Commentary

Dissecting the immunological, antimicrobial and clinical effects of vitamin D therapy in tuberculosis

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Invited Commentary on 'Vitamin D accelerates resolution of inflammatory responses during tuberculosis treatment', Coussens et al.*, Proceedings of the National Academy of Sciences of the United States of America, 2012.*

'Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning', Sir Winston Churchill, 1942.

Vitamin D, in the form of cod-liver oil, was first used as a treatment for tuberculosis (TB) over a century ago. The more recent discovery that macrophages (the intracellular niche of *M. tuberculosis*) can synthesise the biologically active form of vitamin D – $1,25(OH)D_3$ – from its precursor, the association of vitamin D deficiency with TB disease,[1] and the potent effects of $1,25(OH)D_3$ on mycobacterial killing *in vitro* through intracellular expression of the antimicrobial peptide LL-37,[2] led to clinical trials of vitamin D as an adjunct to antimicrobial treatment of pulmonary TB. The results of the latest and most robust study were mixed, showing increased speed of sputum culture conversion only in the subset of vitamin D-treated patients with the *tt* genotype of the TaqI polymorphism of the Vitamin D Receptor.[3]

However, the investigators have now uncovered profound immunomodulatory effects of vitamin D therapy in their cohort.[4] By comparing responses in those given anti-tuberculous therapy alone with those given adjunctive vitamin D, the effects of vitamin D on a range of circulating cytokines and chemokines during recovery from TB were compared. Vitamin D hastened the resolution of *M. tuberculosis* antigen-independent and antigen–dependent hypercytokineaemia in pulmonary TB; these effects were not restricted to patients with the *tt* TaqI polymorphism, but occurred also in patients with *TT* and *Tt* genotypes. Additionally, and in contrast to the original intention-to-treat analysis, an adjusted per-protocol re-analysis of the 96 patients who completed the full course of study medication showed a significant shortening of time to sputum smear conversion in the whole cohort with adjunctive vitamin D. Given the high efficacy of short course antimicrobial chemotherapy for drug-sensitive TB, detection of even a modest incremental effect of vitamin D on clinical endpoints is notable.

Given that vitamin D hastened microbiological clearance, the accelerated resolution of inflammatory responses in patients receiving vitamin D is difficult to interpret. During effective anti-TB drug treatment, mycobacterial load and antigen load progressively decline and a range of *M. tuberculosis*-induced inflammatory responses wane correspondingly. Therefore, it is unclear whether the observed accelerated resolution of inflammatory responses is mediated directly by effects of vitamin D on the adaptive immune system, as concluded by the authors, or indirectly in response to an accelerated decline in bacillary burden and antigen load mediated by enhanced vitamin D-mediated innate intracellular killing of *M. tuberculosis*.

This uncertainty may have clinical implications. If vitamin D directly attenuates inflammatory immune responses during TB treatment, it might have an adjunctive role in limiting immunopathology in certain clinical subtypes of TB, such as TB meningitis. This would be akin to adjunctive immunosuppressive corticosteroids, where net clinical benefit through suppression of immunopathology depends on the host genotype of key innate immune response genes.[5] On the other hand, a number of case-series have posited an association between vitamin D therapy and hyperinflammatory paradoxical 'upgrading' reactions during TB treatment.[6] Future clinical trials of adjunctive vitamin D therapy should therefore correlate the kinetics of immune responses with clinical complications of immunopathology, such as paradoxical reactions, as well vitamin D receptor genotypes, although achieving the necessary sample size will be challenging.

To unmask the full potential of adjunctive vitamin D therapy, future studies should focus on multidrug-resistant TB where the therapeutic effects of anti-tuberculous antibiotics are blunted. Finally, the tantalising potential of vitamin D as preventative therapy, as suggested by a recent pilot study in Mongolia,[7] must not be overlooked.

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