REVIEW ARTICLE

Vitamin D and tuberculosis: Is a change in Public Heath Policy needed?

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The WHO reported 9.4 million incident cases of Tuberculosis (TB) / Phthisis (Greek) in 2008 and accounts for nearly two million deaths each year. The new threats of MDR-TB and XDR-TB over the last decade have resulted in an increase in immigrant screening in Western countries and a renewed interest in Vitamin D deficiency and its association with TB.

At least 1 in every 4 deaths was attributed to 'consumption' during Victorian times and TB was the biggest killer. Poor living conditions, harsh weather and the lack of sunlight, in addition to industrialization contributed to the spread of TB in the United Kingdom and Europe. Prior to the introduction of chemotherapy, a good diet of milk, meat and eggs were recommended for treatment of TB. The administration of cod liver oil, rich in vitamin D, was later used in treatment, as the fatty acids in cod liver oil were found to inhibit the growth of tubercle bacilli.

A Scottish physician, Sir Robert Philip (b.1857), set up two rooms in Edinburgh, developed contact tracing, educated people about containing the spread of disease and was instrumental in making TB a notifiable disease. This was probably the first TB clinic in existence.

In the late 1800's, within Europe and North America, sanatoria were developed to prevent spread of disease, making available plenty of fresh air and nutrition, as were the introduction of solariums, within the sanatoria 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 the disease and provided patients regulated hospital care.

Prior to the development of antibiotics, deaths associated with TB were higher in latter part of winter and early spring than other times of the year[1].

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The mechanism that underlies the fluctuation of TB in a particular time of the year is still not clear. Researchers have suggested that temperature, humidity, sunlight, crowding and person-to-person contact, are a source of TB seasonality, particularly, in the winter season[2]. Seasonal variations of vitamin D levels are seen in several communities. Could this be attributed to a lower level of sunlight in the winter months?

The synthesis of Vitamin D occurs in the skin through a photosynthetic reaction that is triggered by exposure to ultra-violet radiation from the sun. This photosynthesis produces vitamin D_3, which undergoes further transformation, with the end product of 25-hydroxyvitamin D (25[OH]D) that is the major form of vitamin D circulating in the bloodstream and it is this that is measured to determine a person's vitamin D levels.

Approximately 90% of all children living in Europe and North America, in the late 1800's, had some manifestation of rickets secondary to vitamin D deficiency. It was at this time that the medical fraternity in Europe and America advocated whole-body sunbathing to prevent rickets. It was around the same time that TB was also found to respond to sunlight and the Danish physician, Niels Finsen, in 1903, was awarded the Nobel Prize in Medicine and Physiology, for the success of phototherapy in the treatment of lupus vulgaris.

The link between Vitamin D, TB and immigration:

The treatment of TB prior to the availability of antibiotics was Vitamin D. Following the development of antibiotics this 'fell out of fashion'. In Glasgow, Pakistani immigrants were observed[3] to have widespread rickets and osteomalacia secondary to vitamin D deficiency that was not related to a deficiency in dietary intake and it was suggested that advice on the prophylaxis of vitamin D deficiency should be given to all individuals from the Indian Sub-continent, in the United Kingdom. It is well known that vitamin D and mycobacterial infection are closely linked and that patients with tuberculosis have lower levels of Vitamin D than those without[4].

An 8.5 fold increased risk of tuberculosis among immigrants in London, from the Indian subcontinent on a purely vegetarian diet were found compared to

those who ate meat and fish daily. This increased risk is believed to have been caused by deficiencies in possibly iron, vitamin B12 or vitamin D[5].

An inverse relationship exists between serum vitamin D levels and the possibility of both having any mycobacterial TB infection and of having TB/past TB rather than latent TB infection[6], a concept first suggested[7] in 1985 by the corresponding author who by demonstrated lower levels of Vitamin D in patients with TB when compared with matched controls.

In Gujurati Indians living in North West London, a significant association between vitamin D deficiency and active TB disease existed[8] and those with undetectable serum vitamin D levels were found to be at the greatest risk of developing TB. These racial differences have been suggested to be due to a fall in Vitamin D levels that may correlate with a decline in cell-mediated immunity, in a person infected with the tuberculosis bacillus that results in marked differences in rates of TB infection between blacks and whites. One study[9] found these rates among racial/ethnic minorities were 5-10 times higher than those in whites. A decrease in exposure to sunlight, when a person moves from a country with plentiful sunlight to one with less sunlight with a decline in vitamin D[10], may have an important role to play and this is supported by the observation of increased rates of TB during the winter months[1].

Treatment outcomes with Vitamin D:

So far, no randomized control trials looking at vitamin D supplementation in the prevention of TB exist. Martineau et al[11] recently demonstrated that high doses of vitamin D_3 added to anti-tuberculosis treatment helps clear the bacteria more quickly in a subset of patients with a particular variant of the vitamin D receptor. In their study, a single dose of Vitamin D enhanced the ability of an individual who had contact with TB, to restrict mycobacterial bioluminescence at 24 hours post-inoculation ex-vivo. In Guinea-Bissau, a randomized study of 365 adults[12] were administered 3 doses (at initiation of treatment, months 5 and 8) of Vitamin D and no effect was seen on the primary outcome (a specially developed TB score).

