Original Article

Effect of Vitamin D Supplementation on the Treatment of Pulmonary Tuberculosis Patients in Different Polymorphisms of the Vitamin D Receptor

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Abstract

Background: Vitamin D leads to the activation of macrophages and limitation of intracellular growth of Mycobacterium tuberculosis. Vitamin D receptor (VDR) gene polymorphisms can facilitate the development of tuberculosis (TB). Therefore, the present study aimed to investigate the effect of vitamin D supplementation on response to treatment in patients with pulmonary TB for different VDR polymorphisms.

Materials and Methods: This semiexperimental study was carried out over a 2-year period on 73 patients (37 females; 36 males) who suffered from pulmonary TB. Vitamin D supplement at a daily dose of 800 IU was administered to the patients for 8 weeks. The serum levels of vitamin D were measured by electrochemiluminescence immunoassay. The polymerase chain reaction with a sequence-specific primers technique was used to determine the polymorphisms FOK1, Bsm 1, Apa 1, and Taq1 of VDR gene.

Results: The mean serum levels of vitamin D increased significantly after the intervention (44.88 ng/ml vs 27.70 ng/ml, $P < 0.001$). Those with FF genotype of Fok1 polymorphism had a higher chance of a positive response to treatment compared to the other genotypes ($P = 0.044$, 95% CI). Bsm1, Apa1, and Taq1 polymorphisms increased the treatment response, which was not statistically significant.

Conclusion: The results of this study showed that individuals harboring FF genotype of Fok1 polymorphism had a higher chance of a positive response to treatment with vitamin D compared with other genotypes. Therefore, vitamin D supplement can be an appropriate treatment considering the genetic characteristics of TB patients.

Keywords: Genetic, polymorphism, lung, receptors, tuberculosis, Vitamin D

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Submitted: 20-Feb-2024; **Revised:** 09-Mar-2024; **Accepted:** 20-Apr-2024; **Published:** 28-Oct-2024

Introduction

Tuberculosis (TB) is known as one of the most vital infectious disorders and assumed among the top 10 reasons of mortality worldwide.[1] Its causative agent is a bacterium called Mycobacterium tuberculosis (MTB), which involves the lungs.[2] Regarding this disease, based on the recent reports of World Health Organization (WHO), approximately 10 million infected TB cases and 1.5 million deaths happened in 2019.[1] Human immunodeficiency virus (HIV) infection, treatment with immunosuppressive drugs, alcohol consumption, and reduced immune function due to malnutrition (weight loss

Access this article online

Quick Response Code:

Website: www.advbiores.net

DOI: 10.4103/abr.abr_76_24

How to cite this article: Bavi H, Hosseini SA, Ekrami A, Alavi SM, Malehi AS. Effect of vitamin D supplementation on the treatment of pulmonary tuberculosis patients in different polymorphisms of the vitamin D receptor. Adv Biomed Res 2024;13:102.

of >10%) have been mentioned among factors contributing to TB development.[3-6] Additionally, the standard TB therapy is also a prolonged process, and in some conditions like coinfection with HIV, prevalence of drug-resistant TB strains, and situations with side effects, remedial approaches may face with critical restrictions. So, it appears researchers will need to extend the new remedial agents which diminish the course of therapy and can conceal the other barriers in managing TB.[7-9] It has been reported that vitamin D affects responses of the host immune system through activation of the human monocytes and lymphocytes.[10] Stimulation of the physiological processes including monocyte activities, suppression of lymphocyte proliferation, motivated production of both immunoglobulin and cytokine, activation of the reactive oxygen and nitrogen responses, and inhibited activity of the matrix metalloproteinase along with the stimulation of autophagy are regarded among vitamin D functions.[1,11] The regulatory role of vitamin D is mediated when its active form 1,25-dihydroxyvitamin D binds to its receptor (VDR), which is a member of the nuclear receptor family.[10] VDR gene is a relatively large gene which has 10 exons with multiple polymorphisms involving Fok1 in exon 2, Bsm1 and APa1 in intron 8, and Taq1 in exon 9.[12] In current investigations, it has been illustrated that the serum level of vitamin D has a notable association with TB susceptibility rate.[13] The loci of VDR gene are associated with contacting different diseases such as prostate cancer, inflammatory bowel disease, osteoporosis, and TB because of allelic diversity that may increase susceptibility to TB.[14] Strong proof presents that vitamin D deficiency and polymorphism of its receptor gene affect TB susceptibility, development, and the result of the antitubercular therapy. Nevertheless, in the diverse populations, such data were incompatible and even conflicting.[15,16] Regarding all the aforesaid, the aim of this research was to investigate vitamin D receptor polymorphism in patients with TB and its relationship with response to therapy in these patients.

