Review

Relationship between vitamin D level and Bechcet's disease activity: A systematic review and meta-analysis

Alireza Khabbazi[1], Morteza Ghojazadeh[2], Sakineh Hajebrahimi[2], and Zeinab Nikniaz[3]

[1] Connective Tissue Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[2] Research Center for Evidence Based Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[3] Liver and Gastrointestinal Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

Received: January 16, 2018; Accepted: June 17, 2018

Abstract: *Aim:* In the present study, the evidence about the association between vitamin D deficiency and Behcet's disease activity was systematically reviewed and meta-analyzed.
Method: We searched the English and Persian databases of Medline (Ovid), CINHAL, Scopus, Proquest, the Cochrane library and SID, IranDoc, Magiran, Iran Medex for articles published up until May 2018 with the keywords were related to serum vitamin D and active and inactive Behcet's disease in adults. Meta-analysis was done using the CMA software.
Results: A total of 138 titles were retrieved and reduced to 80 titles after deletion of duplicates and finally after close assessing of titles and abstracts eight eligible studies including a total of 939 participants were identified for systematic review and meta-analysis. According to the results of the meta-analysis, the pooled effect size of the differences in the serum level of vitamin D in patients with inactive Behçet's Disease and healthy controls was [OR:−0.05; 95% CI:−2.05, 1.94; p = 0.95]. The serum vitamin D level was significantly lower in active patients compared with healthy controls [OR:1.21; 95%CI: −0.12, 2.31; p = 0.03]. The pooled effect size of the differences in the serum level of vitamin D in active and inactive Behçet's Disease was [OR:−0.71; 95%CI: −1.41, −0.007; p = 0.04]
Conclusion: There is an association between vitamin D deficiency and active Behçet's Disease. Future studies investigating the association of vitamin D deficiency and Behçet's Disease needs to involve following information: dietary intake of calcium and vitamin D, measuring of sun exposure, report of drug consumption and physical activity level.

Keywords: Behçet's Disease, disease activity, vitamin D

Introduction

Behcet's disease is a multisystem, inflammatory and immune-mediated disease characterize by recurrent mucocutaneous, vascular, ocular, gastrointestinal and articular manifestations [1, 2]. Its exact etiology is unclear. However, the combination of genetic, abnormalities in immune response and environmental factors are suggested as triggers of Behcet's Disease [3–5]. Earlier studies have been shown that immune mechanisms including excess production of Th1 cytokine along with higher expression of Toll-like receptor 2 (TLR2) and TLR4 play a major role in the pathogenesis of Behcet's disease [6–8]. Moreover, some studies showed that the deficiency in serum level of some nutrients may decrease the immune responses and adding the deficient nutrient back into the diet restores the immune function [9]. One of the important nutrients with moderating effect on immune system is vitamin D. The receptors of this vitamin are expressed on immune cells, particularly B cells, T cells, and antigen-presenting cells [10].

Previous studies have been suggested the regulatory role of vitamin D in immune responses in addition to its conventional role in calcium and phosphorus metabolism [11]. In this regard, the inhibitory role of this vitamin on immunoglobulin secretion, T-Helper 1 (Th1) cells proliferation and B-lymphocyte differentiation have been shown in numerous studies [12, 13].

Considering the immunoregulatory role of vitamin D, many studies addressed the deficiency of vitamin D and also the presence of anti-vitamin D antibodies in patients with autoimmune disease [14] and showed the low level

of this vitamin in patients with diabetes [15], inflammatory bowel disease [16] and rheumatoid arthritis [17]. In this regard, numbers of studies have also focused on the level of vitamin D in active and inactive Behcet's disease [2, 18–25]. However, there is a discrepancy between the results of different studies and also to the best of our knowledge, there is no systematic review to summarize these studies. Therefore, in the present systematic review and meta-analysis study, for the first time, the level of serum vitamin in Behçet's Disease was evaluated.

Method

Study selection

The present study included observational studies that reported the serum level of vitamin D in active and inactive Behçet's Disease and healthy controls and published as a journal article or conference paper. Editorials, review articles and articles published in other languages rather English or Persian were excluded.

