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Vitamin D supplementation versus placebo for treatment of pulmonary tuberculosis: a meta-analysis

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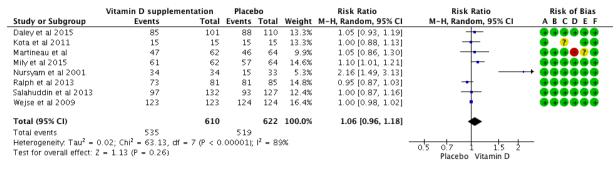
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Background: The benefit of Vitamin D supplementation as an adjunct to standard therapy for pulmonary tuberculosis (PTB) gained from a number of clinical trials remains unclear. Vitamin D has been shown by *in vitro studies* to modulate the immune system by inducing the destruction of mycobacteria. We investigated the effect of vitamin D supplementation on outcomes of PTB treatment of adult patients with active TB. We determined the effect of vitamin D supplementation on the rate of sputum smear conversion at weeks 4 and 8. We also investigated the following secondary outcomes: (1) median time to culture conversion, (2) development of severe adverse events, and (3) hypercalcemia.

Material/methods: We searched electronic databases up to August 2016 to identify studies with vitamin D supplementation and its effect on PTB treatment outcomes. We performed a systematic literature search across MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, Springer, EBSCO, ProQuest, HighWire Press, and Web of Science, published as of August 2016. We estimated pooled risk ratios (RR) and 95% confidence intervals (CI) using random-effect models. Selection criteria were as follows: all randomized controlled trials using vitamin D supplementation for PTB treatment that reported at least one of the desired outcomes (rate of sputum smear conversion, time to culture conversion, and adverse events) among patients ≥ 16 years old. We included all randomized controlled trials comparing vitamin D plus standard PTB regimen *versus* standard PTB regimen with or without placebo.



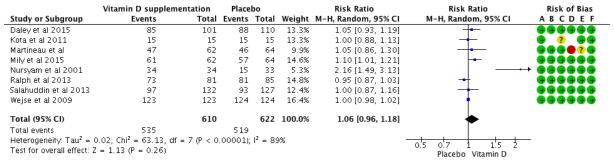
Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)

	Vitamin D supplementation		Placebo		Risk Ratio		Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	ABCDEF
Daley et al 2015	85	101	88	110	13.3%	1.05 [0.93, 1.19]	+-	000000
Kota et al 2011	15	15	15	15	13.3%	1.00 [0.88, 1.13]	+	• ? ••
Martineau et al	47	62	46	64	9.9%	1.05 [0.86, 1.30]		99999 ? 9
Mily et al 2015	61	62	57	64	14.6%	1.10 [1.01, 1.21]		000000
Nursyam et al 2001	34	34	15	33	5.3%	2.16 [1.49, 3.13]		→ ••••••
Ralph et al 2013	73	81	81	85	14.8%	0.95 [0.87, 1.03]		000000
Salahuddin et al 2013	97	132	93	127	12.4%	1.00 [0.87, 1.16]	+	000000
Wejse et al 2009	123	123	124	124	16.4%	1.00 [0.98, 1.02]	†	
Total (95% CI)		610		622	100.0%	1.06 [0.96, 1.18]	•	
Total events	535		519					
Heterogeneity: Tau ² = 0	0.02 ; $Chi^2 = 63.13$, $df =$	7 (P < 0	.00001);	$1^2 = 85$	9%		<u> </u>	_
Test for overall effect: 2	r = 1.13 (P = 0.26)				0.5 0.7 1 1.5 2 Placebo Vitamin D			

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- Figure 1. Effect of vitamin D supplementation on rate of sputum smear conversion at 8 weeks.

Results: A total of nine studies were analysed in our meta-analysis covering 1,601 newly-diagnosed PTB cases, observed over 8 to 32 weeks. The studies were of high quality with low risk of bias. There seemed to be a trend towards benefit in the vitamin D arm, with vitamin D supplementation increasing the rate of conversion by 11% at week 4 and 6% by week 8—although these trends were not statistically (at week 4: RR 1.11, 95% CI 0.86 to 1.43, P=0.42; at week 8: 1.06, 95% CI 0.96 to 1.18, P=0.26). There was no statistically significant trend towards benefit favoring vitamin D supplementation in terms of shortening median time to culture conversion. With vitamin D supplementation, there was no increased risk for adverse events or development of hypercalcemia.

	Vitamin D supplementation		Placebo		Risk Ratio		Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	ABCDEF
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Total (95% CI)		610		622	100.0%	1.06 [0.96, 1.18]	•	
Total events	535		519					
Heterogeneity: Tau ² = 0	0.02; Chi ² = 63.13, df =	7 (P < 0	.00001);	$1^2 = 89$	9%	-	05 07 1 15 2	_
Test for overall effect: Z	= 1.13 (P = 0.26)						Placebo Vitamin D	

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Conclusions: The results indicate that vitamin D supplementation did not significantly increase sputum smear conversion rates at weeks 4 and 8, nor did it significantly shorten sputum smear conversion. Further studies are needed to explore whether vitamin D supplementation at varying doses could shorten treatment and if baseline vitamin D levels have any effect on time of treatment.