Since a similar study has not been conducted on the Iranian population, especially in Khuzestan Province, the context of ethnic diversity in this region can present useful information in this respect.

Materials and Methods

Participants

This research is a semiexperimental study. It was performed over a 2-year period on 73 patients (37 females and 36 males) with pulmonary TB whose disease was confirmed as smear-positive pulmonary TB and who were admitted to health and treatment centers in the city of Ahvaz. The inclusion criteria were being new patients with TB aged ≥18 years and the absence of underlying diseases (liver, kidney, and AIDS). Exclusion criteria were sputum-negative pulmonary TB, patients treated with corticosteroids and cytotoxicity, pregnant and lactating women, those with chronic diarrhea and malabsorption, diabetes, and non-Iranians. After explaining and stating the objective of the study to patients with sputum smear-positive pulmonary TB, written informed consent was taken from them. Considering the social and moral dimensions associated with TB, all patients were assured that medical ethics principles have been complied and that their records, names, and other specifications would remain confidential. All ethics principles were in accordance with Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (IR.ajums.REC.1392.278).

Laboratory assessment of vitamin D levels

All the patients filled the demographic information questionnaire, and their anthropometric indices were measured. Vitamin D supplement at a daily dose of 800IU was given to these patients for 8 weeks, and treatment follow-up was performed for 6 months. At the end of the eighth week, 3 mL of venous blood was taken from patients in a fasting state (at least 4 hours); the serum was removed and frozen at -20°C. To measure the vitamin D level, the samples were taken from the freezer and when thawed, the serum level of vitamin D was measured using electrochemiluminescence immunoassay (ECLIA). The laboratory criterion for serum levels of vitamin D in this method was 25-hydroxycholecalciferol. All experimental kits for this study were obtained from Bioactive Company (Germany), and all the samples were evaluated in the laboratory of Golestan Hospital (Ahvaz, Iran).

SSP-PCR

At the end of the 8 weeks period, the response of patients to treatment was evaluated by examining the result of their sputum culture, and subsequent actions were taken to determine vitamin D polymorphism as follows:[17] In this study, FOK1, Bsm1, Apa1, and Taq1 polymorphisms were examined, which are located in exon 2, intron 8, intron 8, and exon 9 of VDR gene, respectively. To determine different polymorphisms of VDR gene, SSP-PCR (polymerase chain reaction with sequence-specific primers) technique was used. The blood sample taken from each patient was utilized to isolate DNA, which was extracted using salting out method. PCR was carried out in a total volume of 25 µl based on the defined method. This test was performed under the following concentration conditions in two separate reactions to investigate each one of the VDR gene polymorphisms: The DNA content in each reaction was 75–100 ng; the concentrations of dNTPs, control primer, and Taq DNA Polymerase were 200 µM, 0.1 µM, and 0.5 unit, respectively. The PCR was performed using an Eppendorf (Mastercycler model) instrument simultaneously for all polymorphisms under identical temperature and time conditions in the following order: 2 minutes at 94°C for initial denaturation of DNA chains, 10 cycles of 10 s at 94°C and 1 minute at 65°C, 20 cycles of 10 s at 94°C, 50 s at 61°C, and 30 s at 72°C.[18] After performing PCR, electrophoresis of the reaction products was performed in 1.5% agarose gel, and the genotype of individuals was determined after photography. After genotyping, the allele and genotype frequencies of VDR gen polymorphisms were determined.