Data sources and search strategy

For this systematic review and meta-analysis, we searched the databases of Medline (Ovid), CINHAL, Scopus, Embase, Proquest and the Cochrane library and also Persian databases including SID (Scientific Information Database), IranDoc (Iranian Research Institute for Information Science and Technology), Magiran, IranMedex for articles published up until May 2018. Keywords were selected based on Mesh terms and included (but not limited to): "adult*" AND ("Active" AND ("inactive" OR "remission" OR "silent") AND ("Behçet's Disease" OR "Silk Road disease") AND ("Vitamin D OR 25-hyroxy vitamin D"). The references of eligible articles were also manually searched for further studies not identified. After the critical appraisal of articles, eight articles were selected (Fig 1). The PRISMA statement was used in order to build and elaborate this systematic review and meta-analysis.[26]

Data extraction

Two reviewers extracted data independently. Initially, one reviewer screens the results to exclude duplicate data and irrelevant articles. Two reviewers independently screened the remaining records to identify which article met the inclusion/exclusion criteria. For these records, the full-text was obtained and was independently evaluated by two reviewers for relevance. For each eligible study, one reviewer extracted the data about the sample size in each group, methodology, participant's characteristics and outcome. Then the results were checked by a second reviewer. Any inconsistencies were resolved through discussion and by consulting a third reviewer.

Quality assessment

Two investigators independently rated the methodological quality of selected studies using JBI checklist. Each domain appraised for a quality assessment (ranked as low, moderate, or high). A summary of the risk of selection and outcome measurement bias and justification for ratings is included in Table 2.

Quantitative synthesis

The Comprehensive Meta-Analysis version 2.0 was used for analyses of data. We extracted the mean level and standard deviations of vitamin D in patients with active and inactive Behçet's disease and healthy controls and also the sample size of each group. Then the mean difference of vitamin D between patients and healthy controls were computed using the meta-analysis. Q statistic and I^2 were used for determination of heterogeneity. In the present meta-analysis, $I^2 > 50\%$ and also a significance level of $P < 0.10$ for Cochran's Q were considered as clinically important heterogeneity [27, 28]. Based on heterogeneity analysis, fixed or random effect model was used. A funnel plot and an adjusted rank correlation test, according to methods of Begg and Mazumdar and Eggers were used for determination of publication bias.

Results

A total of 138 titles were retrieved and reduced to 80 titles after deletion of duplicates. The number of articles was reduced to 38 in the first assessment of the titles and abstracts and further reduced to 8 on closer assessment of the abstract and fulltext (Fig 1). The characteristics of the included studies are presented in Table 1.

Sample characteristics

Eight articles, including a total of 939 participants (280 active BD patients, 248 inactive BD patients and 411 healthy controls) met our predefined inclusion criteria.

Faezi et al. (2014), in a case control study in Iran, compared the serum level of vitamin D in 21 active Behçet's patients, 91 inactive Behçet's patients and 112 healthy controls. In this study 57.1% of BD patients and also 16.9% of healthy controls had hypovitaminosis D. In this study synchronically, patients and controls were not enrolled in the same season and the observed differences in serum level of vitamin D in two groups may be due to this

