ORIGINAL ARTICLE

Effect of Vitamin D Supplements and Pulmonary Tuberculosis Prognosis in Known Diabetic Patients

MASOOD ALAM[1], ASMA TAHIR[2], RAHMAT ULLAH[3]
[1]*Consultant Pulmonologist, CPEIC Multan.*
[2]*WMO,Children Hospital & Institute of Child, Multan.*
[3]*HO, Nishtar Hospital, Multan.*
Correspondence to Dr. Masood Alam, Email: dr.masood174@gmail.com, Cell No: 0333 6253500

ABSTRACT

Aim: To investigate role of vitamin D supplementation in clinical outcomes of sputum positive pulmonary tuberculosis patients having diabetes mellitus.
Methods: This randomized, placebo-controlled trial was conducted in outpatient department of Chest Medicine in Nishtar Hospital Multan, from June 2017 to November 2017. Total 52 patients who were sputum positive for pulmonary tuberculosis were selected for study by non-probability consecutive sampling. All patients were divided into two groups by lottery methods into group A and group B. both groups receive standard treatment of anti-tuberculosis drugs. Group A (n=26) receive high dose of oral vitamin D3 (2.5mg at 0, 2, 4 and 6 weeks). Group B (n=26) receive placebo. Primary outcome of study was to check sputum conversion after 8weeks of treatment. Written permission of study was signed by each individual participated in study. Data was analyzed by using SPSS volume 23.
Results: Overall, 52 patients were included, in this study; divided into two equal groups i.e., 26(50%) in each, group A (Vitamin D) and group B (Placebo) respectively. Patients with raised ESR were observed as 24(92.3%) and 21(80.8%) for group A and B respectively. Patients with raised CRP were noted as 25(96.2%) and 20(76.9%) for the group A and B respectively. Anemia was observed in 16(61.5%) and 14(53.8%) patients for group A and B respectively. Sputum smear conversation after 2 months, for the group A and B, noted as 23(88.5%) and 21(80.8%) respectively. The differences were statistically insignificant except for raised CRP which was significant (P=0.042).
Conclusion: Study concluded that there was no role of vitamin D supplementation in improving sputum conversion time. Further research is required in this regard. Also further investigation should be done to know the role of vitamin D in prevention and reactivation of pulmonary tuberculosis.
Keywords: Pulmonary tuberculosis, diabetes mellitus, vitamin D, sputum conversion,

INTRODUCTION

It has been estimated that about one third people of the whole world are latently infected by mycobacterium tuberculosis and it is one of the main public health problem internationally. So with the failure of human body immune system, active tuberculosis will be developed in this population[1]. Prevalence of diabetes mellitus in Pakistan is high of which 17.15% are rural and 22.04% are urban[2]. Diabetes mellitus cause immune suppression that can lead to increase susceptibility of diabetic patients with tuberculosis[3]. Diabetes mellitus is also growing pandemic[4]. It is one of major cause of blindness, renal failure, cardiovascular diseases and cerebro vascular accidents. Sunlight exposure and cod liver oil were the main treatment options for tuberculosis before antibiotics discover. Vitamin D is either taken in diet or synthesized in skin after sunlight exposure and then hydroxylation takes place in liver and kidney that converts it into finally 1,25-dihydroxyvitamin D3. Active form of vitamin D3 is $1,25(OH)_2D3$ which acts as immunomodulator[5]. Valid measure of vitamin D in blood serum is 25-hydroxy vitamin D3[6]. Many factors affect vitamin D deficiency like traditional and culture characteristics, decrease sunlight exposure and poor nutritional status with low socioeconomic conditions. It has been investigated that low levels of vitamin D in serum is significantly associated with increased incidence of tuberculosis[7] and also diabetes mellitus[8]. Similarly, normal level of vitamin D is protected against diabetes mellitus and tuberculosis. Immune system may be regulated by the vital role of 1,25-dihydroxyvitamin D3 by interacting with its receptor on T lymphocytes[9]. It has been investigated in studies that 1,25-dihydroxyvitamin D3 can be successful anti-tuberculosis agent. Catheliciden, which is an antimicrobial peptide produced by cells of immune system like monocytes, T lymphocytes and neutrophils, has shown activity against mycobacterium tuberculosis infections both in vivo and vitro models. Low levels of vitamin D in tuberculosis patients can be associated with poor nutritional status.

