

Low serum vitamin D levels and tuberculosis: a systematic review and meta-analysis

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Objective	To explore the association between low serum vitamin D and risk of active tuberculosis in humans.
Design	Systematic review and meta-analysis.
Data sources	Observational studies published between 1980 and July 2006 (identified through Medline) that examined the association between low serum vitamin D and risk of active tuberculosis.
Results	For the review, seven papers were eligible from 151 identified in the search. The pooled effect size in random effects meta-analysis was 0.68 with 95% CI 0.43–0.93. This ‘medium to large’ effect represents a probability of 70% that a healthy individual would have higher serum vitamin D level than an individual with tuberculosis if both were chosen at random from a population. There was little heterogeneity between the studies.
Conclusions	Low serum vitamin D levels are associated with higher risk of active tuberculosis. Although more prospectively designed studies are needed to firmly establish the direction of this association, it is more likely that low body vitamin D levels increase the risk of active tuberculosis. In view of this, the potential role of vitamin D supplementation in people with tuberculosis and hypovitaminosis D-associated conditions like chronic kidney disease should be evaluated.
Keywords	Vitamin D, tuberculosis, systematic review, meta-analysis, vitamin D deficiency

Introduction

Vitamin D modulates monocyte-macrophage activity in the body and plays a role in human innate immunity to certain infectious agents. This role may be important in the body’s defence against tuberculosis, in which attack of macrophages is a key step

in pathogenesis. Vitamin D acts by binding to nuclei receptors on target cells. Therefore both low levels of the vitamin and abnormalities in receptor structure and function may result in impairments in host immunity to the tubercle bacillus.¹ The contribution of vitamin D receptor abnormalities has been examined in a systematic review,² which was inconclusive, but no similar review of low body vitamin D levels has been undertaken. This is in spite of a number of studies reaching varying conclusions about the risk of tuberculosis associated with vitamin D deficiency.

In this review, appropriate community—or hospital-based studies comparing serum vitamin D levels in tuberculosis patients and healthy controls were systematically identified, examined and pooled in a meta-analysis.

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Methods

Identification and selection of papers

This review was restricted to published research articles and abstracts that compared the serum levels of vitamin D in tuberculosis patients (not yet commenced on treatment) with those of an appropriate control group of healthy people. These studies were identified in three ways:

(i) Medline was searched through PubMed for studies published between January 1980 and July 2006. The search was limited to English language papers on research in humans. The key words used included 'tuberculosis', 'vitamin D', 'vitamin D deficiency' and 'cholecalciferol'; (ii) the reference lists of identified publications were searched; (iii) the International Journal of Tuberculosis and Lung Disease was identified as the key journal for hand searching, and editions of this journal from 1980 to June 2006 were searched.

The following inclusion criteria were applied to each publication: (i) studies had to be community or hospital-based, (ii) examined the association of vitamin D deficiency and tuberculosis, (iii) studied untreated adult tuberculosis patients, (iv) used a control group comparable to the cases, and (v) dealt with *Mycobacterium tuberculosis* (studies dealing with other Mycobacteria were excluded). Important details regarding the methods and results were extracted from appropriate papers and summarized.

Defining parameters

Serum vitamin D was defined in each paper as serum levels of 25-(OH)D₃ (25 hydroxycholecalciferol). It is generally accepted that its assay may be a better indicator of vitamin D status than 1,25(OH)₂D₃ (1,25 dihydroxycholecalciferol).³ The study population of cases was estimated as the number of culture positive tuberculosis patients yet to commence treatment. Controls were healthy people and had to be representative of the population from which cases were drawn.

