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The effect of vitamin D on clinical outcomes in tuberculosis ☆

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ABSTRACT

Introduction: Vitamin D enhances immune responses to tubercle bacillus. The aim of our study is to determine the improvements of clinical outcome in patients taking cholecalciferol as supplement accompany anti-tuberculosis treatment.
Materials and methods: In a placebo-controlled and double blinded clinical trial sixty patients with pulmonary tuberculosis from March 2014 to July 2015 in Markazi province of Iran were randomized to take either single dose of 450,000 International Units of cholecalciferol or placebo. Evaluation was carried out at one, two and three months later. The first outcome was reduction in TB score and the secondary outcome was smear conversion and improvement of quality of life.
Results: Mean calcidiol levels for the whole study population were 22.81 ± 10.76 ng/ml and there have been no associations between baseline calcidiol levels and sputum smear burden (P-value = 0.54). There was an association of TB severity score with lower levels of Vitamin D (P-value = 0.043). The Short Form (SF)-12 health survey scoring at enrolment in two arms did not differ significantly (P-value = 0.786). Two months' later findings indicate that Vitamin D treatment had a positive effect on progressing health-related quality of life (P-value = 0.019) in each subscale of physical health score (P-value = 0.028) and mental health score (P-value = 0.025).
Conclusions: Our findings indicated that single dose cholecalciferol supplementation can lead to improving clinical outcome in tuberculous patients especially in those with calcidiol deficiency and improve the health-related quality of life of TB patients.
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Introduction

Tuberculosis (TB) is a serious worldwide health issue. About thirty percent of the world population are infected with *M. tuberculosis*. About 6.1 million tuberculous patients were reported in 2013 and of those, 5.7 million were newly diagnosed and another 0.4 million were under the treatment. Though treatment success rate continued to be high at eighty-six percent among all new cases however Serious efforts are needed to identify and treat new cases. The incidence of tuberculosis in Iran was 21(17–25) per one hundred thousand populations in 2013 [1]. More than ten thousand TB patients receiving directly observed treatment strategy (DOTS) in Iran each year. Dietary supplementation has been used as a mechanism to enhance the immune system [2,3]. Vitamin D mediates activation of the innate immune system in macrophages. Innate immune systems prepare the primary line of defense against infection. After micro-organism detection, toll-like receptors (TLR) on the phagocyte membrane activated to induce transcriptional up-regulation of the vitamin D receptor (VDR) and accountable for the VDR-dependent regulation of Variants of genes containing the up-regulation of cathelicidin expression. Incorporation of cathelicidin into phagosomes containing internalized M. Tuberculosis permits to operate as an antimicrobial agent to kill the offending infective agent [4,5]. Several studies demonstrate the impacts of calcidiol levels, VDR polymorphisms, and vitamin D supplementation on the acquisition of TB and on the outcomes of TB infections [6,7]. Increment risk of TB was reported among the people with lower serum vitamin D levels. Vitamin D supplementation seems to have a positive consequence

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on TB outcomes [8–10]. Vitamin D has been known as an auxiliary agent in preventing various infections [11,12]. We tend to determine the improvements in clinical outcome in patients taking cholecalciferol as supplement accompany anti-tuberculosis treatment.

Methods and materials

Study design

This study was a placebo-controlled and randomized double-blinded clinical trial. The trial was authorized by the institutional review boards of the Arak University of Medical Sciences and is recorded in Iranian registry of clinical trials (IRCT201407029855N5). The study was conducted from March 2014 to July 2015 in Markazi province of Iran. Inclusion criteria contained the diagnosis of tuberculosis by sputum smear microscopy and age $\geqslant$15 years. All participants prepared written, informed consent. Sequentially TB patients with a positive smear that newly recognized at outpatient TB clinics were included. According to clinical information, patients with extra-pulmonary tuberculosis, hepatic disease, renal failure, diabetes mellitus, sarcoidosis, human immunodeficiency virus (HIV) infection, malignancy, pregnancy, those taking any immunosuppressive agents, corticosteroids, thiazide diuretics or drugs which interfere with vitamin D levels (phenobarbital, theophylline, carbamazepine, phenytoin) and hyperparathyroidism were excluded from the study. The randomization arrangement was accomplished by the outpatient TB clinic of Arak University of Medical Sciences. All patients consecutively take Directly Observed Therapy (DOTS) with 6 months of anti-tuberculous drugs according to Iranian national guidelines. Qualified patients enrolled and were assigned using computer-generated randomization to receive either cholecalciferol or placebo. The two trial groups received either single dose of 1.5 ml that equivalent of 450,000 IU of cholecalciferol (Caspian Tamin Pharmaceutical Co.) or 1.5 ml of normal saline intramuscularly given at enrolment. The patient, primary physicians, and investigator physicians, were blinded to the treatment plan allocation.