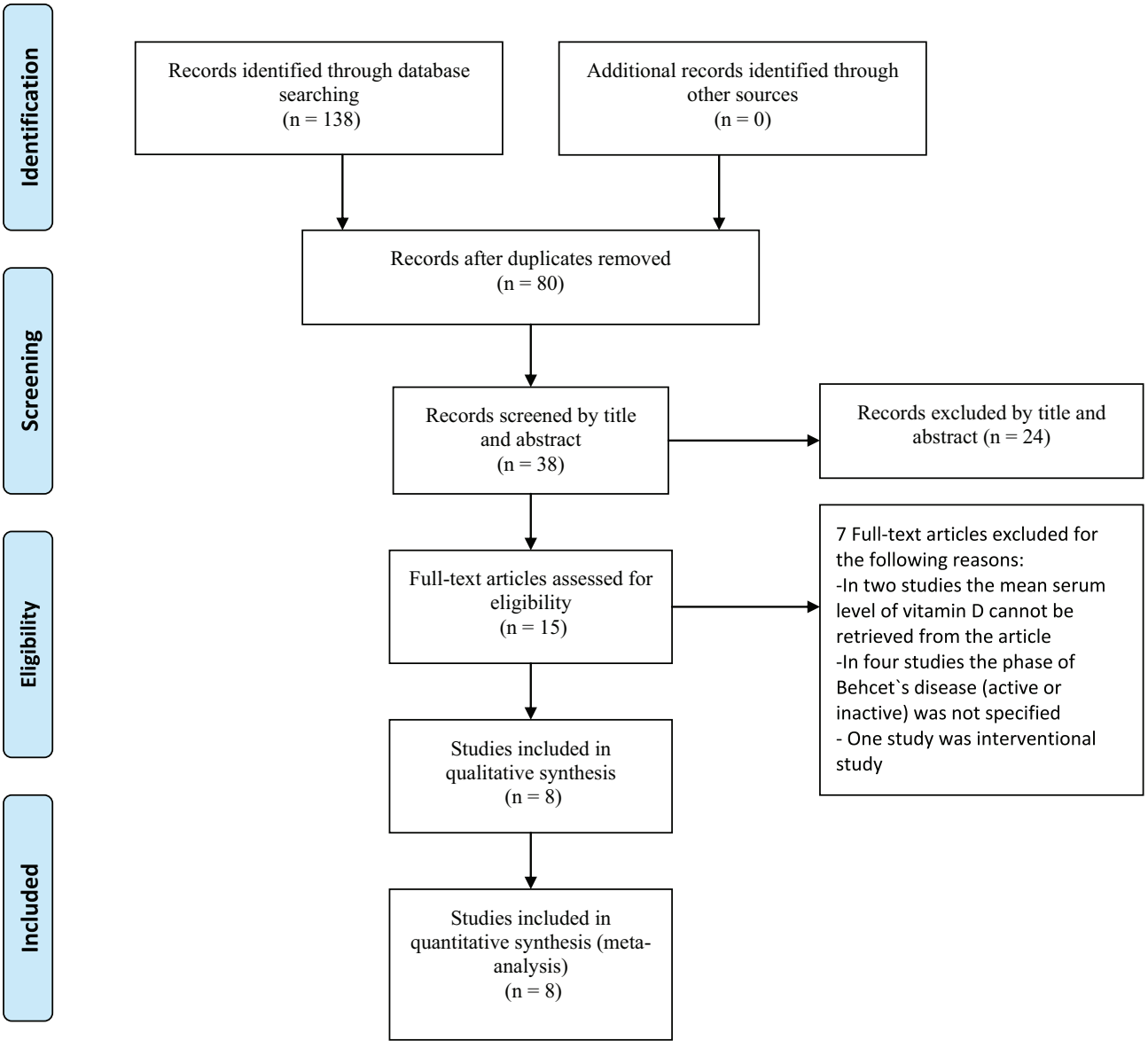


Figure 1. Flow diagram of studies for inclusion in the present study.

reason. The results showed that the mean serum level of vitamin D in active BD was lower than inactive BD patients and healthy controls [20].

In another case–control study in Korea, Do et al (2008) recruited 45 Behçet's patient and 15 healthy controls in the winter time. The results showed that serum 25(OH)D levels tended to be lower in active BD compared with inactive BD and healthy controls [19] but the differences in the mean serum level of vitamin D was not statistically significant between BD patients and healthy controls.

Kandi et al. investigated the level of different vitamins in 40 Behçet's patient (29 active BD and 11 inactive BD and 20 healthy controls) in turkey. The authors did not mention the season of blood sampling. The results of this study showed that there was no statistically significant difference in serum level of vitamin D in Behçet's patient compared with healthy controls.

Hamzaoui et al. (2007), studied the association between serum vitamin D level and Behçet's disease. The blood withdrawal was performed in autumn and winter. They showed the significantly lower levels of vitamin D in active and inactive Behçet's disease compared to healthy controls.

Djeraba et al. (2017), assessed the vitamin D status in 51 Behcet's patients and compared it with healthy controls. All blood samples collected in spring. According to results, the median level of serum vitamin D in active and inactive BD patients was significantly lower than control group [29].