Statistical analysis

All results were expressed in terms of a bias corrected 'effect size' of the difference between serum vitamin D levels in patients and controls.⁴ For continuous measures, an EffectSizeCalculator worksheet was used to derive effect sizes from means and pooled standard deviations.⁵ For three studies⁶⁻⁸ that expressed outcomes in medians and ranges, the medians and ranges were converted to means and standard deviations using Hozo's approach.⁹ These were then used in the worksheet to derive effect sizes. The odds ratio in one study¹ was converted directly to an effect size using the approach described by Chinn.¹⁰ Effect sizes were used in a random effects meta-analysis (Review Manager Version 4.2). We assessed heterogeneity between studies using the

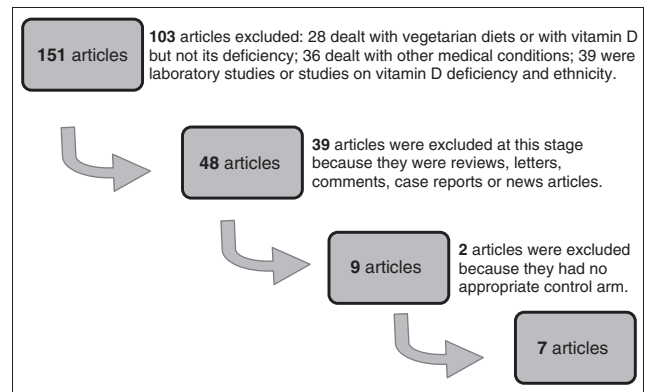


Figure 1 Selection of studies for review

χ^2 test, and estimated the amount of variation due to heterogeneity by calculating the I^2 .

Results

Figure 1 schematically presents the study selection process. One hundred and fifty-one studies were identified from the initial PubMed search. No additional references were identified from other databases. A total of seven studies involving 531 participants met the inclusion and exclusion criteria. They were all published between 1985 and 2002 and compared vitamin D levels in tuberculosis patients and controls (Table 1).

Of five studies based on Asian populations, four were based on indigenous populations^{6,11-13} and one was a study of UK-resident Asians.¹ One study⁷ was based on a predominantly White UK population and one⁸ on an indigenous East African population. Migrants represented one-third of the study population.

We evaluated the quality of primary studies using the Newcastle–Ottawa Scale,¹⁴ a validated technique for assessing the quality of observational and non-randomized studies. The instrument uses a star system to evaluate observational studies based on three criteria: participant selection, comparability of study groups and assessment of outcome or exposure. As shown in Table 2, higher quality studies rigorously controlled for potential confounders¹³ and did better with respect to selection of cases and controls.^{1,8}

All studies investigated untreated culture-positive tuberculosis patients recruited either as inpatients or outpatients. Controls were mostly healthy contacts of tuberculosis cases but one study¹² selected controls from blood donors attending a hospital blood bank. Another study¹¹ recruited controls who were inpatients and outpatients at the same hospital as the cases, but who did not have any condition known to affect calcium or vitamin D deficiency. Information about potential confounders of a relationship between serum vitamin D deficiency and tuberculosis, such as chronic co-morbidity and malnutrition, was variably provided across the studies. Authors in one study¹³ excluded TB patients who had risk factors for