It has been investigated that some elements of anti-tuberculosis therapy cause decrease in serum level of useful vitamin D metabolites. Both hydroxylation processes in liver and kidney are inhibited by isoniazid, while rifampicin degrade 25-hydroxyvitamin D into waste product by another enzyme activity[10]. So both this primary anti-tuberculosis drugs can decrease serum vitamin D metabolites.

So vitamin D has been associated with tuberculosis and diabetes mellitus. Local data is limited regarding this subject and diabetes is associated with poor clinical outcome in pulmonary tuberculosis patients. Purpose of this study was to investigate the role of vitamin D supplementation in sputum positive pulmonary tuberculosis patients, who were also diabetics, on clinical outcome in the form of sputum conversion. This investigation will not

Received on 11-03-2018
Accepted on 25-09-2019

only provide the data regarding this subject but will also create awareness and encouragement to start vitamin D along anti-tuberculosis therapy to achieve better clinical outcome.

MATERIALS AND METHODS

This randomized, placebo-controlled trial was conducted in outpatient department of Chest Medicine in Nishtar Hospital Multan, from June 2017 to November 2017. Total 52 patients who were sputum positive for pulmonary tuberculosis were selected for study by non-probability consecutive sampling. All patients were divided into two groups by lottery methods into group A and group B. both groups receive standard treatment of anti-tuberculosis drugs. Group A receive high dose of oral vitamin D3 (2.5mg at 0, 2, 4 and 6 weeks). Group B receive placebo. Primary outcome of study was to check sputum conversion after 8weeks of treatment. Written permission of study was signed by each individual participated in study. Exclusion criteria of study were following: 1) patients with drug resistance tuberculosis or extra pulmonary tuberculosis 2) patients with renal, cardiovascular, liver and respiratory disease other than tuberculosis 3) seriously ill patients, 4) pregnant or lactating mothers 5) patients with history of any drug that interfere with vitamin D metabolism such as alcohol, vitamin D preparations or steroids. Sample size was calculated by a study done by Farazi A et al for which confidence interval was taken as 95%, study strength as 80, proportion of sputum conversion after two months for vitamin D group and placebo group were 93.3% and 73.3% respectively[11].

After registration, detailed clinical history of all individuals was recorded. Physical examination was conducted in each patient to check the extension and complications of disease and also to document any sign of malignancy or any other systemic disease. Vitals were recorded in each patient. A detailed drug history was also inquired. Personal information like age, gender, duration of disease, living area, body mass index and living area were obtained by filling the Performa.

Venous blood sampling was done in each individual in sitting position. Plasma glucose, vitamin D levels, complete blood count was measured. Sputum conversion was tested for both groups after 8 weeks of treatment.

Data was analyzed by using SPSS volume 23. Percentage and frequency were calculated for qualitative variables like gender, area of living, vitamin D deficiency, sputum conversion and smoking status and chi-square was applied to check the significance. For quantitative variables like age, body mass index, income, plasma glucose and vitamin D were statistically measured and analyzed in mean and standard deviation and t-test was applied to check the significance. p value less than 0.05 was considered as significant.

RESULTS

Overall, 100% (n=52) patients were included, in this study; divided into two equal groups i.e. 26(50%) in each, group A (Vitamin D) and group B (Placebo) respectively. The Mean±S.D age, BMI and 25 (OH) D_3 of the patients of A group was 46.65±5.12 years, 20.11±2.44 kg/m^2 and 17.50±1.90 ng/ml respectively. While, the Mean±S.D age, BMI and 25 (OH) D_3 of the patients of B group was 49.92±4.00 years, 20.85±2.33 kg/m^2 and 18.88±3.21ng/ml respectively. Gender distribution, in A group, was observed as 17(65.4%) males and 6(34.6%) females. While, in B group, there were 14(53.8%) males and 12(46.2%) females. There were 11(42.3%) and 15(57.7%) smokers in A and B group respectively. There were 18(69.2%) patients of group A were lived in rural areas while 8(30.8%) lived in urban areas. In group B, there were 15(57.7%) lived in rural areas while 11(42.3%) patients lived in urban areas. Socio-economic status of the patients was noted as poor, 15(57.7%) patients and 13(50%) patients for the group A and B respectively. The differences were statistically insignificant among the demographic characteristic of the patients, in groups, except age (p=0.013) (Table 1).

Patients with raised ESR were observed as 24(92.3%) and 21(80.8%) for group A and B respectively. Patients with raised CRP were noted as 25(96.2%) and 20(76.9%) for the group A and B respectively. Anemia was observed in 16(61.5%) and 14(53.8%) patients for group A and B respectively. Sputum smear conversation after 2 months, for the group A and B, noted as 23(88.5%) and 21(80.8%) respectively. The differences were statistically insignificant except for raised CRP which was significant (P=0.042) (Table 2).