Statistical analysis

The sample size was calculated as n = 73 using NCSS statistical software with a confidence level of 95% and a test power of 90%. The comparisons of therapeutic outcomes with vitamin D supplementation in different polymorphisms were performed with the statistical package of SPSS (version 21) using Chi-square test.

Results

Out of 73 patients with TB, 37 (50.68%) were female and 36 (49.31%) were male. The mean age of TB patients was 43.45 years. The minimum and maximum ages of patients were 18 and 80 years, respectively. Thirty-three percent of TB patients held high-school diploma, 23% were illiterate, 23% had secondary school education, and only 8% had a university degree. In addition, among 73 samples, 44 were ethnic Arabs, 23 were Bakhtiari, and only 6 samples were from other ethnicities.

According to Figure 1, the mean serum level of vitamin D in TB patients before the intervention was 27.70 ng/ml (SD = 14.42) on average, and after 8 weeks of intervention with a daily dose of 800 IU vitamin D, the mean serum level of vitamin D was 44.88 ng/ml (SD = 21.7). According to our analysis, the serum levels of vitamin D in TB patients had increased significantly after the intervention ($P < 0.001$).

As can be seen in Figure 2, in this study, TB patients were categorized in three subgroups based on serum levels of vitamin D. Four patients (5.5%) were in the first group with vitamin D serum levels < 10 g ml and categorized as vitamin deficiency. In the second group with serum levels of 10–30 ng/ml, 40 patients (54%) had vitamin D insufficiency. The third group, which had vitamin D levels >30 ng/ml, included 29 patients (sufficient or normal group) (39%).

The mean weight of TB patients before intervention was 62.07 kg (SD = 11.87), and after intervention, their mean weight was 63.62 kg (SD = 11.88), which showed no significant difference ($P = 0.079$). The frequency analysis results of different vitamin D receptor polymorphisms are presented in Figure 3.

Figure 4 shows that those with FF genotype of Fok1 receptor had a higher chance of a positive response to treatment than other genotypes ($P = 0.044 < 0.05$, 95% CI).

The results in Figure 5 show that there was no significant difference ($P = 0.053 > 0.05$) in response to treatment between different genotypes from Taq1 gene polymorphism of vitamin D receptor. Also, according to Figure 6, there was no significant difference ($P = 0.192 > 0.05$) in response to treatment between difference genotypes of vitamin D receptor Bsml1. In addition, according to Figure 7, the assessments showed no significant difference ($P = 0.504 > 0.05$) in response to treatment between different genotypes of vitamin D receptor

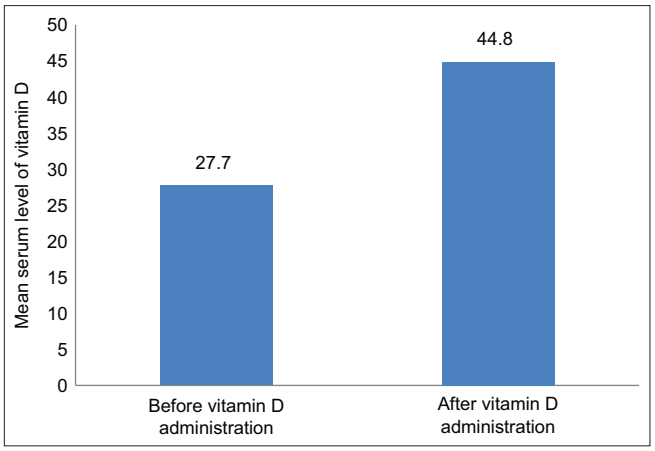

Figure 1: Mean serum levels of vitamin D in TB patients before and after intervention with vitamin D

