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Does vitamin D improve the serum level of anti-TPO and anti-TG in Autoimmune thyroid diseases? A systematic review and meta-analysis

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A B S T R A C T

Objective: We aimed to review and update data on the effectiveness of vitamin D on thyroid auto antibodies, anti-TPO and anti-TG in adults.
Methods: Scopus and PubMed search engines were used up to February 2018 for clinical trials without any restriction in time and language. The outcome parameters were thyroid auto antibodies, anti-TPO and anti-TG. We included studies which reported aim parameters. Results were summarized as mean differences (MD) with 95% confidence intervals (CI). Effect sizes were pooled using random-effects models (the DerSimonian-Laird estimator).
Results: Eight trials involving 526 subjects were included in this meta-analysis. Vitamin D supplementation did not significantly changed the serum level of anti-TPO (MD: -46.901 IU/mL, 95% CI: -111.841, 18.039, p=0.157) and anti-TG (MD: -0.903 IU/mL, 95% CI: -2.208, 0.401, p = 0.175) with high heterogeneity (I2= 77.1%, p= 0.000, I2= 26.5%, p= 0.253). Anti-TPO reduction was considerable in mixed-sex and low quality trials, doses of ≥ 1000 IU, periods of ≥ 2 months , AITD patients and in subjects with lower initial serum levels of vitamin D and higher initial serum level of anti-TPO (p <0.0001).
Conclusions: Vitamin D supplementation did not improve the serum levels of anti-TPO and anti-TG. The effects of vitamin D supplementing on AITD should be further investigated by conducting larger sample size and well-defined trials of long enough duration.

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Introduction

Autoimmune thyroid diseases (AITD) is one of the most prevalent autoimmune diseases which have involved near 5% of the world population and 10-20% of all women worldwide [1, 2]. HT is the most common autoimmune thyroid disease without any iodine deficiency intake [3, 4]. The interaction between environmental factors and genetic may lead to this disorder [5, 6].

The widespread existence of vitamin D receptors (VDRs) in the reproductive system, endocrine system, muscle , brain, skin, liver, kidney, intestine and the immune system cells such as monocytes, macrophages, dendritic cells,

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and activated lymphocytes, supports the idea of the extra-skeletal roles of vitamin D [7]. Several studies have supported the protective roles of vitamin D in autoimmune diseases including type 1 diabetes mellitus (T1DM), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), Crohn's disease and autoimmune thyroid disease (AITD) like Hashimoto thyroiditis (HT) [8-14]. Studies have presented that the frequency of vitamin D deficiency in patients suffering AITD is higher than healthy subjects [15, 16]. Observational studies have revealed that vitamin D deficiency does not increase the risk of AITD [17, 18]. Moreover, clinical trials have evaluated the effect of vitamin D supplementation on patients with AITD autoimmune disease which proposed that vitamin D supplementation can reduce Anti-TPO titters in these patients [19-23]. In non-lactating women with postpartum thyroiditis, vitamin D supplementation not only increased the serum levels of 25-hydroxy vitamin D but also reduced the Anti-TPO [21]. There are controversial results in these studies which may be due to the inter-individual variability in the response to vitamin D supplementation

To investigate whether the effects of vitamin D supplementation on thyroid autoantibodies, anti-TPO and anti-TG, we undertook a comprehensive systematic database search and meta-analysis to evaluate the effects of vitamin D supplementation on serum concentration of anti-TPO and anti-TG in patients with AITD.

Methods

The literature study follows Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines for reporting in systematic reviews and meta-analysis [24] . Our comprehensive search and systematic analysis of inclusion studies and data extraction were performed in a stepwise process in accordance with our specific question: What is the effect of vitamin D on anti-TPO and anti-TG in patients with AITD and healthy subjects?

The PICOS model [25], where the acronym PICOS stands for population (AITD and HT patients), intervention (Vitamin D supplementation), comparison (Healthy subjects), outcome (Reduction in serum levels of anti-TPO and anti-TG), and study design (clinical trials), was applied to formulate our question.

Literature search and selection criteria

This meta-analysis was carried out using electronic search with Scopus and PubMed search engines up to October 24, 2017 and an update to February 7, 2018. The combination of following search terms was used: "Vitamin D", "Vitamin D supplementation", "Cholecalciferol" and "1,25-dihydroxyvitamin" with "Autoimmune Thyroiditis" ,"Hashimoto Disease" and "Hashimoto Thyroiditis". Search strategy was not restricted by time or language. A historical search of reference lists of relevant papers was also conducted.