Table 1. Characteristics of the included studies

Author	Place	Number of patients in active BD group	Number of patients in inactive BD group	Number of patients in Control Group	Vitamin D (μg/ml) Level in active BD group	Vitamin D (μg/ml) Level in inactive BD group	Vitamin D (μg/ml) Level in Control group			
					Mean	SD	Mean	SD	Mean	SD
Djeraba et al (2017)	Algeria	33	18	33	19.3	4.56-53.06	25.12	9.47-56.7	31.39	6.81-55.71
Adeeb et al (2017)	Ireland	4	15	95	14	8.4-16.8	125	14-26.8	8.8	6-12.4
Aslan et al (2017)	Turkey	21	37	70	18.68	7.31	15.08	7.17	18.44	5.79
Khabbazi et al (2014)	Iran	47	-	48	13.9	7.5	-	-	27.4	9.7
Faezi S.T. et al (2014)	Iran	21	91	112	8.3	1.1	11.9	2.1	24.4	2.5
Hamzaoui et al(2010)	Tunisia	102	58	18	9	5.7	11.1	5.2	14.03	5.2
Do J.E. et al(2008)	Korea	23	18	15	10.9	4.3	12.5	3.7	14.01	3.6
Kandi et al (2007)	Turkish	29	11	20	30.1	15.9	29.7	7.4	38.96	16.33

BD: Behcet's patients
SD: Standard deviation

Table 2. Assessment of Risk of bias

Questions	Kandi et al. (2007)	Do et al. (2008)	Hamzaoui et al (2010)	Faezi et al (2014)	Khabbazi et al (2014)	Djerab et al (2017)	Adeeb et al (2017)	Aslan et al (2017)
1. Were the criteria for inclusion in the sample clearly defined?	Y	Y	Y	Y	Y	Y	Y	N
2. Were the study subjects and the setting described in detail?	Y	Y	Y	Y	Y	Y	Y	Y
3. Was the exposure measured in a valid and reliable way?	Y	Y	Y	Y	Y	Y	Y	Y
4. Were objective, standard criteria used for measurement of the condition?	Y	Y	Y	Y	Y	Y	Y	Y
5. Were confounding factors identified?*	UC	NC	NC	NC	NC	NC	NC	NC
6. Were strategies to deal with confounding factors stated?*	UC	NC	NC	NC	NC	NC	NC	NC
7. Were the outcomes measured in a valid and reliable way?	Y	Y	Y	Y	Y	Y	Y	Y
8. Was appropriate statistical analysis used?	Y	Y	Y	Y	Y	Y	Y	Y

Y: Yes; UC: Unclear; NC: Not Completely
*in none of the studies, the confounders including age, sex, steroid uses, physical activity level, type of clothing, dietary factors were considered completely.

Aslan et al. (2017), in a study on 68 BD patients showed that, serum level of vitamin D level was significantly lower in BD patients compared with healthy controls. In both groups, serum level of vitamin D was measured in the same seasons for excluding seasonal differences [30].

Adeeb et al. (2017), in a study on 19 BD patients from Ireland showed that the serum level of BD patients was significantly higher than healthy controls even after control for age, sex and month of blood drawn [31].

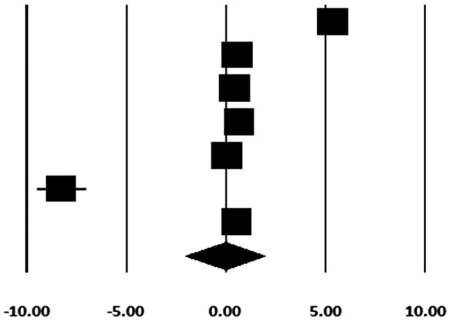
Khabbazi et al. (2014), in a cross-sectional study in active BD patients and healthy controls showed that the mean serum vitamin D level in the BD group was lowerthan the control group [24].

Meta-analysis results:

Three comparisons including the comparison between active BD and healthy controls (Fig. 2A) and also inactive BD and healthy controls (Fig. 2B) and active BD and

