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Tuberculosis and vitamin D: what's the rest of the story?

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Both protein–energy undernutrition and specific micronutrient deficiencies debilitate the cell-mediated immune system important in protection against tuberculosis.[1] However, once tuberculosis de velops, the disease itself induces a catabolic state resulting in negative nitrogen balance and micronutrient deficiencies. Generations of clinicians treating patients with tuberculosis believed that nutritional support was crucial to proper patient care. Why, then, has it been so difficult to prove through randomised controlled clinical trials that nutritional interventions improve tuberculosis treatment outcomes? Findings from systematic reviews[2–6] have not shown any clear, consistent benefit in terms of tuberculosis-specific outcomes, although they do show improvements in nutritional status.

In the past 30 years, researchers have discovered many roles and mechanisms of vitamin D action in both the innate and adaptive immune systems.[7] Vitamin D promotes macrophage-mediated killing of *Mycobacterium tuberculosis*,[8] an observation that has led to several phase 2 trials[2–6] of vitamin D sup plementation, nearly all of which have shown no substantial benefit in terms of tuberculosis treatment outcomes. In *The Lancet Infectious Diseases*, Peter Daley and colleagues[9] report findings from another such trial, and again the findings are negative. The randomised, double-blind, placebo-controlled trial was well designed to address an important issue with use of an inexpensive, simple intervention. Study treatment was given under direct observation; randomisation involved well concealed treatment allocation; masking of the intervention between the groups was reportedly good; at baseline the study groups were reasonably matched, although pulmonary cavitation was unknown; assessment of endpoints was masked; dedicated study staff collected all patient data; smears and cultures were processed in one laboratory by one experienced technologist who was masked to treatment allocation; and withdrawals, exclusions, and dropouts were noted. Thus, the methods seem to be robust, despite the absence of a traditional CONSORT diagram or use of multivariable regression methods in the analysis. Furthermore, the trial was reasonably powered for its primary outcome of time to sputum culture conversion. Median time to sputum culture conversion was similar between participants in the vitamin D and placebo groups (43·0 days [95% CI 33·3–52·8] and 42·0 days [33·9–50·1], respectively), as were the proportions of patients with positive sputum cultures at 2 months. Does this mean that vitamin D supplementation is of no value in the management of pulmonary

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tuberculosis? The answer is not yet clear, but different questions should now be asked. Although vitamin D stimulates macrophage-mediated killing of *M tuberculosis* through the innate immune system, it also regulates this response by inducing mechanisms to inactivate some aspects of the immune responses and modulate others. Vitamin D itself induces mechanisms for inactivation of vitamin D and vitamin D-mediated innate immune responses and inflammation.[10] In terms of the adaptive immune response, vitamin D suppresses T-helper type 1 cellular responses crucial in host defense against tuberculosis, promoting a T-helper type 2 predominance associated with immunological tolerance, humoral immunity, and defense against viral infections.[11] An extensive body of scientific literature has developed elucidating the effects of vitamin D on these and other cellular components of the immune system, many of which have suppressor functions.[7,12]

Some research has suggested that the antimyco-bacterial activity of vitamin D might operate at the level of the initial implantation and ingestion of bacilli by alveolar macrophages and tissue dendritic cells.[13,14] In other words, vitamin D might also be important for prevention of symptomatic disease. Rather than pharmacological doses given at discrete moments after a patient develops active disease, a constant level of vitamin D sufficiency might be important in the bolstering of resistance to tuberculosis so that the initial response to an inhaled bacillus is optimum at the moment it happens. This initial response is dependent not only on vitamin D, but also on various micronutrients and protein–energy nutrition, so optimisation of this initial response might require consideration of nutritional status more broadly.

Trials assessing sputum conversion could be misdirected if the major action of vitamin D, in the context of active tuberculosis disease, is to mitigate the inflammatory and immune response.[4,5] This function would be better shown through restriction of tissue damage or prevention of relapse, rather than with acceleration of sputum conversion; however, such trials are longer and more difficult and costly to perform. A therapeutic effect might be assessed by addition of a vitamin D intervention to a large phase 3 trial with a factorial design. The results of recent clinical trials and advances in immunology suggest that investigation of the role of vitamin D in tuberculosis prevention might be fruitful.

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