Another trial[13] showed that adding vitamin D to the treatment of tuberculosis made no difference to the outcome. This was substantiated by a recent multicentre randomized control trial[11] that demonstrated that the

administration of four doses of 2·5 mg vitamin D_3 in patients receiving intensive-phase treatment for smear positive pulmonary tuberculosis, did not significantly affect time to sputum culture conversion in the study population.

These differences in outcomes could be due to a variety of factors. It is postulated that the intrinsic hydroxylase enzyme activity in some Asians may be higher compared to non-Asian controls and the effect of rifampicin and isoniazid on Vitamin D metabolism, may exacerbate the above effect[14]. In addition, it is possible that more severe disease leads to the depletion of Vitamin D metabolism during treatment – a paradoxical reaction.

Could vitamin D supplementation add anything, when the current drugs in TB treatment are so powerful? What about its effect in resistance patterns in TB? Resistance to the two most powerful first-line anti-TB drugs - isoniazid and rifampicin is known as MDR-TB and XDR-TB is due to 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. It is becoming increasingly difficult to contain the disease and its spread and there has been a limited reduction in drug resistance patterns. However, where does treatment with Vitamin D find a place, with an increasing incidence of MDR and XDR-TB and its association with significant mortality and the decreased effectiveness of routine anti-TB drugs? The literature is significantly limited in the evaluation of the factors that influence the development of these resistance patterns and there may be a place for a trial of Vitamin D in drug resistant TB, to determine if augmentation of current treatment will have a positive effect.

Is there a place for Vitamin D supplementation in the prevention of TB?

To reduce the risk of tuberculosis, the treatment of severe vitamin D deficiency could be sufficient. 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, brought about by Vitamin D deficiency. On emigration from Asia to Britain, the mean serum vitamin D concentration has been shown to drop 4 times, or more[15]. To prevent the development of TB in susceptible individuals, 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. Vitamin D supplementation did not improve the clinical outcome[11] among patients with

TB; however, Vitamin D as a prophylactic treatment would be more effective as a treatment for latent rather than active TB infection.

Undertaking large-scale population studies with large numbers is one way of determining if Vitamin D supplementation would actually benefit in preventing the development of TB. There are inherent difficulties in doing such a study, such as ensuring that supplementation was taken and that the sunlight exposure was controlled in a way that the trial subjects were not exposed to sunlight more than those without supplementation. This would be a very difficult study to control and undertake currently.

The genetic association with Vitamin D and TB:

Vitamin D binding protein is a glycoprotein encoded on chromosome 4. It has been shown[16] that no association exists between this genotype and the susceptibility to TB. This was shown to the contrary by Martineau et al[17] who demonstrated an association between this genotype and susceptibility to TB in Gujurati Asian TB contacts. Several host genes have been attributed to contribute to the development of disease and the genetic susceptibility of a host has been suggested as an important factor for the differences in TB risk among individuals. This was first seen[16] in the Gambian population where people with active TB were found to have, an association with the carriage of the T allele of the TaqI VDR polymorphism. Vitamin D deficient Gujurati Asians were also found to carry the T allele of the TaqI VDR polymorphism and the ff genotype of the FokI VDR polymorphism[8]. As described earlier, Martineau et al[11] showed that in a subgroup of patients with a particular genotype (*tt* genotype of the TaqI vitamin D receptor polymorphism) there was a decreased time to sputum culture conversion in those on vitamin D supplementation.

Although the results are varied and often contradictory, the studies determining the factors of genetic host susceptibility allows us to understand the pathogenesis of TB and forms a base to develop new treatment strategies in the future and perhaps target treatment to susceptible groups.

Is a change in Public Health Policy needed?

What we know so far is that there is an association between low serum vitamin D and tuberculosis in certain population and ethnic groups. Our knowledge of the potent immuno-modulatory activity of vitamin D has grown

but it is still not known whether a lower level of Vitamin D contributes to people developing TB or does TB alter the metabolism of Vitamin D?
In non-western immigrants with vitamin D deficiency, Vitamin D supplementation is more effective[12] than the recommended sunlight exposure and Vitamin D supplementation may augment current treatment regimes and enable a more rapid conversion to a sputum negative status.

We are aware that genetic factors play a role in the risk of developing TB. There is an inbuilt inefficiency to control bacterial numbers in genetically susceptible individuals, thereby leading to the development of TB that often is multi-resistant. Further work should be based on the Vitamin D receptor gene *tt* that is thought to offer protection against disease.

To definitively prove a relationship between Vitamin D and TB, the interaction of TB mycobacteria on cellular Vitamin D metabolism needs to be further examined.
In future, public health policy aimed at the prevention of TB should include and encourage the need for adequate dietary intake of vitamin D in all groups that are vulnerable including immigrants from the Asian sub-continent. Adding Vitamin D to a stable food such as milk or bread should also be considered.
In conclusion, modification of the treatment duration and efficacy in treating TB with the administration of Vitamin D to all immigrants and those with drug resistant TB may be the future.

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