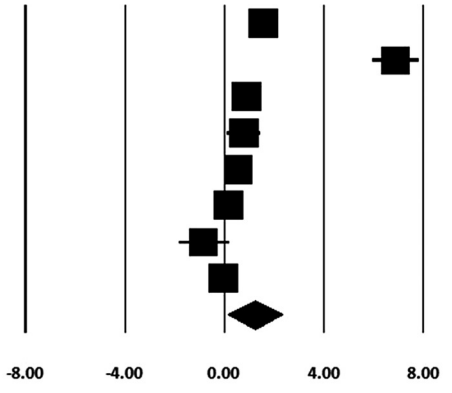
Inactive BD vs Control

Model	Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
	Faezi S.T. et al (2014)	5.366	0.301	0.091	4.775	5.957	17.804	0.000
	Hamzaoui et al(2010)	0.563	0.274	0.075	0.027	1.100	2.059	0.039
	Do J.E. et al(2008)	0.413	0.353	0.125	-0.279	1.106	1.169	0.242
	Kandi et al (2007)	0.666	0.385	0.148	-0.089	1.420	1.730	0.084
	Djeraba et al (2017)	0.024	0.293	0.086	-0.550	0.599	0.083	0.934
	Adeeb et al (2017)	-8.269	0.623	0.388	-9.490	-7.048	-13.275	0.000
	Aslan et al (2017)	0.534	0.207	0.043	0.129	0.938	2.584	0.010
Random		-0.054	1.019	1.039	-2.053	1.944	-0.053	0.957



Active-Control

Model	Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
	Khabbazi et al (2017)	1.555	0.234	0.055	1.096	2.014	6.640	0.000
	Faezi S.T. et al (2014)	6.877	0.484	0.234	5.928	7.826	14.206	0.000
	Hamzaoui et al(2010)	0.893	0.262	0.069	0.380	1.407	3.409	0.001
	Do J.E. et al(2008)	0.769	0.343	0.118	0.096	1.442	2.240	0.025
	Kandi et al (2007)	0.551	0.296	0.088	-0.029	1.131	1.862	0.063
	Djeraba et al (2017)	0.157	0.247	0.061	-0.326	0.640	0.637	0.524
	Adeeb et al (2017)	-0.834	0.514	0.264	-1.842	0.173	-1.624	0.104
	Aslan et al (2017)	-0.039	0.249	0.062	-0.527	0.449	-0.156	0.876
Random		1.217	0.560	0.313	0.120	2.313	2.174	0.030



Active-Inactive

Model	Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
	Faezi S.T. et al (2014)	-1.840	0.272	0.074	-2.372	-1.308	-6.777	0.000
	Hamzaoui et al(2010)	-0.380	0.166	0.027	-0.705	-0.055	-2.292	0.022
	Do J.E. et al(2008)	-0.395	0.318	0.101	-1.018	0.228	-1.244	0.214
	Kandi et al (2007)	0.028	0.354	0.125	-0.666	0.722	0.080	0.936
	Djeraba et al (2017)	-0.135	0.293	0.086	-0.709	0.440	-0.459	0.646
	Adeeb et al (2017)	-4.693	0.947	0.896	-6.548	-2.837	-4.957	0.000
	Aslan et al (2017)	0.499	0.277	0.077	-0.045	1.042	1.799	0.072
Random		-0.712	0.360	0.129	-1.418	-0.007	-1.981	0.048

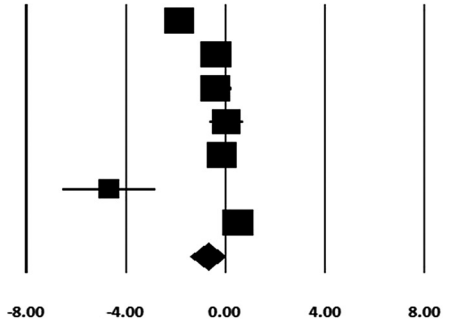


Figure 2. Forest plot showing the differences in serum level of vitamin D in A:inactive Behcet's disease and Controls; B: inactive Behcet's disease and Controls C: inactive Behcet's disease and active Behcet's disease.

inactive BD (Fig 2C) were included in the meta-analysis. The random effect model showed the insignificant difference between serum level of vitamin D in inactive BD and healthy controls (SDM = -0.054, 95% CI: -2.05, 1.94, p = 0.95). Moreover, the serum level of vitamin D in active BD was significantly lower than healthy controls (SDM = 1.21, 95% CI: 0.12, 2.31, p = 0.03). Comparison between active BD and inactive BD patients showed that serum level of vitamin D in Active patients was significantly lower than inactive patients (SDM:−0.71, 95%CI:−1.41—0.007, p = 0.04).

Heterogeneity was high for all comparisons [(Inactive BD and healthy controls $I^2 = 98.67$ Q-value = 451.98, $p < 0.001$), active BD and healthy controls ($I^2 = 90.20$ Q-value = 61.19, $p < 0.001$) and active BD and inactive BD ($I^2 = 90.20$, Q-value = 61.19, $p < 0.001$)] (Table 2).

