been linked to decreased risk of inflammatory bowel diseases by epidemiological studies. Animal studies have suggested that vitamin D could have a causal effect on inflammation in the GI tract and now small studies suggest that vitamin D supplementation could prevent relapse. Additional large prospective trials are necessary to demonstrate this causal link definitively.

There is increasing interest in the role of vitamin D in autoimmune diseases. Among patients with inflammatory bowel disease (IBD), a significant percentage are vitamin D deficient.[1-4] It remains unclear whether this deficiency is related to the disease or is rather a result of malabsorption from the disease. Epidemiological studies led to the initial hypothesis that there was a role of vitamin D outside of calcium metabolism and bone health. This was followed by basic science experiments demonstrating the role of vitamin D in immunological processes. More recently, there have been small clinical trials demonstrating an effect of vitamin D supplementation on the course of IBD. Here, we will review the evidence linking vitamin D to inflammatory bowel diseases.

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The association between latitude and autoimmune diseases dates back to at least the 1960s when researchers studying multiple sclerosis (MS) noted an association between the incidence of the disease and latitude.[5] The relationship between inflammatory bowel disease and latitude was explored in the 1990s in Europe.[6] This study examined new cases of IBD between 1991 and 1993 across 20 centers in Europe and found higher incidences of both ulcerative colitis (UC) and Crohn's disease (CD) in northern Europe compared to southern centers. More recent studies in Europe have focused on single countries in a retrospective manner. A French study showed an association between latitude and CD incidence in France between 2000 and 2002 but

(continued on page 48)

(continued from page 46)

failed to find a similar association for UC.[7] In contrast, a more recent population study in Finland found an association between UC incidence and latitude.[8] These European population studies were in countries that are relatively genetically homogenous compared to the United States. A lingering confounder in those studies was the possibility that another environmental or genetic factor was playing a role in the incidence of IBD. Using the Nurses Health Study dataset in the United States, Khalili et al. found a relationship between both UC and CD and latitude.[9] The risk of CD among women in the southern US was 0.48 (95%CI: 0.30-0.77) while the risk of UC in the southern US was 0.62 (95%CI: 0.42-0.90). Looking at this possible association from another perspective, Kurtzke et al. found a relationship between altitude of residence and incidence of MS, with those living in the lowest lying regions in Switzerland exposed to less UV light which was associated with the highest MS incidence rate.[10] More recently, a large database of hospitalizations in the United States has been used to show an association between the risk of inpatient surgery for Crohn's disease and average UV light exposure in the patient's state of

