Vitamin D as an adjuvant therapy for tuberculosis: pharmacogenomic implications

Dilip Nazareth¹ & Peter Davies²

It is estimated that in the UK alone, tuberculosis (TB) or phthisis (Greek) affects approximately 9000 people every year and the WHO reports that worldwide, there were 9.4 million incidents of TB in 2008. Over the last 10 years, there have been new threats from MDR-TB and XDR-TB and there has been a renewed interest in vitamin D, its deficiency and its association with TB.

Tuberculosis was the biggest killer during the Victorian era with at least one in every four deaths being attributed to ‘consumption’. Poor living conditions, harsh weather and the lack of sunlight, in addition to industrialization, contributed to the spread of TB. Prior to the introduction of chemotherapy, milk, meat and eggs were recommended for the treatment of TB. Subsequently the administration of cod liver oil, rich in vitamin D, was used [1], as the fatty acids in cod liver oil were found to inhibit the growth of the tubercle bacilli. At the beginning of the 20th century TB was the biggest health problem in the UK. Sir Robert Philip (b.1857), set up two small rooms in Edinburgh, probably the first TB clinic and concentrated his efforts on contact tracing, educating people about containing the spread of disease and making TB a notifiable disease.

In the late 1800’s, sanatoriums were developed to ensure containment of disease, with plenty of fresh air and nutrition, as were the introduction of solariums, to provide light. The sanatorium method of treatment became popular in continental Europe and America, as it provided isolation of infected individuals, thereby making it possible to control the spread of disease and provided patients with regulated hospital care.

Vitamin D is synthesized in the skin through a photosynthetic reaction triggered by exposure to UV radiation. This photosynthesis produces vitamin D₃, which undergoes further transformations, with the production of 25-hydroxyvitamin D (25[OH D), the major form of vitamin D circulating in the bloodstream, which is measured to determine a person’s vitamin D levels. By the late 1800s, approximately 90% of all children living in Europe and North America had some manifestation of rickets secondary to vitamin D deficiency. The medical fraternity throughout Europe and America began promoting whole-body sunbathing to help prevent rickets. Around this same time, TB was also found to respond to sunlight and in 1903, the Danish physician, Niels Finsen was awarded the Nobel Prize in Medicine and Physiology for his successful treatment of lupus vulgaris with phototherapy.

Epidemiological link between TB & vitamin D deficiency

Vitamin D in high doses was used to treat TB prior to the availability of antibiotics and subsequently moved to the back burner. In 1961, it was observed that Pakistani immigrants in Glasgow had widespread rickets and osteomalacia secondary 

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to vitamin D deficiency that was not related to dietary deficiency and it was suggested that advice on the prophylaxis of vitamin D deficiency should be given to all Pakistanis and Indians in the UK [2]. There is growing evidence that vitamin D and mycobacterial infection are closely linked and that patients with TB have lower levels of vitamin D than those without [3].

Immigrants in London, from the Indian subcontinent, on a purely vegetarian diet were found to have an 8.5-fold increased risk of TB, compared with those who ate meat and fish daily. This increased risk is postulated to have been caused by deficiencies in possibly iron, vitamin B12 or vitamin D [4].

There is evidence of an inverse relationship between serum vitamin D levels and the likelihood of both having any mycobacterial TB infection and the likelihood of having TB/past TB rather than latent TB infection [5], a concept first suggested by the corresponding author, over 25 years ago, by demonstrating lower levels of vitamin D in patients with TB when compared with matched controls [6]. A case–control study by Wilkinson in Gujarati Indians residing in northwest London, demonstrated that vitamin D deficiency was significantly associated with active TB disease and those with undetectable serum vitamin D levels, carried the greatest risk of TB [7]. Racial differences in the pathogenesis of TB have been suggested to be due to a decline in vitamin D levels, that may correlate with a decline in cell-mediated immunity, in a person infected with the tuberculosis bacillus, resulting in marked differences in rates of TB infection between black and white patients, one study reporting rates among racial/ethnic minorities were five- to ten-times higher than those in white patients [8]. It is postulated, that a decrease in the exposure to sunlight when a person moves from a country with plentiful sunlight to one with less sunlight with a decline in vitamin D [9], may have an important role to play and is supported by the pattern of increased rates of TB during the winter season [10].

**Disappointing trials of therapy**

There have been no randomized control trials looking at the supplementation of vitamin D in the prevention of TB. Martineau et al. demonstrated that a single dose of vitamin D enhanced the ability of an individual who had contact with TB to restrict mycobacterial bioluminescence at 24 h post-inoculation *ex vivo* [11]. In a randomized study of 365 adults in Guinea-Bissau after the administration of three doses (at initiation of treatment, months 5 and 8) no effect was seen on the primary outcome (a specially developed TB score) [12].

Another trial has shown that adding vitamin D to the treatment of TB makes no difference to the outcome [13]. Moreover, a recent multicenter randomized controlled trial has shown that the administration of four doses of 2.5 mg vitamin D, in patients receiving intensive-phase treatment for smear positive pulmonary TB, did not significantly affect time to sputum culture conversion in the study population [14].

