Vitamin D and tuberculosis: hope or hype?

It may be worthwhile to test for and treat vitamin D deficiency in latent infection, but not in active TB

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In this issue of the Journal, MacLachlan and Cowie advocate increased testing of vitamin D (serum 25-hydroxyvitamin D [25-OHD]) for people with risk factors for vitamin D deficiency and tuberculosis (TB).[1] This pertinent suggestion is based on the assumption that vitamin D deficiency is a risk factor for progression from latent to active TB, and that correction of deficiency could reduce this risk (the demonstration by MacLachlan and colleagues[2] of TB seasonality in Australia is consistent with this hypothesis). The proposal presents a timely opportunity to scrutinise evidence of an association between vitamin D deficiency and TB, temper the high hopes that vitamin D might be an important adjunctive treatment for active TB, and remind clinicians about problems with testing and interpreting 25-OHD levels.

Many communicable diseases are seasonal — for example, influenza, rotavirus and TB. But many potential risk factors are also seasonal — temperature, time spent indoors, household crowding, humidity, ultraviolet radiation (which has immunological effects independent of vitamin D),[3] incidence of co-infections, and, potentially, nutritional intake. An important maxim to remember when interpreting the literature showing associations between vitamin D and seasonality — and a wide range of conditions from cancer to cardiovascular disease, schizophrenia to bacterial vaginosis — is that, as MacLachlan and Cowie point out, correlation does not imply causation.[1]

We know that serum 25-OHD levels are low in active TB.[3] What might be the explanation? One hypothesis is that it is appropriately low due to conversion to 1,25-dihydroxyvitamin D (activated vitamin D [calcitriol]). Indeed, calcitriol, an important factor in human innate antimycobacterial immunological responses,[4,5] has been found to be elevated in active TB.[6] Also, 25-OHD concentration can spontaneously recover over time with TB treatment,[3] but has been shown to fall during TB immune restoration syndrome,[7] suggesting that low 25-OHD concentration could be a consequence of immunological activation (a negative acute phase reactant). Further data are needed; there may be many factors accounting for low 25-OHD levels in active TB, and the relationship could be bidirectional.

There is increasing evidence that in high TB-burden settings — using doses considered safe for programmatic deployment where calcium, 25-OHD or calcitriol levels cannot readily be measured — vitamin D supplementation in active TB is not beneficial for TB outcomes.[8,9] The situation may be different in well resourced settings, where management of TB and underlying conditions (HIV, diabetes and, possibly, vitamin D deficiency) can be individually tailored. Using high vitamin D doses in a well resourced, monitored setting is generally safe[10] (but not always)[11] and may confer more rapid sputum smear conversion time.[12] In a small subset of TB patients with a specific vitamin D receptor genotype and low mean baseline 25-OHD concentration, it may be associated with faster sputum culture conversion.[10] Two other trials of vitamin D supplementation for active TB have been published, but methodological issues impair the ability to draw firm conclusions.[13,14] A further article has been submitted for publication. A meta-analysis is needed — it would probably conclude that supplementary vitamin D is not helpful in active TB overall, but may benefit some outcomes in a selected minority of patients. However, treating vitamin D deficiency in patients with TB may be relevant for non-TB end points.

Contrastingly, MacLachlan and Cowie are advocating a test-and-treat strategy for vitamin D status before active TB development. This makes immunological sense.[4,5] The single prospective study examining risk of progression to active TB after exposure found that seven of 30 people with serum 25-OHD levels < 17 nmol/L developed TB, but that only one of 64 people with 25-OHD levels ⩾ 17 nmol/L did so.[15] Other factors may have explained both the profoundly low 25-OHD levels and increased TB risk; nevertheless, in light of the accumulating evidence, maintenance of latency appears to be the most appropriate stage of infection to target with a vitamin D intervention.[16] However, since the 25-OHD concentration associated with TB reactivation in the above study was quite low (< 17 nmol/L), the impact of correcting all cases of vitamin D deficiency (< 50 nmol/L) on TB incidence at the population level may be small. A prospective study of vitamin D replacement in latent TB would help in improving the evidence base for the association between vitamin D deficiency and TB. However, clinical trials in this field are challenging to conduct, due to the large sample sizes required, the fact that tests for latent TB (relying on immunological responses) may themselves be influenced by vitamin D status, and because correction of deficiency would need to show benefits over and above recognised latent TB treatments (eg, isoniazid preventive therapy and HIV treatment). This raises the question of whether we need to await randomised controlled trial evidence before making a public health recommendation. Given the potential benefits of correction of vitamin D deficiency independent of TB risk, MacLachlan and Cowie's recommendation seems reasonable.

Notably, promotion of 25-OHD testing coincides with the Royal College of Pathologists of Australasia calling for restraint.[17] They recommend measurement of 25-OHD in people with listed risks or clinical/laboratory evidence of deficiency only,[17] as MacLachlan and Cowie advocate. A reason for restraint in ordering a 25-OHD test is that many widely used automated assays can lack accuracy and reproducibility.[3,17] Clinicians need to understand the test's

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limitations, including that different methods may give different results.[17] Liquid chromatography–tandem mass spectrometry has better performance characteristics, but is less widely available and results are user-dependent.

It is becoming popular to routinely test 25-OHD in people with active TB. Based on the information above, this is misplaced, since not all patients with TB have vitamin D deficiency risk factors, there is potential for spontaneous recovery of low 25-OHD levels in active TB, and correction of low 25-OHD levels appears to be non-beneficial for TB outcomes.

Finally, to address the contentious issue of vitamin D reference intervals — these are unusual among laboratory assays, being no longer based on normal population data. The lower limit of normal has gradually crept up from 25 nmol/L to 75 nmol/L or higher.[3] Inevitably, increasing proportions of the population are therefore now "deficient". Although this move is motivated by concerns for bone health, the appropriateness of such targets requires scrutiny. Recent reviews conclude that most (> 80%) of the potential benefits of vitamin D for a range of diseases are achieved with 25-OHD levels around 50 nmol/L, with only marginal additional gains for higher levels.[18] Further, there appears to be an upper safety limit which, although still poorly defined, should be recognised. U-shaped curves of disease risk in relation to 25-OHD concentration are reported for mortality (cancer, cardiovascular and all-cause) and active TB likelihood, with risks increasing at 25-OHD levels above 80–140 nmol/L.[19-21] Popular advice promoting high target levels (eg, 125 nmol/L[22]) is unhelpful and potentially risky.

In summary, we support appropriately targeted testing and treatment of vitamin D deficiency, bearing in mind assay limitations and the implausibility of some proposed 25-OHD targets. Any effect that this strategy would have on risk of progression from latent to active TB remains hypothetical. Given that vitamin D deficiency is an easily preventable problem requiring a high index of suspicion, it is sensible to promote testing in at-risk groups. Correcting deficiency after the horse has bolted (after development of active TB) appears to be too late to have appreciable effects on TB outcome. 25-OHD deficiency detected at the time of active TB diagnosis may be self-limiting; a better assessment of vitamin D status might be gained by deferring testing for 2 months after treatment initiation, when the inflammatory milieu has subsided. More prospective studies of TB-exposed people would help answer the persisting question of the relationship between vitamin D deficiency and failure of latency. However, ethical considerations generally prohibit such studies if they exclude interventions to correct vitamin D deficiency or treat latent TB. In the meantime, further exploration of why 25-OHD levels are low in people with active TB will help answer this question.

> "25-OHD deficiency detected at the time of active TB diagnosis may be self-limiting"

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