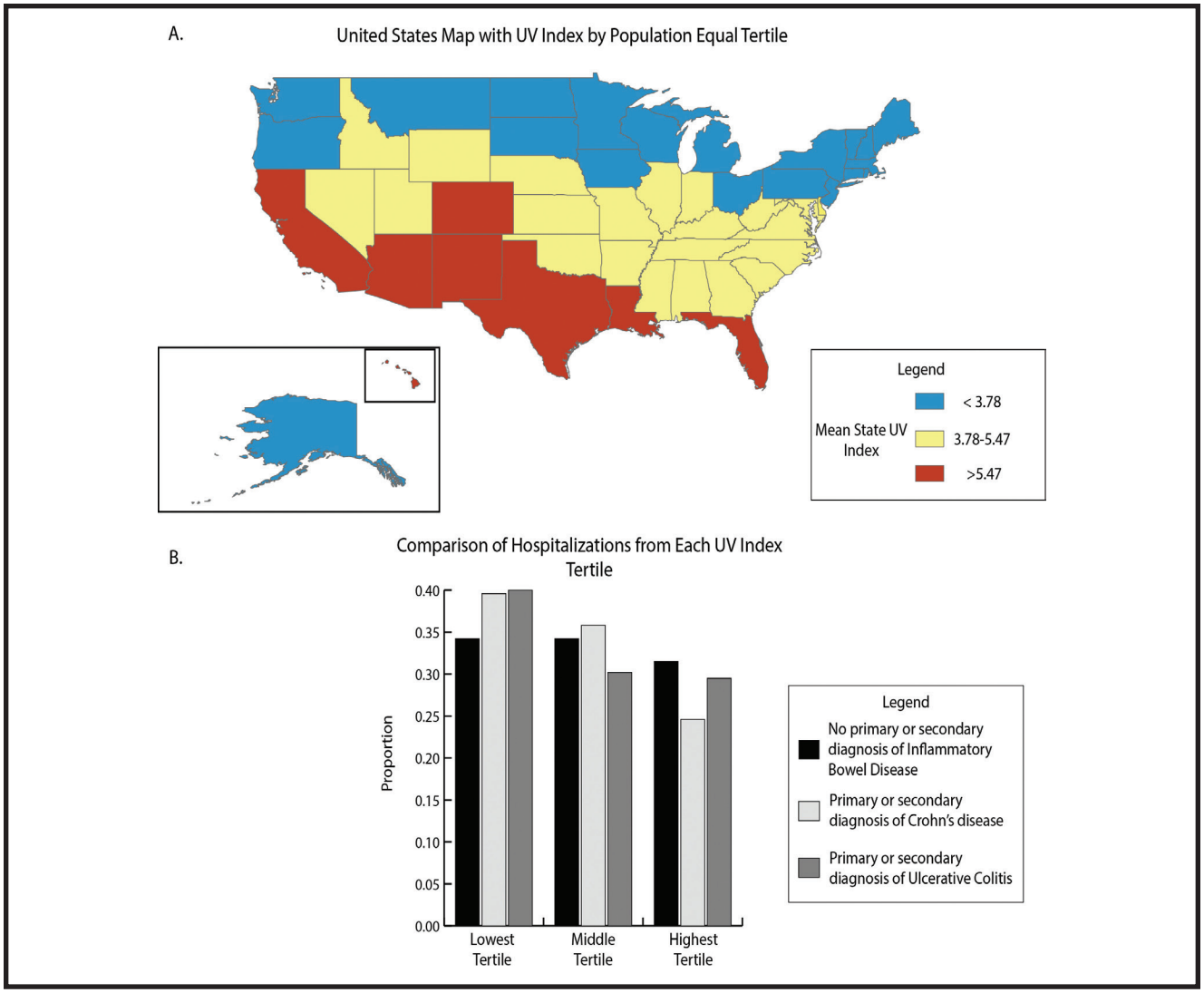

Figure 1. A map of the United States shows the average UV radiation exposure in each state and indicates that UV light is highest in the Southwest (A). Examining the number of hospitalizations per UV tertile, the highest number of hospitalizations for Crohn's disease and Ulcerative Colitis is in the lowest UV exposure tertile (B). For comparison, the percentage of total hospitalizations without a diagnosis of IBD is also displayed.[11]

residence.[11] These studies taken together suggest there is some relationship between latitude, UV exposure, and autoimmune diseases such as IBD.

While these studies show an association exists, it is difficult to prove a causal relationship between autoimmune diseases and a deficiency of UV light, or indirect causality via a deficiency of vitamin D using epidemiological studies. Rodent experiments allow more direct assessment of the case for a causal link between vitamin D and inflammatory bowel diseases. The first step was confirmation of the expression of vitamin D receptor protein in immune cells.[12,13] In further experiments with IL-10 knockout mice, models for inflammatory bowel disease, Cantorna et al. compared vitamin D deficient IL-10 knockout mice to knockout mice with sufficient vitamin D.[14] Those mice with vitamin D deficiency had significantly more inflammation in the small intestine, lower body weight, and higher mortality. Further experiments with IL-10 knockout mice found that calcium and 1,25 dihydroxyvitamin D supplementation ameliorates inflammatory colitis, and that this benefit is mediated through the tumor necrosis factor-alpha (TNF-a) pathway.[15]

