VITAMIN D AND TUBERCULOSIS

Gemma M Hawthorne, David R Thickett

College of Clinical and Experimental Medicine,
University of Birmingham, Birmingham – United Kingdom

Tuberculosis (TB) remains a major global healthcare issue. The incidence of TB in sub-Saharan Africa is around 350 per 100,000, compared with an incidence of 50 per 100,000 in Europe and approximately 231/100000 in Pakistan. Around 1.7 million people died in 2009 due to TB and the absolute number of cases rises each year due to increasing global population. The emergence of drug resistance, worsening malnutrition in the settings of political instability and civil unrest, and the detrimental effects of HIV coinfection have challenged TB eradication programs worldwide.

Historically treatment of TB included exposure to sunlight and was effective particularly in the treatment of lupus vulgaris. The isolation of vitamin D_3 from cod liver oil, which was used to treat TB in the 1930s, led to its widespread use in TB treatment and prevention, until the introduction of effective chemotherapy in the 1950s. The occurrence of drug resistant tuberculosis has necessitated development of new adjuvant or chemo-therapeutic agents. This editorial will discuss whether vitamin D is one such adjuvant treatment.

The majority of Vitamin D is obtained from sunlight with ~10% obtained from the diet, especially from fish, meat and fortified foods. During exposure to sunlight, UVB is absorbed by 7-dehydrocholesterol which forms pre-vitamin D_3. This is then converted to vitamin D_3 and moves from the skin to the plasma . This circulates bound to vitamin D binding protein (DBP), and is converted by hydroxylation to 25-hydroxyvitamin D_3 ($25(OH)D_3$) in the liver and then in the kidneys or local tissues to the biologically active form 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$).

The classical effects of vitamin D relate to calcium absorption and osteoclastic activity. It has however become increasingly recognised that vitamin D also has profound effects on human immunity acting as an immune system modulator, preventing excessive expression of inflammatory cytokines and increasing the 'oxidative burst' potential of macrophages, therefore enhancing bacterial killing. Vitamin D stimulates the release of antimicrobial peptides such as LL-37 (cathelicidin) and human beta defensin 4 within the lung. Recent data have further implicated vitamin D in adaptive immunity because of its influence upon the differentiation of T cells between the regulatory Treg and the pro-inflammatory Th17 subsets (9-11). Th17s stimulate tissue inflammation and neutrophil chemotaxis, both of which are seen in tuberculosis, predominantly by IL-17 production. It also appears that there is a greater degree of plasticity in T cell differentiation than previously appreciated (10) such that vitamin D may alter the balance between proinflammatory and regulatory T cells (Tregs).

The definition of what level of vitamin D counts as deficient is increasingly controversial as the multiple non-calcium related effects of vitamin D have become more clearly identified. Serum 25(OH)D is used to assess vitamin D status as it is the main circulating form. A recent expert panel review recommended 25(OH)D level > 30ng/ml (75 nmol/l) as an ideal sufficient level of vitamin D. Inadequate/ deficient levels will be taken as $\leq$ 20ng/ml (50nmol/l) for the ongoing discussion.

Numerous studies have assessed vitamin D status in TB in different populations and ethnicities. Talat et al from Karachi assessed vitamin D levels in a cohort of tuberculosis patients and their contacts (N = 129) in Pakistan. Most (79%) persons showed deficiency. Low vitamin D levels were associated with a 5-fold increased risk for progression to tuberculosis. These data are backed up by studies of Davies et al in the UK, as well as Thai, Chinese, Indian and Indonesian cohorts. Not all studies support this as confounders maybe related to socioeconomic and demographic differences between TB patients and controls. Exposure to sunlight and high dietary intake of vitamin D (e.g. Greenland Inuits who have high dietary intake despite little sun exposure) further mean that not all populations of TB patients worldwide are deficient. Vitamin D is known to have numerous functions in the response to infection, involving the

innate and acquired immune systems. All of these functions are involved in the antimicrobial response to TB. Thus if TB patients are very vitamin D deficient does replacing the vitamin D aid clinical treatment?

Initial studies to assess the effects of 25OHD status on *ex vivo* macrophage function have shown that supplementation with a single oral dose of 2.5 mg vitamin D enhances the ability of recipient macrophages to combat BCG infection *in vitro*. Using this dose in patients with TB induces a 109.5 nmol/l increase in serum 25(OH)D but deficiency recurred in 10/11 patients 8 weeks after dosing.

In a small study Nursyam et al showed that 0.25mg/day of vitamin D for 6 weeks improved sputum conversion rates from 76% in the placebo group to 100% in the treatment group (p=0.002). In contrast, a double-blind randomized placebo-controlled trial by Wejse et al. in Guinea-Bissau showed that 2 doses of 100,000 IU vitamin D3 had no effect on clinical outcomes or mortality amongst TB patients, although none of the supplemented patients in this study showed a significant rise in serum vitamin D levels suggesting insufficient dosing.

Recently Martineaux et al. studied the effect of 2.5 mg of vitamin D3 monthly versus placebo upon sputum conversion after 6 weeks of therapy in 124 London based patients. They found no differences in conversion time between the groups for the whole cohort despite the fact that the regime successfully increased vitamin D levels to 101 nmol/l in the treated group versus 22 nmol/l in the placebo group.

Interestingly genetic analysis of these patients demonstrated that patients with the *tt* genotype of the *TaqI* vitamin D receptor polymorphism (~8% of the total cohort) had enhanced sputum culture conversion from adjuvant therapy . Genetic polymorphisms in the vitamin D binding protein gene have also recently been shown to relate to susceptibility to active tuberculosis in Gujurati Asians. However the genetic influence was only seen in those with vitamin D deficiency.

CONCLUSIONS

Can we currently recommend adjuvant vitamin D therapy in routine practice for patients with TB? The biology and basic science of vitamin D function suggest it should have beneficial effects upon TB patients. Clinical studies of efficacy are currently disappointing in this regard. Several issues over drug dosing and compliance in some of the trials make firm conclusions difficult. The recent trials that relate genetic polymorphisms to the effectiveness of vitamin D suggest that some subgroups of TB patients may indeed benefit from vitamin D therapy but preclude recommending it for all patients. Whether patients with multidrug resistant TB or HIV might benefit more from adjuvant vitamin D therapy is also worthy of further study in properly powered randomised clinical trials.

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Address for Correspondence:
Dr. David R Thickett,
Reader in Clinical and Experimental Medicine,
University of Birmingham, Birmingham – United Kingdom
E-mail: d.thickett@bham.ac.uk