These differences in outcomes could be due to a variety of factors, explained well by Awumey and colleagues, that the intrinsic hydroxylase activity in some Asians may be higher compared with non-Asian controls and the possible effect of rifampicin and isoniazid on vitamin D metabolism, exacerbating the above effect [15]. In addition, there is the possibility of a paradoxical reaction, in which more severe disease leads to the paradoxical depletion of vitamin D metabolism during treatment.

> “...with an increasing incidence of MDR- and XDR-TB, its associated mortality and the decreased effectiveness of routine anti-TB drugs, where does treatment with vitamin D find a place?”

The current drugs in TB treatment are so powerful, that vitamin D supplementation can add very little. That brings us to resistance patterns in TB. MDR-TB is caused by resistance to the two most powerful first-line anti-TB drugs – isoniazid and rifampicin. XDR-TB is caused by resistance to isoniazid and rifampicin, in addition to any fluoroquinolone and at least one of three injectable second-line drugs. The exact scale of the problem of MDR- and XDR-TB is not known and there has been limited reduction in drug-resistance patterns making it increasingly difficult to contain the disease. However, with an increasing incidence of MDR- and XDR-TB, its associated mortality and the decreased effectiveness of routine anti-TB drugs, where does treatment with vitamin D find a place? There is limited knowledge of the factors influencing the development of these resistance patterns and there may be a place for a trial of vitamin D in MDR- or XDR-TB to determine if augmentation of current treatment will be effective.

**Prevention with vitamin D supplementation may be more valuable**

Could the dose of vitamin D have an effect on the outcome? The treatment of severe vitamin D deficiency could be ample to reduce the risk of TB. Vitamin D deficiency, brought about by immigration from tropical to temperate climates and from an area of abundant sunlight to that of less, appears to be a risk factor for TB. The mean serum vitamin D concentration has been shown to drop fourfold or more, on emigration from Asia to Britain [16]. The implication for vitamin D therapy is that it should be given to individuals, probably lifelong, as they move from a tropical to a temperate climate, to prevent the development of TB in...
susceptible individuals. As vitamin D supplementation did not improve the clinical outcome among patients with TB [14], vitamin D as a prophylactic treatment would be more effective as a treatment for latent rather than active TB infection.

To determine if vitamin D would actually benefit in preventing the development of TB would mean undertaking a large-scale population study with large numbers. The obvious difficulties in doing such studies would be ensuring that supplementation was taken and that the sunlight exposure was controlled, that is, the trial subjects were not exposed to sunlight more than those without supplementation. Such a study would be very difficult to undertake at present.

Genetic subgroups & TB
The genetic susceptibility of a host has been suggested as an important factor for the differences in the risk of TB in individuals and several host genes have been attributed to contribute to the development of the disease. This was first demonstrated in the Gambian population with active TB where an association with the carriage of the T allele of the TaqI VDR polymorphism was found [17]. Gujarati Asians, found to be vitamin D deficient, were also found to carry the T allele of the TaqI VDR polymorphism and the ff genotype of the FokI VDR polymorphism [7]. It has been shown that in a subgroup of patients with a particular genotype (tt genotype of the TaqI vitamin D receptor polymorphism) vitamin D supplementation decreased the time to sputum culture conversion [14].

Vitamin D binding protein is a glycoprotein encoded on chromosome 4. It has been previously shown that there is no association between this genotype and the susceptibility to TB [18]; however, a recent study has demonstrated an association between this genotype and susceptibility to TB [19]. Although the results are varied, the studies determining the factors of genetic host susceptibility increasing our understanding of the pathogenesis of TB and forms a base for further studies with a view of developing new treatment strategies.

Future perspective
Evidence, so far, suggests an association between low serum vitamin D and TB in certain population groups. Despite advances in the knowledge of the potent immunomodulatory activity of vitamin D, it is not known whether the lower level of vitamin D contributes to people developing TB or if having TB alters the metabolism of vitamin D.

Vitamin D supplementation is more effective than the recommended sunlight exposure for treating vitamin D deficiency in non-western immigrants and vitamin D supplementation may augment current treatment regimens to enable a more rapid conversion to a sputum negative status [20].

In addition, there are genetic factors that play a role. In genetically susceptible individuals, there is an inherent inefficiency to control bacterial numbers, leading to the development of drug-resistant TB. However, the vitamin D receptor gene t is thought to offer protection against disease and this area needs exploring further.

The interaction of TB infection on cellular vitamin D metabolism needs to be further examined in addition to definitively prove a relationship between vitamin D and TB.

In future, public health policy aimed at the prevention of TB should stress the need for adequate dietary intake of vitamin D in all vulnerable groups including immigrants from the Indian subcontinent. Ultimately, there could be a role for administering vitamin D to all immigrants and those with drug-resistant TB, in order to modify the treatment duration and efficacy in treating TB.

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Bibliography