This meta-analysis is including articles which (1) the intervention group was patients with autoimmune thyroid disease and the control group (healthy subjects), (2) included adult participants (age $\geq$ 18) and (3) was written in English. All title and abstracts were screened by two reviewers (MS and NS) for eligibility. If a consensus was reached, an article was excluded or selected to full-text screening. If a consensus was not reached, another reviewer (HT) was consulted regarding the disagreements. After reading the title and abstract, articles excluded which was an animal study, in vitro, gene expression experiment, cross sectional studies and in pregnant and lactating women. Also studies that did not contain original data, were not related to AITD, did not contain data on vitamin D, anti-TPO and anti-TG levels, and were excluded. After reading the full texts, we discarded publications from the study if did not contain final anti-TPO and anti-TG level plus SD.

Data extraction and outcome measures

Data was extracted from each study: the author name, journal details, publication year, participant characteristics (age, gender, number and BMI), dose of vitamin D supplementation (IU), the mean ± SD of vitamin D (nmol/L), anti-TPO (U/ml) and anti-TG (U/ml) before and after the intervention. Data was independently extracted by MS and ZA, and all data were confirmed by another author (HT).

Quality assessment in individual studies

The quantitative 5-point Jadad score was used to assess the quality of the inclusive studies; a score of $\leq$3 indicates high quality, whereas a score of $\leq$ 2 indicates low quality [26].

Statistical analysis

Meta-analysis was performed using STATA software (version 12.0; StatCorp, College Station, TX, USA). Pooled effect size was expressed as weighted mean differences (MD) and

Table 1. Characteristics of included studies (n = 8)

Study, Country (Year)	Participants (M/F)	Intervention/ Placebo	Age (Range)	Mean Baseline Anti-TPO (SD)	Dose (IU/Day)	Duration (Month)	Study design
Vondra, Czech Republic, 2017	AITD (0:30)	30:30	(31-48)	178 (469)	4300	3	Pre-post assessment Clinical Trial
Knutsen,Norway, 2017	Healthy (43:124)	85:82	(18-50)	92(202)	400	4	double-blind RCT
Knutsen,Norway, 2017	Healthy (45:120)	83:82	(18-50)	131(300)	1000	4	double-blind RCT
Krysiak, Poland, 2017	HT (0:34)	18:16	(20-50)	1430 (597)	2000	6	Quasi-Clinical Trial
Anaraki, Iran, 2017	HT (20:36)	30:26	(35-55)	830 (528)	7142	3	double-blind RCT
Simsek, Turkey, 2016	HT (14:68)	46:36	(25-50)	278.3 (218)	1000	1	RCT
Chaudhary, India, 2016	AITD (24:76)	50:50	(18-35)	713 (299)	8571	2	Open-labeled RCT
Mazokopakis, Greece, 2015	HT (13:173)	186:186	(31-43)	296.7 (115)	2600	4	Pre-post assessment Clinical Trial

corresponding 95% CI for each parameter in this meta-analysis. Serum levels of anti-TPO and anti-TG were collated in IU/ml. Standard deviations (SDs) of the mean difference were calculated using the following formula: SD = square root [(SD pre-treatment) 2 + (SD post-treatment) 2 – (2R × SD pre-treatment × SD post-treatment)], assuming a correlation coefficient (R) = 0.5. Where standard error of the mean (SEM) was only reported, standard deviation (SD) was estimated using the following formula: SD = SEM × sqrt (n) (n is the number of subjects). The heterogeneity of the studies was examined by $\chi 2$ tests and the degree of heterogeneity was estimated using I2 statistic. According to Cochrane criteria, I2 statistic of 0%–40% indicates unimportant heterogeneity, 30%–60% indicates moderate heterogeneity, 50%–90% indicates substantial heterogeneity, and 75%–100% indicates considerable heterogeneity [27]. The fixed-effect model (I2 was below 50%) or the random-effects model (I2 was above 50%) was selected for meta-analysis of the comparison of each parameter due to vitamin D arm compared to placebo arm.

Leave-one-out sensitivity analysis was performed to assess the size effect sensitivity to inclusion studies. Random-effects models (using DerSimonian-Laird method) were used to compensate for the heterogeneity of studies. Subgroup analysis was exert to explore the sources of heterogeneity by using age, sex , study population , baseline values of serum vitamin D and anti-TPO) , dose of vitamin D supplementation, intervention duration, and quality of trials.

Results

Literature search, study characteristics, and quality Assessment

FNumber of relevant citations initially found were 221 after duplicate exclusion (duplicates=63). Through screening titles and abstracts, a total of 217 references were discarded due to various reasons (search overlap, animal, in vitro, and gene expression study, irrelevant study population or intervention, review articles, case reports or letter to editors). After reference checking of remained articles, 5 trials were added. Among the 9 studies which selected for full text assessment, 3 studies were excluded because did not contain final endpoint of aim parameters [28] and the overlap study population [20, 21].One study was added after updating search [29].