Outcome variables

The clinical improvement as assessed by TB score [13], smear conversion and health-related quality of life by making use of the SF-12 questionnaire were primary outcomes. The TB score is a tool targeted to the valuation of change in the clinical condition in TB patients. It is based on scores assigned to symptoms and signs, comprising dyspnea, chest pain, tachycardia, hemoptysis, cough, lung auscultation finding, fever, night sweating, anemia, low mid–upper arm circumference and low body mass index, giving patients a TB score from 0 to 13, a high TB score correlates with increased mortality and morbidity and low TB scores predicate with desirable consequences. Improvement of C-reactive protein (CRP), Erythrocyte Sedimentation Rate (ESR), hemoglobin concentration (Hgb) and sputum conversion in patients that obtained at baseline, one, two and three months after starting treatment were secondary outcomes. Sputum microscopic examinations and clinical assessments were performed at all visits (0, 1, 2 and 3 months of therapy). Blood samples were obtained at 0, 1, 2 and 3 months of therapy. Clinical examination was used to assess a TB score for all patients in each visit. The TB score is an authentic evaluation tool created to objectively evaluate the change in the clinical condition of TB patients. Its ingredients consist of clinical signs (Auscultatory findings, tachycardia, fever, paleness) mid-upper arm circumference (MUAC), body mass index (BMI), and patient symptoms (hemoptysis, cough, night sweats, chest pain, and dyspnea). Mid Upper Arm Circumference (MUAC) was measured to a precision of 0.5 cm at the mid-point of the olecranon process and acromion over the biceps muscle of the non-dominant side, using a suitable measuring tape. Height was measured in metres, and weight in kilograms by using a standard electronic weighing scale (Beurer PS45 BMI Digital Scale) at all visits and body mass index (BMI) = weight (kg)/height (m^2). The TB score varies from zero to thirteen. All patients according to TB scores were divided into three intensity levels; Class III (TB score $\geqslant$8), Class II (TB score 6–7) and Class I (TB score 0–5). Baseline calcidiol levels were measured and categorized into insufficient 20–30 ng/ml, deficient <20 ng/ml and optimal >30 ng/ml.

For serum calcidiol measurement using the chemiluminescence immunoassay method (Roche Elecsys 2010 immunoassay analyzer). CRP was measured by latex agglutination tests, WBC was measured by hematology analyzer (Sysmex K1000) and ESR by Westergren method. Sputum conversion in patients obtained at one, two and three months after starting treatment. All laboratory measurements were done in one laboratory with the same personnel and calibrated equipment and all clinical signs and symptoms were measured by one person.

Quality of life assessment

The SF-12 Questionnaire (a concise version of the SF-36 Health Questionnaire) was used to evaluate the quality of life (QoL) of the patients of two arms at the beginning and two months later of treatment. The 12 questions indicant the consecutive eight sub- domains: vitality (1 item), physical functioning (2 items), bodily pain (1 item), general health perceptions (1 item), physical role functioning (2 items), emotional role functioning (2 items), social role functioning (1 item), mental health (2 items). Cronbach alpha was 0.86 in this study. For each patient, the SF-12 scoring algorithm creates a physical health scale (PCS-12) and mental health scale (MCS-12). These scores are calculated by weighting and then summing-up with a total score from 0 to 100 [14]. The lower the PCS-12 or MCS-12 accompanied the more activity limitations of patients.

Statistics

For the sample size estimation, we hypothesized that cholecalciferol supplement therapy could result in a sputum conversion about 20 percent more than placebo group [15]. The formula of calculating sample size was:

$$N_1 = N_2 = (Z_{\alpha/2} + Z_{\beta})^2 \times [p_1(1-p_1) + p_2(1-p_2)]/(p_1 - p_2)^2$$

With a power of 85% and α level of 0.05, and taking into account 10% drop-out, the sample size was calculated to be 34 for each group a total of 68 patients were enrolled in two groups of case and control. Analyses were conducted using SPSS software (ver. 18) and data were summarized as frequencies or percentages for categorical variables and as means and standard deviations for continuous variables. Differences between the groups were compared by the chi-square or Fisher exact test for categorical variables and *t*-test or Mann–Whitney test for continuous variables depending on the result of the Kolmogorov-Smirnov test for normality of distributions and repeated-measures analysis of variance (ANOVA) was used to test for difference between group means over time. Odds ratios are reported with 95% confidence intervals. $P < 0.05$ was considered to be statistically significant.