Discussion

Considering the immunosuppressive effects of vitamin D and also the possible relation between the low level of serum vitamin D and autoimmune diseases (34), vitamin D has been investigated as a possible pathogenetic factor in autoimmune diseases such as Behçet's disease (10). Many studies have focused on the relationship between serum level of vitamin D and Behçet's disease and in the present systematic review and meta-analysis, we aimed to systematically review and analyze the differences in the serum level of vitamin D in active Behçet's disease and healthy controls. Overall, eight studies were included in the present systematic review and meta-analysis. Inclusion criteria were considered in all except one study [30], none of the studies completely considered confounders including age, sex, steroid use, PTH level, physical activity level, dietary factors and clothing type. In all studies, disease and outcome were measured in valid ways. The mean serum level of vitamin D in patients (active and inactive) and also healthy controls in 7 of 8 studies were lower than normal level of this vitamin (30 ng/ml). According to previous reports, hypovitaminosis D is a global public health problem and different factors such as latitude, type of clothing, low exposure to sun, body fat, using calcium supplements and genetic factors are considered as main determinants of hypovitaminosis D [32].

According to the results of meta-analysis, we showed that the pooled effect size of the differences in the serum level of vitamin D in inactive patients and healthy controls was [SDM = −0.05, 95% CI: −2.05, 1.94, p = 0.95]. Moreover, the random effect model showed that the level of serum vitamin D in active BD was significantly lower than healthy. Vitamin D has the immunomodulatory role and previous studies showed that it had the inhibitory effect on Th1 cells and could regulate the balance between the Th1 and Th2. So, it had been suggested that the adequate serum level of vitamin D could prevent autoimmune disease development [18]. Behçet's Disease is also immune-related disease mainly driven by Th1cells. In previous studies, Hamzaoui et al. showed that vitamin D deficiency in Behçet's Disease was associated with skewing of the Th1/Th2 balance towards Th1 production [25]. Moreover, Do et al. in the in-vitro study showed the high expression of toll-like receptor (TLR) 2 and TLR4 in the monocytes of patient's with Behcet's disease [19]. Moreover, in a recent study, Djeraba et al, showed that vitamin D inhibit iNOS and NF-kB expression and consequently nitric oxide (NO) production in BD patients [29]. In another in-vitro study in necrotic mucocitanous lesion of patients with Behçet's Disease, Imamura et al., showed the enhanced expression of Heat shock protein (HSP) 60 [8]. It has been shown that HSP60 induce TLR 2 and TLR4 and via this could induce inflammatory responses [8]. Do et al. demonstrated that serum level of vitamin D is inversely correlated with the expression of TLR2 and TLR4 [19]. TLR2 and TLR4 have been identified as signaling receptors activated by bacterial cell wall components and have a major role in the innate-activation of Behçet's Disease [33].

We also showed that serum vitamin D in active BD patients was lower than inactive patients that may be due to receiving high doses of corticosteroids in active BD patients that increase degradation of 25(OH)D and 1,25 (OH)2D due to activation of the pregnane X receptor [34].

The main strength of our systematic review like any other systematic reviews is the low risk of subjective data selection. Study searches, assessment, and data synthesis were all based on predefined criteria and were performed with the use of well-established repetitive tools by two reviewers independently. Nevertheless, our analysis has some limitations. First, the publication bias could not be fully excluded, i.e. negative findings being less likely to be published. Second, any systematic review is only as good as the included studies. Almost none of the included studies seemed methodologically sound. In most of the included studies the serum PTH level, calcium intake, physical activity level, steroid use and sun exposure were not analyzed. So, the results were not adjusted for these confounding factors.

Conclusion

In conclusion, the result of this systematic review and the Meta analysis showed that the serum level of vitamin D in active Behcet's disease was significantly lower than healthy controls. It suggested that vitamin D deficiency is a possible risk factor for BD activity. Future studies investigating the association of vitamin D deficiency and Behçet's Disease

needs to involve the following information: dietary intake of calcium and vitamin D, measuring of sun exposure, detail assessment and report of drug consumption, assessment and report of physical activity level.