Table 1 Summary of included studies

Author, date, place	Study population	Design	Cases	Controls	Parameter measured	Results (serum Vitamin D levels)
Davies PD <i>et al.</i> , 1985, UK ⁷	UK Whites (84%); Indian ^a (8%); others ^b (8%)	Prospective study	40 untreated inpatients and outpatients with mainly culture-positive pulmonary TB. Mean age 43.1 years	40 controls were either members of patients' families or age and sex-matched healthy volunteers. Mean age 42.2 years	Serum vitamin D levels	Median (range) in: Cases—16.0 nmol/L (2.25–74.25 nmol/l) Controls—27.25 nmol/l (9.0–132.5 nmol/l) $P < 0.005$
Grange <i>et al.</i> , 1985, Indonesia ⁶	Indigenous Indonesian population	Case-control study	40 untreated patients with smear-positive pulmonary TB (source of recruitment unclear). Age range 18–50 years.	38 apparently healthy age-matched controls (mean or range of ages not stated)	Serum vitamin D levels	Median (range) in: Cases—65.75 nmol/l (43.75–130.5 nmol/l) Controls—69.5 nmol/l (48.5–125 nmol/l) $P > 0.25$
Davies <i>et al.</i> , 1987, Kenya ⁸	Indigenous African population (Kenyans)	Prospective study	15 untreated culture-positive pulmonary TB patients presenting to hospital. Mean age 33 years	15 age and sex-matched healthy controls selected from patients' families. Mean age 35 years	Serum vitamin D levels	Median (range) in: Cases—39.75 nmol/l (16.75–89.25 nmol/l) Controls—65.5 nmol/l (26.25–114.75 nmol/l) $P < 0.05$
Davies <i>et al.</i> , 1988, Thailand ¹²	Indigenous Thai population	Prospective study	51 untreated smear-positive pulmonary TB patients presenting to a chest clinic. Mean age 30.5 years	51 age and sex-matched healthy controls selected from blood donors attending a hospital blood bank. Mean age 30.4 years	Serum vitamin D levels	Mean (SD) in: Cases—69.5 nmol/l (24.5 nmol/l) Controls—95.5 nmol/l (29.25 nmol/l) $P < 0.001$
Chan <i>et al.</i> , 1994, Hong Kong ¹¹	Indigenous Chinese population	Case-control study	22 untreated hospital in-patients with culture-positive pulmonary TB. Mean age 56.3 years	23 in-patients and out-patients receiving care at same time as cases	Serum vitamin D levels	Mean (SD) in: Cases—46.5 nmol/l (18.5 nmol/l) Controls—52.25 nmol/l (15.75 nmol/l)
Wilkinson <i>et al.</i> , 2000, UK ¹	Gujarati Hindus resident in London	Case-control study	103 untreated patients with localized ^c - and severe ^d TB, recruited from a hospital. Mean age 45.5 years	42 household multiple contacts of TB patients attending TB contact clinics of same hospital. Mean age 42.7 years	Serum Vitamin D deficiency	Odds ratio (CI) for vitamin D deficiency in cases compared to controls—2.9 (1.3–6.5) $P = 0.008$
Sasidharan <i>et al.</i> , 2002, India ¹⁵	Indigenous Indian population	Case-control study	35 untreated hospital in-patients with pulmonary (15) and extra-pulmonary (20) TB. Mean age 37.5 years	16 healthy age- and sex-matched controls (source of recruitment not stated). Mean age 34.1 years	Serum vitamin D levels (in fasting blood samples)	Mean (range) in: Cases—26.75 nmol/l (2.5–75 nmol/l) Controls—48.5 nmol/l (22.5–145 nmol/l) $P < 0.005$

^aIndian—refers to those whose ethnic origin is in the Indian subcontinent (Indian, Pakistani or Bangladeshi).^bIncludes one person each of West Indian, African, Malaysian and Chinese ethnic origin.^cLocalized disease defined by author as TB confined to one anatomical site.^dSevere disease defined by author as pulmonary or miliary tuberculosis.

Table 2 Assessing the quality of included studies using the Newcastle–Ottawa Scale

Author	Selection				Comparability		Exposure		Score
Davies ⁷	★	★	★			★	★	★	6
Grange ⁶	★			★	★		★	★	5
Davies ⁸	★	★	★	★	★		★	★	7
Davies ¹³	★	★				★	★	★	5
Chan ¹¹	★	★		★	★		★	★	6
Wilkinson ¹	★	★	★	★	★		★	★	7
Sasidharan ¹³	★	★		★	★	★	★	★	7

Table 3 Effect size estimates from studies on low serum vitamin D and tuberculosis

Study and place	Total <i>n</i>	Estimated effect size (bias corrected)	95% confidence interval
Davies, UK	80	0.86	0.40–1.32
Grange, Indonesia	78	0.18	–0.26–0.63
Davies, Kenya	30	1.04	0.28–1.80
Davies, Thailand	102	0.96	0.55–1.37
Chan, Hong Kong	45	0.33	–0.26–0.92
Wilkinson, UK	145	0.59 ^a	0.14–1.04
Sasidharan, India	51	0.94	0.32–1.56

^aThis effect size was derived directly from the odd ratio in the study.

hypovitaminosis D (such as malnutrition, liver disease, renal disease, gastric or bowel resection, malabsorption states, intake of drugs antagonistic to Vitamin D). In other studies, risk factors for hypovitaminosis D were generally adequately controlled for but in one study,¹ women comprised 65% of the cases and 45% of the controls and in another,¹¹ the mean weight of patients was lower than that of controls. In all studies except two,^{1,6} the collection of blood samples was done at about the same period in cases and controls, and investigators in all studies used either radioimmunoassay^{6–8,12,13} or competitive protein binding assay^{1,11} to measure serum vitamin D levels.

