Vitamin D is best known for its effects on bone health, but a growing appreciation of its many immunomodulatory actions has prompted significant recent interest in its potential to prevent and treat diverse viral and bacterial infections [1–4]. Much of this research has focused on the question of whether vitamin D supplementation might slow progression of disease caused by human immunodeficiency virus (HIV) and prevent tuberculosis and other opportunistic infections in HIV-infected people [5]. Physiological concentrations of calcitriol, the active vitamin D metabolite, inhibit HIV replication in human macrophages in vitro and restrict growth of Mycobacterium tuberculosis through the induction of autophagy [6,7]. Observational studies conducted in HIV-infected people who are not taking antiretroviral therapy (ART) have reported associations between vitamin D deficiency and susceptibility to tuberculosis, upper respiratory tract infection, and oral candidiasis [8,9], raising the possibility that supplementation might reduce susceptibility to infections in this patient group. Surely, though, once a potent pharmacological therapy like ART is initiated, isn’t deficiency in a mere micronutrient unlikely to influence clinical outcomes in HIV-infected people?

Not so, according to a cohort study published in this issue of the Journal [10]. Sudfeld and colleagues studied 1103 HIV-infected adults in Tanzania who were taking ART and participating in a randomized controlled trial of a multivitamin supplement that did not contain vitamin D. Clinical assessments were performed at monthly intervals, and the median duration of follow-up was 20.6 months. After multivariate adjustment, vitamin D deficiency (defined as a serum concentration of 25-hydroxyvitamin D of <20 ng/mL) was found to be associated with increased risk of incident smear-positive pulmonary tuberculosis (hazard ratio [HR], 2.89; \( P = .03 \)), oral thrush (HR, 1.96; \( P = .046 \)), wasting (HR, 3.10; \( P = .009 \)), and >10% weight loss (HR, 2.10; \( P = .02 \)) but not with risk of malaria, pneumonia, or anemia. A milder degree of deficiency, termed “vitamin D insufficiency” and defined as a serum 25-hydroxyvitamin D concentration of 20–30 ng/mL, did not associate with any of these outcomes.

Is the reported association between baseline vitamin D deficiency and increased risk of tuberculosis likely to be causal? In favor of this conclusion, the association survived statistical adjustment for a number of potential confounders of the relationship between vitamin D status and risk of opportunistic infection, including sex, age, season of sampling, body mass index, measures of HIV disease stage at baseline, and ART regimen. The authors also went to considerable lengths to investigate whether this association arose as a result of reverse causality, by excluding from their analysis individuals who developed tuberculosis within a month of enrollment. Notably, the association between baseline vitamin D deficiency and increased risk of subsequent tuberculosis was still observed even when diagnoses of pulmonary tuberculosis arising in the first 2 months of the study were excluded in a sensitivity analysis. This finding is significant, as tuberculosis itself might contribute to vitamin D deficiency, by reducing patients’ sun exposure or increasing consumption of 25-hydroxyvitamin D by activated macrophages. The observation that vitamin D deficiency preceded the onset of tuberculosis in the present study is consistent with findings from a cohort study conducted in HIV-uninfected patients [11], and it effectively excludes reverse causality as an explanation for the association between vitamin D deficiency and tuberculosis risk reported here. A final point in favor of a causal interpretation is the biological plausibility of the hypothesis: in...
addition to the wealth of supportive laboratory work, clinical trials conducted in HIV-uninfected subjects have reported that oral vitamin D supplementation can exert both antimicrobial and antiinflammatory activity [12, 13], which could explain the observed associations between vitamin D repletion and decreased tuberculosis risk and better maintenance of body mass. Interestingly, no association between vitamin D status and CD4+ T-cell count was observed in this study. This finding is consistent with reports from randomized controlled trials conducted in HIV-infected children that showed no effect of vitamin D supplementation on CD4+ T-cell count [14, 15]; it suggests that any effects of vitamin D on risk of opportunistic infection are not mediated via maintenance of this cell population.

The possibility that the associations reported are noncausal must also be considered. Two factors merit particular consideration. First, observational studies evaluating the influence of nutritional factors on disease risk are notoriously susceptible to confounding between micronutrient levels and other exposures—known and unknown—that could increase disease risk [16]. Cigarette smoking is a case in point: it has been posited both to lower vitamin D status [17] and to increase tuberculosis risk [18], but it was not adjusted for in the analysis presented. Causal inference might be strengthened in future observational studies by investigating whether any influence of vitamin D status on tuberculosis risk is modified by polymorphisms in genes involved in the vitamin D pathway, as previously demonstrated in HIV-uninfected people [19, 20]. A second reason for skepticism relates to the finding that vitamin D deficiency was associated with increased risk of tuberculosis but not of pneumonia. Vitamin D-inducible antimycobacterial activity in vitro is mediated at least in part by induction of the antimicrobial peptide cathelicidin LL-37 [21, 22], which possesses activity against pneumonia-causing organisms, including Streptococcus pneumonia [23]; one might, therefore, expect vitamin D deficiency to associate with susceptibility to pneumonia. Failure to demonstrate such an association in the present study may have arisen as a result of type 2 error: although the study was large, deficiency was uncommon, affecting <10% of participants. Accordingly, power to detect weaker disease associations was limited. An alternative interpretation is that vitamin-D-inducible antimicrobial responses are protective against M. tuberculosis but not against other pathogens causing pneumonia. The concept that vitamin-D-inducible responses may be pathogen specific is supported by findings of a recent clinical trial reporting that vitamin D afforded protection against infection with influenza A virus but not with influenza B virus [24].

On balance, although the findings of Sudfeld et al are insufficient to justify offering routine vitamin D supplementation to vitamin-D-deficient HIV-infected people, they add to the evidence suggesting that vitamin D deficiency is an important risk factor for the development of tuberculosis. Clinical trials are required to resolve this issue, and the results presented here provide a rationale to include ART-treated HIV-infected patients in these studies. The observation that vitamin D deficiency but not insufficiency was associated with tuberculosis risk suggests that such trials will need to be conducted in populations with high baseline rates of vitamin D deficiency if they are to yield positive results. On the evidence presented by the current study and by others [25, 26], vitamin D deficiency is not highly prevalent among HIV-infected people in peri-equatorial Africa. However, one does not need to travel to Europe or North America to find a high prevalence of vitamin D deficiency in HIV-infected people: rates as high as 86% have been reported in Cape Town, South Africa [8], and rates in India are similar [27]. If clinical trials confirm that vitamin D supplementation is, indeed, effective in preventing tuberculosis in vitamin-D-deficient HIV-infected people, this nontoxic and potentially highly cost-effective intervention could have a significant impact on public health in many of the countries most affected by the HIV pandemic.

Note

Potential conflicts of interest. Author certifies no potential conflicts of interest.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editor consider relevant to the content of the manuscript have been disclosed.

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