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Results

Sixty-eight patients were entered and randomized to the two - trial groups; 34 in the cholecalciferol arm and 34 in the placebo arm (Fig. 1).

Thirty patients in each trial group completed the study with a drop-out of 11.8%; four in the cholecalciferol group and four in the placebo group. Baseline characteristics of the two study populations are explained in Table 1 and the two groups did not differ significantly.

The mean age for the total population was 52.1 ± 17.9 years and 26 subjects (43.3%) had ⩾+2 AFB on sputum smear microscopy. Mean calcidiol levels for the entire population were in the insufficient range; 22.81 ± 10.76 ng/ml. and calcidiol levels were considered to be lower in females [26(89.7%)v/s21(67.7%) had levels <30 ng/mL, P-value = 0.039]. There were no associations between calcidiol levels and sputum smear microscopy (p-value = 0.54). There was an association of TB severity score with lower levels of serum calcidiol (P-value = 0.043). Alteration in clinical variables after 1, 2 and 3 months of treatment are shown in Table 2.

The overall SF-12 scoring at enrolment in two arms did not differ significantly [44.7 ± 8.4 v/s 45.3 ± 8.7, P-value = 0.786] but after two months' findings indicate that cholecalciferol adjunctive treatment had a positive effect on improving health-related quality of life [52.3 ± 9.6 v/s 46.2 ± 10.1, P-value = 0.019] in both subscale of physical health (0.028) and mental health (0.025) that are shown in Table 3.

Table 1
Baseline characteristics of patients with active TB in the vitamin D and placebo study arms at enrollment.

Parameter	Group		
	Vitamin D	Placebo	P-value
Age, years, mean (SD)	52.4(17.6)	51.8(18.2)	0.897
Male (%), Female (%)	16(53.3), 14(46.7)	15(50), 15(50)	0.795
Urban (%), Rural (%)	18(60), 12(40)	17(56.7), 13(43.3)	0.794
Smear ⩾ 2+	14(46.7)	12(40)	0.603
PPD ⩾ 10 mm	25(83.3)	24(80)	0.741
Mean BMI (SD)	20.75(3.8)	21.2(4.1)	0.660
MUAC, cm, mean (SD)	22.8(4.6)	23.1(4.8)	0.805
TB score mean (SD)	6.3(2.4)	6.1(2.2)	0.737
TB severity class I, II, III	11(36.7), 12(40), 7 (23.3)	12(40), 11(36.7), 7 (23.3)	0.955
Mean(ng/ml) 25(OH)D3 (SD)*	22.17(10.38)	23.45(11.14)	0.646
Patients with ESR↑** (%)	25(83.3)	27(90)	0.447
Patients with CRP↑*** (%)	26(86.7)	25(83.3)	0.718
Patients with anemia**** (%)	15(50)	14(46.7)	0.794

* Vitamin D insufficiency reported as 21–29 ng/mL and deficiency <20 ng/mL
** Hg <13 g/dl in men and Hg <12 g/dl in women.
*** The normal range (Westergren method) for males is 0–15 mm/h and for females is 0–20 mm/h.
**** CRP >10 mg/L.

Discussion

We showed that adjuvant treatment of single dose of 450000 IU cholecalciferol, in patients with pulmonary tuberculosis, smear in comparison with placebo. It has been offered that Vitamin D supplementation accelerates immunity responses and enhances cell-mediated immunity against mycobacterium and this may make a contribution to the development of vitamin D adjunctive treatment in tuberculosis patients [16]. Vitamin D is well-known as an immune-modulator in tuberculosis and 1,25-dihydroxy-cholecalciferol adjoins to vitamin D receptors and actuates cathelicidin-mediated killing of mycobacterium [17] while vitamin D deficiency raises the susceptibility and predisposes to tuberculosis infection [18]. Weight gain is an outpatient marker of betterment in TB and our study showed increases in health status in vitamin D arm in comparison with the placebo arm. These results were similar to the earliest stories of the advantages of vitamin D in TB treatment [19] that demonstrate weight gain and reduction in mortality in tuberculous patients treated with cod liver oil in comparison with standard treatment lonely. Also Martineau et al.