Retrospective studies of the relationship between vitamin D levels and IBD have recently been published and show a link between disease activity and deficiency. The Endocrine Society defines vitamin D insufficiency as levels of serum 25-OH vitamin D below 75 nmol/L (30 ng/ml) and deficiency as levels below 50 nmol/L (20 ng/ml).[16] Vitamin D insufficiency among the IBD population is very high, affecting up to 78% of our patient population[2] and deficiency affects a significant portion, up to 60%.[17] As expected, there is significant variation in deficiency rates depending on the time of year the level is checked. In a study of CD patients in Ireland, 50% of the patients were deficient during winter months while only 19% were deficient during the summer.[1] Comparing the rates of deficiency among healthy controls and CD patients, there does appear to be a difference. In another study from Ireland, 44 patients with CD and 44 age-matched controls were compared with regards to vitamin D levels in winter and summer.[18] Of the patients with CD, 18% were deficient in the summer months compared to just 5% of the healthy controls. In the winter months, the rate of deficiency among the CD patients was 50% compared to 25% of the controls. A few studies have examined the effect of vitamin D levels on disease activity. IBD patients in Boston are deficient in vitamin D approximately 1/3 of the time, but those who normalize their vitamin D levels have a reduced risk of surgery (OR 0.56, 95%CI 0.32-0.98) compared to those who remain deficient.[19]

While the number of studies linking vitamin D and IBD is significant, only a few studies have examined the effect of supplementation on disease activity or outcomes. The largest study of the effect of supplementation was conducted in Denmark in 2005 in 108 patients with Crohn's in remission based on CDAI and CRP.[20] Patients were randomized to 1200 IU of vitamin D3 plus 1200mg calcium daily for a year versus only 1200mg calcium. Notably, the patients were not selected based on initial vitamin D status so only 1/3 of the population was deficient at initiation. The primary outcome of the study was risk of relapse based on CDAI increase of 100 or more and an absolute CDAI of 150 over the course of the year. Among those given vitamin D, the relapse rate was 13% whereas those given only calcium had a relapse rate of 29%. Using Cox proportional hazards, the hazard ratio of relapse was 0.42 among those taking the vitamin with a p value of 0.06. Despite a relatively low dose of supplementation, the average 25-OH vitamin D level did rise from 69 nmol/L to 96 nmol/L within 3 months in the treatment group. A recently published study from Ireland enrolled a similar group of patients with CD, i.e. those in remission and administered 2000 IU D3 versus placebo for 3 months.[21] Among the 13 patients on therapy, only 9 achieved sufficient levels and it was among these 9 that the clinical and biochemical benefits were seen. Those with levels >75nmol/L had lower CRPs, and higher quality of life scores based on the IBDQ. The fact that 2000 IU was not sufficient to increase vitamin D3 to sufficient levels is not surprising based on prior research and the guidelines regarding supplementation. The Endocrine Society guidelines suggest that the patients that patients with deficiency receive 50,000 IU weekly and those patients with a malabsorption syndrome such as Crohn's disease receive 6,000-10,000 IU daily.[16] A pilot study of vitamin D supplementation in the Crohn's population has corroborated the need for higher doses of supplementation.[22] In that study, patients with Crohn's were enrolled if they had evidence of moderately active disease based on CDAI between 150 and 400 and vitamin D levels <40. Patients were then started on 1,000 IU daily with a dose escalation every 2 weeks until their levels reached 40 ng/ml or 5,000 IU. Of the 18 patients enrolled, 14 required escalation

to 5,000 IU daily and even among these, half did not reach the goal of 40 ng/ml suggesting that even higher doses would have been required to reach this target.

In conclusion, there appears to be mounting evidence that vitamin D plays a role in immune regulation and may influence the risk and activity of inflammatory bowel diseases. Higher levels appear to correlate with improved disease activity. The Crohn's and Colitis Foundation of America is currently sponsoring a pilot clinical trial to examine the effects of 10,000 IU of daily vitamin D3 on clinical outcomes among patients with Crohn's disease and vitamin D deficiency with patients receiving continued supplementation until they reach 50ng/ml. This randomized controlled trial will provide important prospective data on whether higher blood vitamin D levels do lead to improved outcomes. ■

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