The characteristics of the included articles were shown in Table 1. Eight trials including 526 subjects were published from 2015-2017, in India [30], Greece [31], Turkey [23], Iran [32], Czech Republic [19] , Poland [22] and Norway [29], respectively, which enrolled subjects with AITD or HT or healthy subject . The intervention duration lasted from 1 to 6 months. In one study vitamin D was administered 30 drops twice a week (average to 4300 IU/day) [19]. Another study had three arms , 400 IU , 1000 IU of daily vitamin D and placebo in healthy subjects which was considered as two separate studies [29]. Three studies used daily vitamin D supplements (1000 IU, 2000 IU and 1200-4000 IU) [22, 23, 33] and in two studies patients received weekly vitamin D supplements (60.000 IU and 50.000 IU) corresponding in approximately 8571 IU/day

Table 2. Subgroup analysis for effectiveness of vitamin D supplementation on serum level of anti-TPO

	No.	MD* (95% CI)	P-heterogeneity	I^2 (%)†
Age				
< 35 years	3	-70.914 (-120.574 , -21.225)	0.001	85.6
> 35 years	5	-41.033 (-67.171 , -14.895)	0.004	74.3
Sex				
Female	2	-169.571 (-343.623, 4.481)	0.005	87.5
Both	6	-45.321 (-68.658 , -21.984)	0.001	75.7
Population				
AITD/HT	6	-61.675 (-88.192 , -35.158)	0.000	79.4
Healthy	2	-2.469 (-49.765 , 44.827)	0.200	39.2
Vitamin D Baseline				
> 25 nmol/L	5	-38.013 (-79.901 , 3.875)	0.001	79.7
< 25 nmol/L	3	-51.684 (-79.426 , -23.941)	0.005	81.0
Anti-TPO Baseline				
> 500 IU/mL	3	-187.306 (-280.184 , -94.428)	0.066	63.2
< 500 IU/mL	3	13.764 (-24.387 , 51.915)	0.230	32.0
Trial dose				
≤ 1000 IU/day	3	13.764 (-24.387, 51.915)	0.230	32.0
> 1500 IU/day	5	-83.130 (-112.215 , -54.046)	0.018	66.4
Trial duration				
≤ 2 Month	2	-13.347 (-68.405 , 41.712)	0.001	91.0
> 2 Month	6	-54.838 (-80.326 , -29.350)	0.004	71.6
Jadad Score				
< 2	4	-54.944 (-82.461 , -27.427)	0.000	85.2
> 3	4	-29.630 (-72.326 , 13.067)	0.025	68.0

and 7142 IU/day [30, 32], respectively therefore the daily dose of vitamin D varied from 1000 to 8571 IU. All control groups in 4 trials received placebo. Of 8 included studies, all of them reported final serum level of anti TPO and 4 for anti-TG. Their sample sizes ranged from 30 to 186 subjects and mean age of included trials for participants varied from 18 to 55 years old.

Overall, three trials had Jadad score of 5 [29, 32] , 1 scored 3[34] , 1 scored 1[34], and 3 remaining scored 0 [19, 22, 31]. Among selected trials, two of them compared the before and after aim parameters in intervention groups and not involved control group [19, 33] but remainder of articles were control clinical trial studies while three of them were double-blind RCTs [29, 32], one of them was an open-labeled RCT [30], an study was random but had no detailed information about random sequence generation [34] and an study was not randomized [22].

Publication bias

Potential publication bias was assessed Egger line regression test (Egger's test) which showed no evidence of publication bias for the outcomes of anti-TPO (p=0.965) and anti-TG (p=0.759) level changes.

Anti-TPO and anti-TG assay methods

Different assays methods were used to measure serum anti-TPO ad anti-TG. In this regard three studies determined serum level of anti-TPO by chemiluminescent immunoassay method [29, 32, 34] while one of them measured anti-TG too [34]. Another trial used enzyme-linked immunosorbent assays using reagents obtained from ALPCO Diagnostics and IBL International (Hamburg, Germany) to estimate levels of anti-TPO and anti-TG respectively [22]. The measurement of anti-TPO and anti-TG were performed using