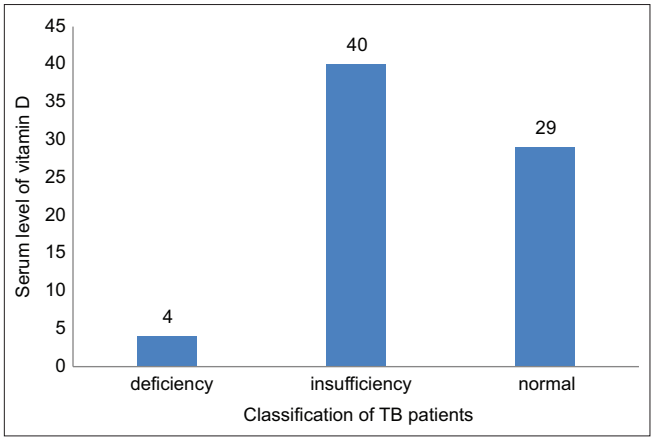

Figure 2: Classification of TB patients based on the levels of vitamin D

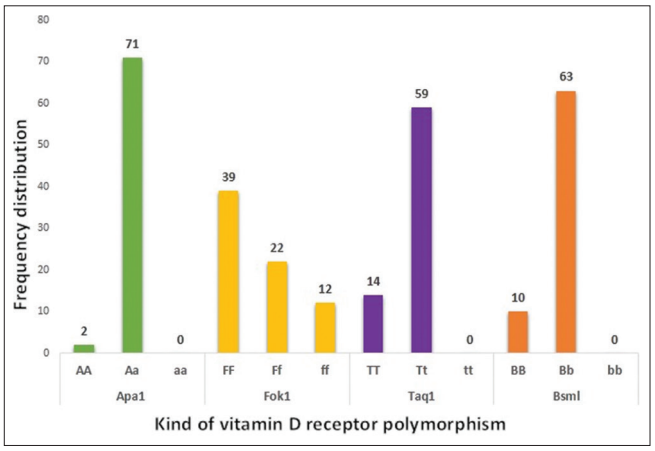

Figure 3: Frequency distribution of different vitamin D receptor polymorphisms versus genotype

Apa1. Table 1 shows the sequence of primers and the size of PCR products. Statistical analyses did not indicate a significant difference between different genotypes of vitamin D receptor with the period of response to treatment. Finally, a summary of the four mentioned polymorphisms is shown in Table 2.

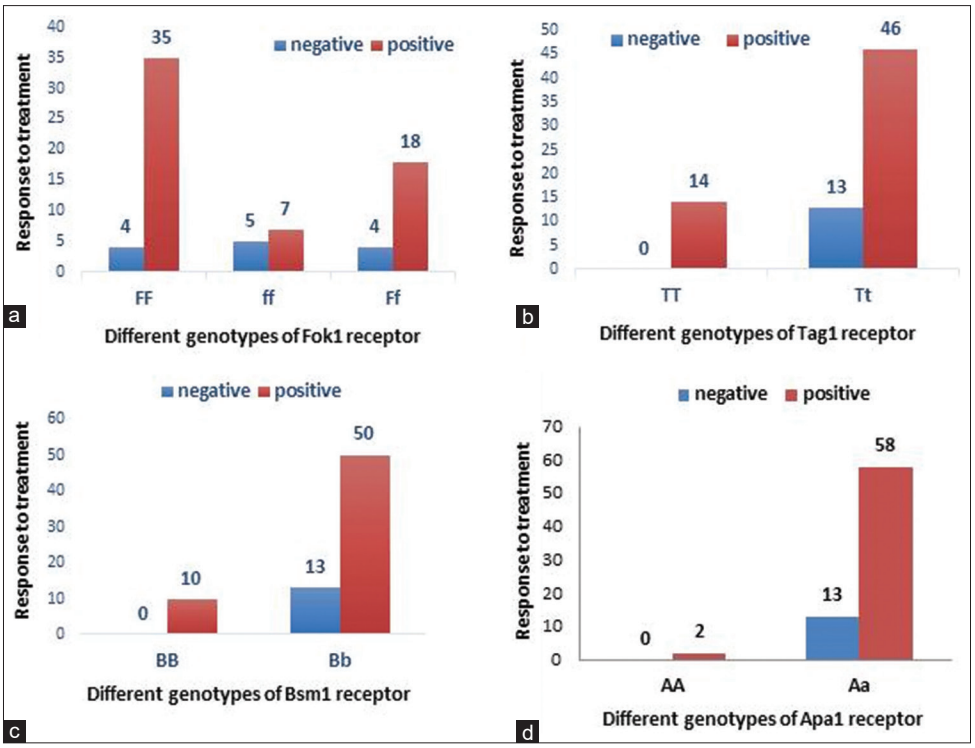

Figure 4: Comparison of therapy response in different genotypes of vitamin D receptor: (a) Fork 1 receptor, (b) Tag1 receptor, (c) Bsm1 receptor, (d) Apa1 receptor