References

1. Onal, S., Tugal-Tutkun, I., & Tugal-Tutkun, I. (2016) Behçet disease. In Uveitis: An Update (pp. 17–31). Springer.
2. Kandi, B., Cicek, D, & Ilhan, N (2007) Vitamin levels in Behçet's disease. J Dermatolog Treat. 18(2), 69–75.
3. Gul, A. (2001) Behcet's disease: an update on the pathogenesis. Clin Exp Rheumato. 19(5; SUPP/24), S6–00.
4. Protogerou, A.D., Sfikakis, P.P., Stamatelopoulos, K.S., Papamichael, C., Aznaouridis, K., Karatzis, E., Papaioannou, T.G., Ikonomidis, I., Kaklamanis, P., & Mavrikakis, M. (2007) Interrelated modulation of endothelial function in Behcet's disease by clinical activity and corticosteroid treatment. Arthritis Res Ther. 9(5), R90.
5. Zouboulis, C.C., & May, T. (2003) Pathogenesis of Adamantiades-Behçet's disease. Med Microbiol Immunol. 192(3), 149–155.
6. Hamzaoui, K., Hamzaoui, A., Guemira, F., Bessioud, M., Hamza, M.H., & Ayed, K. (2002) Cytokine profile in Behçet's disease patients. Scand J Rheumatol. 31(4), 205–210.
7. Mege, J., Dilsen, N., Sanguedolce, V., Gul, A., Bongrand, P., Roux, H., Ocal, L., Inanc, M., & Capo, C. (1993) Overproduction of monocyte derived tumor necrosis factor alpha, interleukin (IL) 6, IL-8 and increased neutrophil superoxide generation in Behcet's disease. A comparative study with familial Mediterranean fever and healthy subjects. J Rheumatol. 20(9), 1544–1549.
8. Imamura, Y., Kurokawa, M.S., Yoshikawa, H., Nara, K., Takada, E., Masuda, C., Tsukikawa, S., Ozaki, S., Matsuda, T., & Suzuki, N. (2005) Involvement of Th1 cells and heat shock protein 60 in the pathogenesis of intestinal Behcet's disease. Clin Exp Immunol. 139(2), 371–378.
9. Wintergerst, E.S., Maggini, S., & Hornig, D.H. (2007) Contribution of selected vitamins and trace elements to immune function. Ann Nutr Metab. 51(4), 301–323.
10. Alpert, P.T. (2017) The Role of Vitamins and Minerals on the Immune System. Home Health Care Manag Pract. 29(3), 199–202.
11. Li, Y.C., Bolt, M.J., Cao, L.-P., & Sitrin, M.D. (2001) Effects of vitamin D receptor inactivation on the expression of calbindins and calcium metabolism. Am J Physiol Endocrinol Metab. 281(3), E558–E564.
12. Lemire, J.M. (1992) Immunomodulatory role of 1, 25-dihydroxyvitamin D3. J Cell Biochem. 49(1), 26–31.
13. Veldman, C.M., Cantorna, M.T., & DeLuca, H.F. (2000) Expression of 1, 25-dihydroxyvitamin D3 receptor in the immune system. Arch Biochem Biophys. 374(2), 334–338.
14. Cantorna, M. (2000) Vitamin D and autoimmunity: is vitamin D status an environmental factor affecting autoimmune disease prevalence? Proc Soc Exp Biol Med. 223(3), 230–2333.
15. Song, Y., Wang, L., Pittas, A.G., Del Gobbo, L.C., Zhang, C., Manson, J.E., & Hu, F.B. (2013) Blood 25-hydroxy vitamin D levels and incident type 2 diabetes. Diabetes Care. 36(5), 1422–1428.
16. Del Pinto, R., Pietropaoli, D., Chandar, A.K., Ferri, C., & Cominelli, F. (2015) Association between inflammatory bowel disease and vitamin D deficiency: a systematic review and meta-analysis. Inflamm Bowel Dis. 21(11), 2708.
17. Raczkiewicz, A., Kisiel, B., Kulig, M., & Tlustochowicz, W. (2015) Vitamin D status and its association with quality of life, physical activity, and disease activity in rheumatoid arthritis patients. J Clin Rheumatol. 21(3), 126–130.
18. Can, M., Eren, R., Baykan, O., Asmaz-Haliloglu, O., Gogas-Yavuz, D., Haklar, G., & Direskeneli, H. (2014) AB0582 Effect of Vitamin D Deficiency and Replacement on Endothelial Functions in Familial Mediterranean Fever. Ann Rheum Dis. 73(Suppl 2), 998–998.