Two studies reported means of serum vitamin D levels and standard deviations;^{11,12} one study reported means and ranges of serum vitamin D levels¹³ (with standard deviations estimated from the ranges⁹); three studies reported medians of serum vitamin D levels and ranges,^{6–8} and one study reported odds ratios for vitamin D deficiency in tuberculosis cases compared to controls.¹

All effect sizes were positive, ranging from 0.18 to 1.04 (Table 3). Positive effect sizes suggest that tuberculosis patients have lower vitamin D levels than controls. In five of the studies, the lower limits of the effect size confidence intervals were greater than zero.^{1,7,8,12,13} In two studies, the lower limits of the confidence intervals were negative.^{6,11}

A summary effect size of 0.68 suggested that serum vitamin D levels are 0.68 SD lower in people with

tuberculosis compared to controls (Table 4). The average member of the control group has a serum vitamin D level that is 0.68 SD above the average level of serum vitamin D for tuberculosis patients, representing a ‘medium to large’ association of vitamin D deficiency with tuberculosis risk.¹⁵ Using the ‘Common Language Effect Size’ approach of McGraw and Wong, the probability is about 70% that an individual without tuberculosis would have a higher serum vitamin D level than an individual with tuberculosis if both individuals were chosen at random from a population.¹⁶

Heterogeneity between studies was low, although only five of seven studies showed a clear difference between serum vitamin D levels in tuberculosis patients and controls.