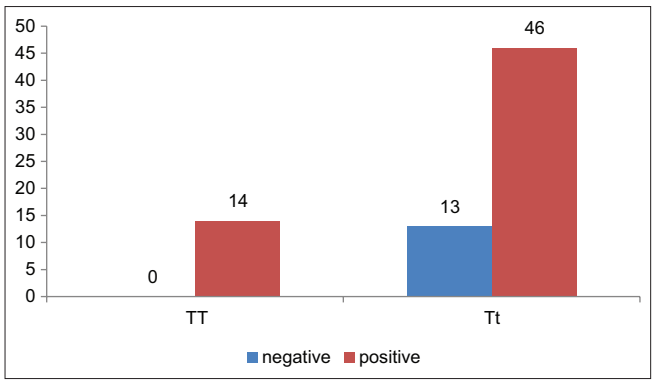

Figure 5: Comparison of response to treatment in different genotypes of Taq1 receptor. Among different genotypes of vitamin D receptor Taq1 polymorphism, there is no significant difference in response to treatment (*P* Value = 0.053 > 0.05)

Discussion

The aim of this study was to investigate the impact of vitamin D supplementation on response to treatment in patients with pulmonary TB in different vitamin D receptor polymorphisms. There are diverse viewpoints regarding the efficacy of vitamin D supplementation on treatment of pulmonary TB and its association with various vitamin D receptor polymorphisms. The study of Alavi *et al*. (2008)[19] on TB patients showed that despite accelerating the clearing time of TB bacilli from the body, f vitamin D supplementation as a complementary therapy does not cause an improvement in overall treatment outcome.

On the other hand, researchers have shown that vitamin D causes the acceleration of clinical recovery and relief from the signs and symptoms of TB such as fever, cough with sputum, weight loss, and night sweats.[20,21]

This study found that vitamin D supplementation in patients with pulmonary TB shows different results with respect to different vitamin D receptor polymorphisms. This research showed that patients with TB who possess FF genotype of FOK1 polymorphism have a higher chance of responding to treatment with vitamin D. Fok1 polymorphism is generated through the replacement of C with T in the first translation start codon in exon 2. The VDR encoded by "f" allele is three amino acids longer than normal, and the translation of receptor of this allele has 1–7 orders less effect than F allele that can change the rate of VDR production.[22,23] Moreover, other studies have also demonstrated that ff genotype increases the expression of VDR molecule. It has also been found that individuals with ff genotype of Fok1 polymorphism have a lower bone density than FF genotype due to lower response to vitamin D.[24,25]

On the other hand, in other polymorphisms, despite the higher number of cases of response to treatment, no significant difference was observed in this respect. However, given $P = 0.053 > 0.05$ of the response to treatment among different genotypes of Taq1, it can be noted that it is possible if the sample size was larger; a significant relationship would have existed. Selvaraj *et al*.[26] reported the impact of 1-week earlier clearing of tubercular patients receiving supplement, especially Taq1 homozygous genotype, and on the other hand, the studies

Table 1: Primers used for genotyping VDR gene polymorphisms and the size of PCR product