19. Do, J.E., Kwon, S.Y., Park, S., & Lee, E.-S. (2008) Effects of vitamin D on expression of Toll-like receptors of monocytes from patients with Behcet's disease. Rheumatology. 47(6), 840–848.
20. Faezi, S.T., Ansari, N., Paragomi, P., Akhlaghi, M., Ghanavat, M., & Davatchi, F. (2014) Vitamin D deficiency in patients with Behcet's disease. J Diabetes Metab Disord. 13(1), 18.
21. Ganeb, S.S., Sabry, H.H., El-Assal, M.M., Kamal, H.M., & Fayed, A.A. (2013) Vitamin D levels in patients with Behçet's disease: Significance and impact on disease measures. Egypt Rheumatol. 35(3), 151–157.
22. Karatay, S., Yildirim, K., Karakuzu, A., Kiziltunc, A., Engin, R.I., Eren, Y.B., & Aktas, A. (2011) Vitamin D status in patients with Behcet's Disease. Clinics. 66(5), 721–723.
23. Kechida, M., Harzallah, O., Hellara, I., Klii, R., Naffeti, F., Najjar, M.F., & Mahjoub, S. (2015) Vitamin D Status of Behcet's Patients. Analysis of Correlation with Activity and Severity of the Disease as well as with the Quality of Life of Patients. Int Arch Med. 8, 1–7.
24. Khabbazi, A., Rashtchizadeh, N., Ghorbanihaghjo, A., Hajialiloo, M., Ghojazadeh, M., Taei, R., & Kolahi, S. (2014) The status of serum vitamin D in patients with active Behcet's disease compared with controls. Int J Rheum Dis. 17(4), 430–434.
25. Hamzaoui, K., Dhtfallah, I., Karray, E., Sassi, F., & Hamzaoui, A. (2010) Vitamin D modulates peripheral immunity in patients with Behcet's disease. Clin Exp Rheumato. 28(4), S50.
26. Liberati, A., Altman, D.G., Tetzlaff, J., Mulrow, C., Gotzsche, P. C., Ioannidis, J.P., Clarke, M., Devereaux, P.J., Kleijnen, J., & Moher, D. (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med. 151(4), W65–94.
27. Higgins, J., & Green, S. (2014) Cochrane handbook for systematic reviews of interventions version 5.1. 0. 2011. Oxford, UK: The Cochrane Collaboration.
28. Higgins, J.P., Thompson, S.G., Deeks, J.J., & Altman, D.G. (2003) Measuring inconsistency in meta-analyses. Bmj. 327 (7414), 557–560.
29. Djeraba, Z., Benlabidi, F., Djaballah-Ider, F.Z., Medjeber, O., Arroul-Lammali, A., Belguendouz, H., Otmani, F., & Touil-Boukoffa, C. (2017) Vitamin D status in Algerian Behçet's disease patients: an immunomodulatory effect on NO pathway. Immunopharmacol Immunotoxicol. 39(4), 243–250.
30. Aslan, N., Demirci, K., Güler, T., Dörtbaş, F., & Kale, E. (2017) The effect of vitamin D on clinical manifestations and activity of Behçet's disease. Advances in Dermatology and Allergology/Post□py Dermatologii i Alergologii. 34(1), 15.
31. Adeeb, F., Khan, M.U., Li, X., Stack, A.G., Devlin, J., & Fraser, A. D. (2017) High Vitamin D Levels May Downregulate Inflammation in Patients with Behçet's Disease. Int J Inflam. 2017.
32. Thacher, T.D., & Clarke, B.L. (2011) Vitamin D insufficiency. In Mayo Clin Proc. Elsevier.
33. Arnson, Y., Amital, H., & Shoenfeld, Y. (2007) Vitamin D and autoimmunity: new aetiological and therapeutic considerations. Ann Rheum Dis. 66(9), 1137–1142.

34. Gröber, U., & Kisters, K. (2012) Influence of drugs on vitamin D and calcium metabolism. Dermatoendocrinol. 4(2), 158–166.

Acknowledgments
We would like to appreciate the editors and referees for considering our studies and also thanks for support of Iranian center for evidence based medicine, Tabriz University of Medical Sciences, Tabriz, Iran

Zeinab Nikniaz
Liver and Gastrointestinal Diseases Research Center
Tabriz University of Medical Sciences
Tabriz
Iran

znikniaz@hotmail.com