Table 1: Demographic characteristics among the groups

Characteristics	Group A (n=26)	Group B (n=26)	Test of Sig.
Age (years)	46.65±5.12	49.92±4.00	t=-2.56, p=0.013
BMI* (kg/m^2)	20.11±2.44	20.85±2.33	t=-1.1, p=0.274
25 (OH) D_3 (ng/ml)	17.50±1.90	18.88±3.21	t=-1.8, p=0.065
Gender	M=65.4%, F=34.6%	M=53.8%, F=46.2%	χ^2=0.72, p=0.397
Smoking Status	Smokers=42.3%	Smokers=57.7	χ^2=1.23, p=0.267
Socio-economic status	Poor=57.7%	Poor=50%	χ^2=0.31, p=0.578
Area	Rural=69.2%, Urban=30.8%	Rural=57.7%, Urban=42.3%	χ^2=0.75, p=0.388

*Body mass index

Table 2

Characteristics	Group A (n=26)	Group B (n=26)	Test of Sig.
Patients with raised ESR	92.3% (n=24)	80.8% (n=21)	χ^2=1.5, p=0.223
Patients with raised CRP	96.2% (n=25)	76.9% (n=20)	χ^2=4.13, p=0.042
Anemia	61.5% (n=16)	53.8% (n=14)	χ^2=0.32, p=0.575
Sputum smear conversation after 2 months	88.5% (n=23)	80.8% (n=21)	χ^2=0.59, p=0.442

DISCUSSION

Results of study reported sputum conversion in both groups after two months of treatment were 88.5% in vitamin D group which was labelled as group A and 80.8% in group B which was placebo group. This difference was statistically not significant. So vitamin D supplementation did not influence any significant impact on sputum conversion in comparison with placebo in sputum positive pulmonary tuberculosis patients having diabetes mellitus.

Some investigations had been reported on this subject. Their results are contradictory. Reason behind adjoining vitamin D with anti-tuberculosis therapy was because vitamin D accelerates cell mediated immunity against mycobacterium tuberculosis and so enhanced the immunity[12]. Immune modulation results from adjoining of vitamin D receptor with 1,25 dihydroxyvitamin D3 which in turn cause acceleration of killing of mycobacterium tuberculosis by cathelicidin mediation[13]. Study done in Egypt by A Farazi et al. reported that role of vitamin D with anti-tuberculosis therapy in sputum conversion was not significant[11]. Similarly some investigation supported result of this study. A randomized controlled trial done in Mongolia reported that high dose of vitamin D3 did not show any improvement in sputum conversion[14]. In another placebo controlled trial done by Wejse C et al. reported no significant improvement in clinical outcomes with vitamin D in pulmonary tuberculosis patients[15]. Similarly high dose vitamin D3 did not show any improvement in sputum conversion in adults having tuberculosis in another double blind randomized controlled trial done in 2015[16]. A trial in 2011 done by Martineau AR et al reported that high dose of vitamin D did not affect significantly sputum conversion time in whole study population[17]. In our regional country India, a trial was done to treat active tuberculosis with anti-tuberculosis therapy with adjuvant vitamin D supplementation. Results of study showed that time of sputum conversion was not reduced significantly[18] so all these studies supported result of this study by concluding that vitamin D supplementation along with anti-tuberculosis drugs did not improve sputum conversion time.

Some studies contradicted result of this study. A trial done in Indonesia reported that patients who were using vitamin D supplementation showed higher sputum conversion[19] a study by Anna K et al. reported inflammatory response resolution was accelerated by vitamin D in tuberculosis treatment[20].

CONCLUSION

Study concluded that there was no role of vitamin D supplementation in improving sputum conversion time. Further research is required in this regard. Also further investigation should be done to know the role of vitamin D in prevention and reactivation of pulmonary tuberculosis.