	Gene Locatie	Primers	Amplicon size (bp)
Exon 2	FokI F (46559145-46559162)	5'-TGGCCGCCATTGCCTCCG-3'	77
	FokI f (46559145-46559162)	5'-TGGCCGCCATTGCCTCCA-3	
	FokI C (46559204-46559221)	5'-AGCTGGCCCTGGCACTGA-3'	
Intron8	BsmI B (46526083-46526102)	5'-AGCCTGAGTACTGGGAATGT-3'	534
	Bsml b (46526083-46526102)	5'-AGCCTGAGTACTGGGAATGC-3	
	BsmI C (46526599-46526616)	5'-GGGAGGGAGTTAGGCACC-3'	
Intron8	ApaI A (46525104-46525123)	5'-TGGGATTGAGCAGTGAGGT-3'	229
	ApaI a (46525104-46525123)	5'-TGGGATTGAGCAGTGAGGG-3'	
	ApaI C (46524894-46524912)	5'-CCTCATTGAGGCTGCGCAG-3'	
Exon 9	TaqI T (46525024-46525041)	5'-CAGGACGCCGCGCTGATT-3'	148
	TaqI t (46525024-46525041)	5'-CAGGACGCCGCGCTGATC-3'	
	TaqI C (46524894-46524912)	5'-CCTCATTGAGGCTGCGCAG-3'	

Table 2: Kind of VDR gene polymorphism

Polymorphism	Allele	Time response				*P*
		2 month	4 month	6 month	No response	
Bsml	BB	7 (70%)	2 (20%)	1 (10%)	0 (0%)	0.65
	Bb	40 (63/5%)	20 (31/7%)	0 (0%)	3 (4.8%)	
	bb	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Taq	TT	7 (50%)	7 (50%)	0 (0%)	0 (0%)	0.287
	Tt	40 (67/8%)	15 (25/4%)	1 (1/7%)	3 (5/1%)	
	tt	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Apa	AA	2 (100%)	0 (0%)	0 (0%)	0 (0%)	0.768
	Aa	45 (63/4%)	22 (31%)	1 (1/4%)	3 (4/2%)	
	aa	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
FoK1	FF	22 (56/4%)	15 (38/5%)	1 (2/6%)	1 (2/6%)	0.143
	Ff	17 (77/3%)	5 (22/7%)	0 (0%)	0 (0%)	
	ff	8 (66/8%)	2 (16/7%)	0 (0%)	2 (16/7%)	
age			43.45			

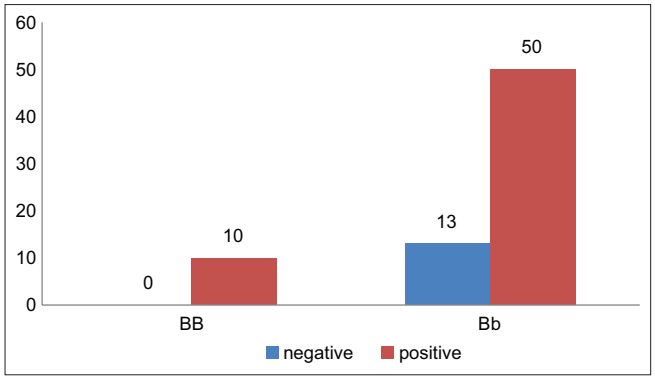

Figure 6: Comparison of response to treatment in different genotypes of Bsm1 receptor. Among different genotypes of vitamin D receptor Taq1 polymorphism, there is no significant difference in response to treatment (*P* Value = 0.192 > 0.05)

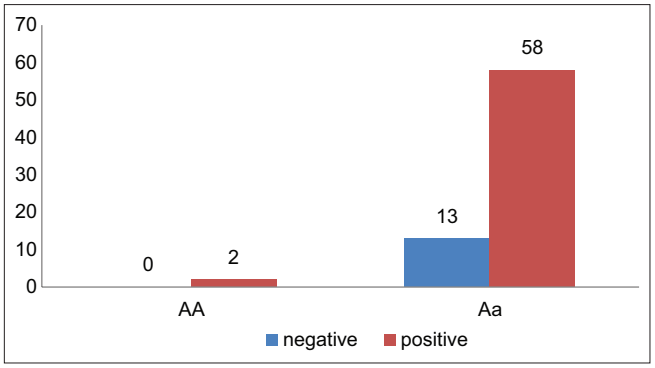

Figure 7: Comparison of response to treatment in different genotypes of Apa1 receptor. Among different genotypes of vitamin D receptor Taq1 polymorphism, there is no significant difference in response to treatment (*P* Value = 0.504 > 0.05)