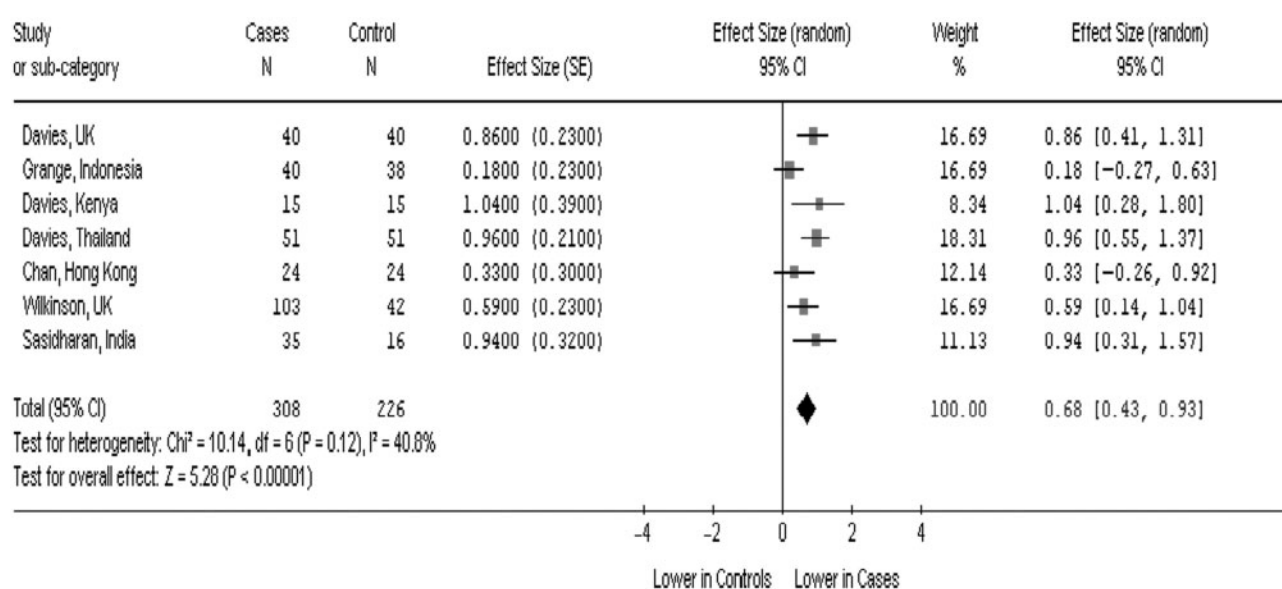
Discussion

Our review finds that patients with tuberculosis have, on average, lower serum levels of vitamin D than healthy controls matched on sex, age, ethnicity, diet and geographical location (Table 4). As antituberculous chemotherapy can lower serum vitamin D levels, we reviewed only studies of tuberculosis patients who were yet to commence treatment at the time of their study. Five of the primary studies included in the review found lower levels of serum vitamin D in tuberculosis patients compared to controls.^{1,7,8,12,13} In one study that found no such difference in indigenous Indonesians,⁶ there was insufficient information about controls to establish that they were completely free of any conditions associated with low serum vitamin D levels. In another study with similar conclusion, 50% of the controls had either hypertension or diabetes, conditions which may be associated with vitamin D metabolism.¹⁷

Although there is good evidence to suggest that a fall in serum vitamin D levels compromises cell-mediated immunity and leads to the activation of latent tuberculosis,¹⁸ it is also possible that low serum vitamin D levels result from tuberculosis itself. The design of the primary studies in this review only permits the medium to large association of TB and low serum vitamin D to be established in the populations investigated in those studies. Determining the direction of the association will need larger prospectively designed studies.

Two facts from other research lend plausibility to the direction of the relationship being from low serum vitamin D to tuberculosis, rather than the reverse. First, the active form of vitamin D enhances the ability of macrophages to suppress the intracellular growth of *Mycobacterium tuberculosis*. Secondly, on triggering of toll-like receptors by molecules of the tubercle bacillus, the production of microbe-killing cathelicidin is impaired in the absence of adequate serum vitamin D.¹⁹ One limitation of the primary studies included in our review however raise the

Table 4 Effect sizes of low serum vitamin D in tuberculosis patients and controls



possibility of confounding. Smoking is a risk factor for tuberculosis disease but, although vitamin D is important for calcium absorption (which is impaired by smoking), there is no evidence to suggest that vitamin D absorption is impaired directly by smoking. However, women who smoke also tend to ingest less vitamin D than non-smoking women.²⁰ Therefore, if reduced intake of vitamin D caused vitamin D deficiency, smoking would not only be associated with vitamin D deficiency but also be an independent risk factor for tuberculosis, making it an important confounder of the low vitamin D-tuberculosis association. Since only one primary study controlled for this effect, more smokers amongst the TB cases than amongst controls could have accounted for the lower vitamin D levels in cases compared to controls.

Much remains to be known of the relative contributions of sunlight and diet to body vitamin D levels. A study of indigenous Indonesians suggested that in populations with good year-round sunshine, people could maintain adequate serum levels of vitamin D in spite of poor dietary intake.⁶ A similar study in India however found low vitamin D levels in the study population despite adequate sun exposure, concluding that diet was the more important factor.¹³ The latter study did not take into account the actual time spent outdoors, extent of body exposed to the sun or level of cutaneous pigmentation. On migration away from home, Hindu Asians largely maintain socio-religiously determined adherence to vegetarian diets but exposure to sunshine is reduced. The observation that Asian migrants have lower serum vitamin D than matched controls in their home countries²¹ have led some authors to conclude that the fall in vitamin D levels associated with migration from sunshine-rich to sunshine-poor areas is probably the most important

contributory factor as far as migrants are concerned.²² Our review however finds an association between low serum vitamin D and active tuberculosis in predominantly indigenous populations, most of whom have adequate year-round sunshine, suggesting that other factors in addition to sunlight exposure may influence the association, at least in such populations.