REFERENCES

1. O'Garra A, Redford PS, McNab FW, Bloom CI, Wilkinson RJ, Berry MP. The immune response in tuberculosis. Annu Rev Immunol. 2013;31:475-527.
2. Bahadar H, Mostafalou S, Abdollahi M. Growing burden of diabetes in Pakistan and the possible role of arsenic and pesticides. J Diabet Metabolic Dis. 2014;13(1):117.
3. Martinez N, Kornfeld H. Diabetes and immunity to tuberculosis. Eur J Immunol. 2014;44(3):617-26.
4. Mahishale V, Avuthu S, Patil B, Lolly M, Eti A, Khan S. Effect of Poor Glycemic Control in Newly Diagnosed Patients with Smear-Positive Pulmonary Tuberculosis and Type-2 Diabetes Mellitus. Iran J Med Sci. 2017;42(2):144.
5. Chun RF, Adams JS, Hewison M. Immunomodulation by vitamin D: implications for TB. Expert Rev Clin Pharmacol. 2011;4(5):583-91.
6. Friis H, Range N, Pedersen ML, Mølgaard C, Changalucha J, et al. Hypovitaminosis D is common among pulmonary tuberculosis patients in Tanzania but is not explained by the acute phase response. J Nutr. 2008;138(12): 2474-80.
7. Zeng J, Wu G, Yang W, Gu X, Liang W, Yao Y, et al. A serum vitamin D level< 25nmol/l pose high tuberculosis risk: a meta-analysis. PLoS One. 2015;10(5):e0126014.
8. Lim S, Kim MJ, Choi SH, Shin CS, Park KS, et al. Association of vitamin D deficiency with incidence of type 2 diabetes in high-risk Asian subjects. Am J Clin Nutr. 2013;97(3):524-30.
9. Biyoudi-Vouenze R, Cadranel J, Valeyre D, Milleron B,. Expression of 1, 25 (OH) 2D3 receptors on alveolar lymphocytes from patients with pulmonary granulomatous diseases. Am Rev Respir Dis. 1991;143(6): 1376-80.
10. Sloan DJ, Mwandumba HC, Kamdolozi M, Shani D, Chisale B, Dutton J, et al. Vitamin D deficiency in Malawian adults with pulmonary tuberculosis: risk factors and treatment outcomes. Int J Tuberc Lung Dis. 2015;19(8):904-11.
11. Farazi A, Didgar F, Sarafraz A. The effect of vitamin D on clinical outcomes in tuberculosis. Egypt J Chest Dis Tuberc. 2017;66(3):419-23.
12. Coussens AK, Wilkinson RJ, Hanifa Y, Nikolayevskyy V, Elkington PT, Islam K, et al. Vitamin D accelerates resolution of inflammatory responses during tuberculosis treatment. Proc Natl Acad Sci U S A. 2012;109(38):15449-54.
13. Liu PT, Stenger S, Tang DH, Modlin RL. Cutting edge: vitamin D-mediated human antimicrobial activity against Mycobacterium tuberculosis is dependent on the induction of cathelicidin. J Immunol. 2007;179(4):2060-3.
14. Ganmaa D, Munkhzul B, Fawzi W, Spiegelman D, Willett WC, et al. high-dose Vitamin D3 during Tuberculosis Treatment in Mongolia. A Randomized Controlled Trial. Am J Respir Crit Care Med. 2017;196(5): 628-37.
15. Wejse C, Gomes VF, Rabna P, Gustafson P, Aaby P, Lisse IM, et al. Vitamin D as supplementary treatment for tuberculosis: a double-blind, randomized, placebo-controlled trial. Am J Respir Crit Care Med. 2009;179(9):843-50.
16. Tukvadze N, Sanikidze E, Kipiani M, Hebbar G, Easley KA, Shenvi N, et al. High-dose vitamin D3 in adults with pulmonary tuberculosis: a double-blind randomized controlled trial. Am J Clin Nutr. 2015;102(5):1059-69.
17. Martineau AR, Timms PM, Bothamley GH, Hanifa Yet al. High-dose vitamin D 3 during intensive-phase antimicrobial treatment of pulmonary tuberculosis: a double-blind randomised controlled trial. Lancet. 2011;377(9761):242-50.
18. Daley P, Jagannathan V, John KR, Sarojini J, Latha A, Vieth R, et al. Adjunctive vitamin D for treatment of active tuberculosis in India: a randomised, double-blind, placebo-controlled trial. Lancet Infec Dis. 2015;15(5):528-34.
19. Nursyam EW, Amin Z, Rumende CM. The effect of vitamin D as supplementary treatment in patients with moderately advanced pulmonary TB lesion. Acta Med Indones.2006; 38(1): 3-5.
20. Coussens AK, Wilkinson RJ, Hanifa Y, Nikolayevskyy V, Elkington PT, Islam K, et al. Vitamin D accelerates resolution of inflammatory responses during tuberculosis treatment. Proc Natl Acad Sci USA. 2012;109(38):15449-54.