consider this allele a factor in the quality of the immune system's efficiency. Similarly, Martineau *et al.*[27] showed that the tt allele of genotype had higher response to treatment outcome with vitamin D supplement compared to other polymorphisms, and they recommend using a high dose of vitamin D for the treatment of pulmonary TB patients. It should be noted that the three polymorphisms of Bsm1, Taq1, and Apa1 do not alter the translated protein because BSM1 and APa1 are located in the intron region of the gene and Taq1 is also the result of the change in silent codon in exon 9. Both

generated codons in the polymorphism (ATT, TaqI, and ATC) are related to amino acid isoleucine, but t allele causes the increase of mRNA VDR stability; hence, it has been proven that tt genotype reduces the risk of TB.[23] Accordingly, we can say that individuals with FF and tt due to higher VDR receptor expression and since vitamin D plays a role in macrophage activation, NO increase in macrophages, and an increase in antimicrobial peptide cathelicidin and reduces the risk of contracting TB disease, these people can be categorized individuals resistant to pulmonary TB.

In addition, out of 73 individuals participating in this study, a majority belonged to the Arab ethnic group with 44 people, 23 individuals were Bakhtiari, and only 6 were from other ethnicities. These diversities indicate the influence of ethnicity in contacting pulmonary TB. Studies in tropical countries have shown that vitamin D deficiency might be associated with a number of risk factors such as insufficient food source, sunshine exposure, use of sunscreen, religion, pollution, and skin color (ethnicity).[28-31] Khuzestan Province (Southern Iran) is a sunny region with high ethnic diversity; therefore, the risk of TB in some ethnic groups of this region could be higher than that in other regions.

However, the role of vitamin D in improving the treatment of pulmonary TB in molecular cellular level was demonstrated; however, geographic area, polymorphisms and different genetics, supplemented drug dose, serum levels of vitamin D, immune status, and food are influential factors on the efficacy of supplement therapy.[32-35] In fact, it seems that some polymorphisms increase the susceptibility to TB in a population, and although the effect of each of them is mild to moderate, their synergistic effects can cause significant risk.[36] By the same token, some vitamin D receptor polymorphisms can also cause disease in case of interaction with other genes and polymorphisms; some other polymorphisms reduce the severity of disease or augment the response to treatment.[37,38] With the emergence of drug-resistant MTB strains around the world, it is expected that the progress of our knowledge about the host genetics causes the revelation of unknown corners of biology and pathogenesis of TB disease.

In addition, findings of this study can be used to identify at risk populations; the innovation of pharmacogenetics solutions can prevent the spread of Mycobacterial infection to active TB disease. The small sample size of the studied population is a limitation of this study. However, in case of an increase in the sample size, some genotypes could have found significant correlation with the response to treatment. In this regard, it is recommended to perform the present study with larger samples in future among different human populations with diverse ethnicities.

Conclusion

The results of this study showed that individuals with ff genotype of Fok1 receptor have a higher chance of positive response to treatment with vitamin D compared to other genotypes, but no significant relationship was observed in other genotypes. Therefore, it is suggested that appropriate medical treatment be considered with regard to the genetics of TB patients. For more accurate and generalized results, a study with a larger sample size is needed.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of the Ahvaz Jundishapur University of Medical Sciences (IR.ajums.REC.1392.278). After explaining and stating the aim of the study to patients with sputum smear-positive pulmonary TB, written consent was obtained from them and because of the social and moral dimensions that tuberculosis disease has, all patients were assured that medical ethics have been complied and their records, names, and other specifications will remain confidential.

Authors' contributions

All authors contributed equally in this research

Acknowledgements

The authors would like to thank the Research Deputy of Ahvaz Jundishapur University of Medical Sciences for financial support of this research. We also thank the faculty members of the Nutrition department, School of Paramedical Sciences who assisted us in performing the laboratory experiments of this research.

Financial support and sponsorship

This study was supported by Ahvaz Jundishapur University of Medical Sciences and Shahid Beheshti University of Medical Sciences, with a TB-10 grant number.

Conflicts of interest

There are no conflicts of interest.

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