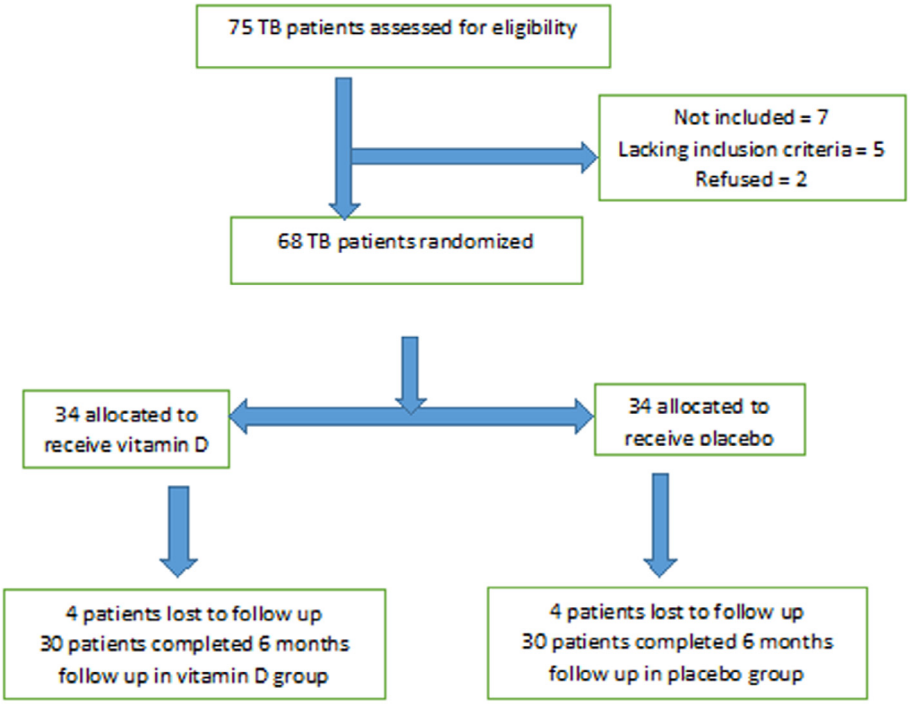

Fig. 1. Flowchart of participants.

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Table 2
Changes in measured clinical variables of patients with active TB in the vitamin D and placebo study arms after one, two and three months.

Time		Parameter					
		Smear conversion No. (%)	TB score mean (SD)	Mean BMI (SD)	Patients with ESR↑	Patients with CRP↑	Patients with Anemia
After 1 Months	Vitamin D	18(60)	4.7(1.8)	21.84(4)	19(63.3)	11(36.7)	5(16.7)
	Placebo	15(50)	5.6(1.9)	21.87(3.9)	20(66.7)	18(60)	13(43.3)
	OR (95%CI)	0.66(0.24–1.85)	(−1.86, 0.06)	(−2.07, 2.01)	0.86(0.29–2.49)	2.98(1.04–8.52)	3.82(1.15–12.71)
	P-value	0.435	0.064	0.976	0.787	0.038	0.024
After 2 Months	Vitamin D	28(93.3)	2.4(1.5)	24.66(4.3)	15(50)	5(16.7)	3(10)
	Placebo	22(73.3)	3.7(1.7)	22.31(3.9)	17(56.7)	12(40)	7(23.3)
	OR (95%CI)	0.20(0.04–1.02)	(−2.13, −0.47)	(0.23, 4.47)	0.76(0.28–2.11)	3.33(1–11.14)	0.37(0.08–1.58)
	P-value	0.037	0.003	0.033	0.603	0.044	0.164
After 3 Months	Vitamin D	29(96.7)	1.6(1.2)	24.86(4.5)	11(36.7)	1(3.3)	2(6.7)
	Placebo	27(90)	2.4(1.3)	23.82(4.3)	13(43.3)	4(13.3)	6(20)
	OR (95%CI)	0.31(0.03–3.17)	(−1.45, −0.15)	(−1.24, 3.32)	0.76(0.27–2.13)	0.22(0.02–2.14)	0.29(0.05–1.55)
	P-value	0.298	0.016	0.363	0.596	0.161	0.128

Table 3
SF-12 health survey scale means for patients with active TB in the vitamin D and placebo study arms.