In one of the primary studies demonstrating lower serum vitamin D levels in TB patients than in controls, 84% of the patients were of White ethnicity.⁷ Concerns about vitamin D deficiency and the risk of tuberculosis may therefore not be limited to Afro-Asian indigenous and migrant communities. Indeed, half of people in Europe over 60 years of age are vitamin D deficient²³ and recently, concerns have been expressed in the UK about increasing malnutrition in the elderly.²⁴ More attention needs to be paid to the nutritional and vitamin D needs of older vulnerable people who may be prone to hypovitaminosis D.

The significance of an association between vitamin D deficiency and tuberculosis is 2-fold. First, already low vitamin D levels in tuberculosis patients may fall further on commencement of treatment.¹⁶ Further drops can predispose to other vitamin D deficient states. Although the potential role of vitamin D supplementation in contacts of tuberculosis cases has been the subject of recent investigations,²⁵ there is a case for more evaluations of vitamin D supplementation in tuberculosis patients on treatment. Second, the prevalence of diabetes mellitus (DM) is increasing globally²⁶ and people with DM are 4–5 times more likely than those without DM to have clinically significant chronic kidney disease (CKD).²⁷ In addition, patients with CKD or those who are dialysis-dependent are more likely to have low levels of vitamin D in comparison to those without kidney

disease.²⁸ The incidence of tuberculosis is high in CKD partly as a result of impaired cell-mediated immunity²⁹ but if low serum vitamin D levels also predisposed to tuberculosis, the growing population of people with CKD from underlying causes like DM may need early attention to their body vitamin D levels to mitigate the risk of active tuberculosis. In renal failure, vitamin D supplementation normalizes bone metabolism by correcting elevated parathyroid hormone. However, the hydroxylase systems that convert vitamin D to its biologically active form become substrate dependent in renal failure (i.e. higher doses of vitamin D increase the rate of production of its active form). There is therefore the possibility that vitamin D supplementation can impact other clinical outcomes in renal failure, such as prevention of active tuberculosis. This application would need to be explored by appropriate studies.

A limitation of this review regards the methodology. A meta-analysis of odds ratios is equivalent to a meta-analysis of effect sizes when there is an underlying continuous distribution, albeit with loss of power.¹⁰ The method of meta-analysis using effect sizes assumes an underlying normal distribution and common variance. These assumptions are however not entirely correct in our population, as the use of medians and ranges in some of the studies would have presumably

been because of the non-normality of the distributions. In addition, Chinn's approach involving the use of the factor of 1.81 for converting log odds ratio to effect size is an approximation, although it is believed to be a good one over the likely range of use.

It seems from knowledge of the causal factors of vitamin D deficiency that exposure to sunlight and adequate dietary intakes are key ways to ensuring enough levels of vitamin D in the body. However, the wisdom in espousing the message of sunlight exposure to people who avoid it for cultural and religious reasons is dubious. Addressing dietary intake of vitamin D seems a more desirable option. Engineering changes in dietary habits may however be fraught with difficulties if these habits are rooted in cultural and religious persuasions. Therefore, while public health education should stress the need for adequate dietary intake of vitamin D in all vulnerable groups, there is need to explore a potential role for vitamin D supplementation in treatment of TB and hypovitaminosis D-associated conditions like CKD. Large and well-designed prospective studies examining the vitamin D-TB association, in which possible confounders are exhaustively controlled for, will provide a foundation for such evaluations.

Conflict of interest: None declared.

KEY MESSAGES

What this paper adds

- There is a medium to large association between low serum vitamin D and tuberculosis in the populations from which the samples in the primary studies were drawn.
- As the observational primary studies in this review are unable to conclusively establish the direction of the association between low serum vitamin D and tuberculosis, this review highlights the need for larger, well-designed prospective studies clarifying the association.

Policy and research implications

- Public health education stressing the need for adequate dietary intake of vitamin D in all vulnerable groups is necessary.
- Prospective studies to firmly establish the direction of the relationship between vitamin D and tuberculosis as well as evaluations of vitamin D supplementation in tuberculosis and renal failure patients are needed.

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