SF-12 subscale	Sub-domains	Before Treatment			Two months after treatment		
		Vitamin D	Placebo	P-value	Vitamin D	Placebo	P-value
		M ± SD	M ± SD		M ± SD	M ± SD	
Physical health Component	Physical functioning	44.4 ± 11.3	46.6 ± 10.4	0.434	56.8 ± 9.6	48.7 ± 10.5	0.003
	Physical role	49.6 ± 11.2	51.3 ± 8.5	0.511	54.6 ± 8.9	51.4 ± 9.1	0.174
	General health	43.5 ± 6.8	42.5 ± 8.4	0.613	52.3 ± 9.2	44.7 ± 8.8	0.002
	Bodily pain	48.7 ± 9.7	51.4 ± 9.3	0.275	52.6 ± 10.3	48.2 ± 9.2	0.084
Mental health Component	Vitality	40.4 ± 8.2	41.5 ± 10.3	0.646	51.6 ± 10.6	45.6 ± 9.4	0.024
	Mental health	42.2 ± 8.7	40.8 ± 8.9	0.540	46.6 ± 7.2	41.2 ± 8.6	0.011
	Social functioning	47.7 ± 8.8	44.9 ± 8.3	0.209	50.1 ± 8.2	51.4 ± 9.4	0.570
	Emotional role	42.1 ± 8.2	43.5 ± 8.5	0.518	49.5 ± 9.8	41.3 ± 8.7	0.001
SF-12							
Physical health		47.3 ± 9.4	48.3 ± 9.8	0.688	54.3 ± 9.5	48.6 ± 10.1	0.028
Mental health		42.5 ± 9.2	42.2 ± 8.3	0.893	49.7 ± 9.3	44.1 ± 9.6	0.025
Total score		44.7 ± 8.4	45.3 ± 8.7	0.786	52.3 ± 9.6	46.2 ± 10.1	0.019

described that a single oral dose of 100,000 IUs of vitamin D2 tremendously suppressed mycobacteria [9]. A clinical trial on 67 Indonesian TB patients, by Nursyam et al. showed that supplementation in tuberculous patients with 420,000 IUs of vitamin D had greater sputum conversion [15]. Martineau et al. confirmed that 100,000 IUs of cholecalciferol supplementation did drastically hasten the conversion of sputum culture in patients with vitamin D receptor polymorphism [7]. Our study showed that the vitamin D group had lesser TB score (in comparison with placebo) after two and three months of treatment. This result is according to a clinical trial in Egypt that showed better healing after one thousand IUs of oral vitamin D supplementation on 24 children [20]. Two controlled trials by Martineau et al. and Wejse et al. showed no change in disease outcome or mortality after cholecalciferol supplementation versus placebo were given to 146 TB patients in the United Kingdom and 365 in Guinea-Bissau [7,21]. Daley et al. showed that vitamin D supplementation did not reduce time to sputum culture conversion [22]. According to a systematic review done in 2009, anti-TB treatment improving the quality of life, more so on the physical health of patients than the mental health [23]. Probably the discrepancy in the effect of cholecalciferol visible between our study and different studies might be as a result of variants in vitamin D receptor polymorphisms, variability in vitamin D dosages or differing phases of baseline serum calcidiol level. We found cholecalciferol supplementation to be very safe, even in patients with adequate serum calcidiol and improve health-related quality of life in both domains of physical health and mental health concomitantly. No patients had hypercalcemia, and none of the serious adverse events were related to the intervention. One limitation of our study was the lack of follow up our patients for long period. It is probable that advantage of cholecalciferol supplementation may become more manifest with longer follow-up. Another limitation was that we did not acquire dietary information.

Conclusion

Our findings indicated that However, at the end of treatment, there was no difference in Laboratory findings and BMI of patients in two groups, but a high single dose cholecalciferol supplementation leads to faster recovery of symptoms of patients and can lead to improving clinical outcome in tuberculous patients. Tuberculosis alleviate quality of life and necessary at TB clinics to apply strategies to improve the health-related quality of life of TB patients. Therefore, we recommend vitamin D supplement therapy for this purpose.

Competing interests

The authors declare they have no competing interests.

Authors' contributions

All authors contributed to study design, data collection, analysis, interpretation of data, drafting, revision of the manuscript and confirmation of the final manuscript.

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