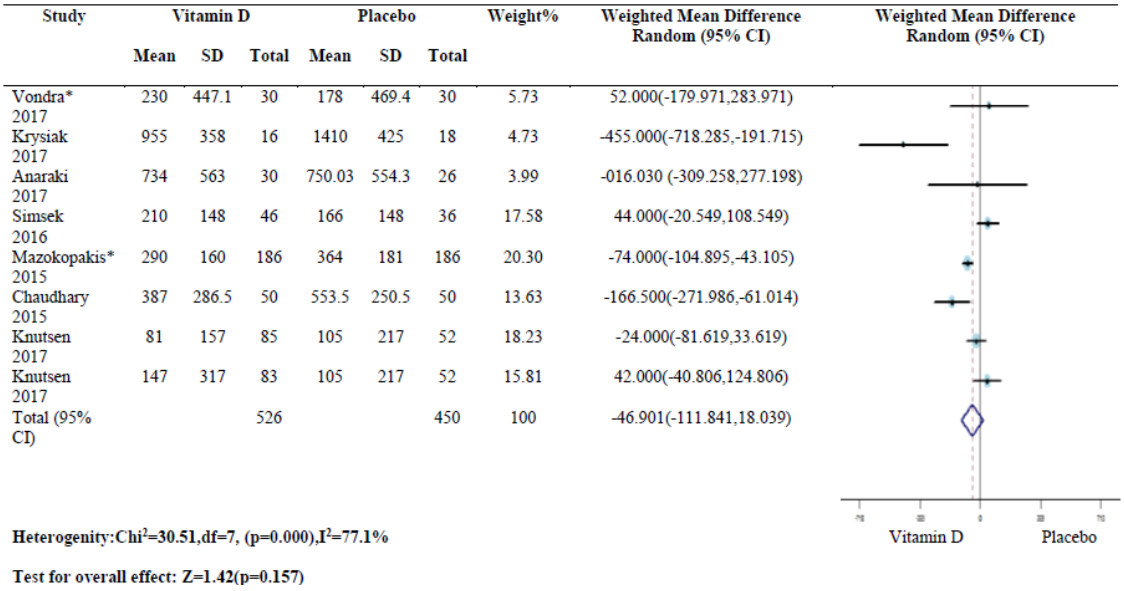

Figure 1. Comparisons of vitamin D supplementation versus placebo on serum Anti-TPO

chemiluminescent microparticle immunoassay method in two trials [33, 35] and an study used ELISA method (Aesku.Diagnostics, Wendelsheim, Germany) on an Immunomat BASE (Serion Immunologics, Germany) for anti-TPO and anti-TG determination [19] .

Effect of vitamin D on anti-TPO level and anti-TG level

The impact of vitamin D supplementation on serum level of anti-TPO was reported in 8 trials which are presented in Figure 1. The pooled effect analysis suggested that level of anti-TPO had no significant reduction following receiving vitamin D supplementation (MD: -46.901 IU/mL, 95% CI: -111.841, 18.039, p=0.157). Leave-one-out sensitivity analysis showed that this effect size is not sensitive to any study. The heterogeneity of publication was 77.1% after pooled effect analysis. Subgroup analyses were exerted to examine the effect of sex, age, population, baseline values of serum vitamin D and anti-TPO, supplementation dose and duration of supplementation and quality of trials (Jadad Score) (Table 2). Our results revealed that the pooled effect was significant after sex subgroup analysis (WMD: -47.515 IU/mL, 95% CI: -70.645, -24.386, p <0.0001). While the mentioned reduction was remarkable in studies involved both sexes (p=0.000) but in female subjects it was marginally significant (p=0.056). In case of dose and duration of administration subgroup analysis, the pool effect was noticeable (p=000) whether in doses of ≤ 1000 (WMD: 13.764 IU/mL, 95% CI: -24.387, 51.915, p = 0.479 and WMD: -13.347 IU/mL, 95% CI: -68.405, 41.712, p = 0.635 respectively). Baseline Anti-TPO as a prominent factors altered the pooled effect size (WMD: -15.264 IU/mL, 95% CI: -50.554, 20.026, p = 0.397) as alternation was noticeable at baseline of > 500 IU/mL of anti-TPO serum levels (WMD: -187.306 IU/mL, 95% CI: -280.184, -94.428, p = 0.000). Also, anti-TPO reduction was higher in those who had baseline < 25 nmol/L of vitamin D serum levels (WMD: -51.684, 95% CI: -79.426, -23.941, p <0.0001). Regarding study population, the effect of vitamin D was only observed in AITD/HT patients (WMD: -61.675 IU/mL, 95% CI: -88.192, -35.158, p <0.0001) in comparison to healthy subjects (WMD: -2.469 IU/mL, 95% CI: -49.765, 44.827, p = 0.919). Interestingly, the impact of vitamin D supplementation was not considerable in high quality trials (WMD: -29.630 IU/mL, 95% CI: -72.326, 13.067, P = 0.174) versus low quality trials (WMD: -54.944 IU/mL, 95% CI: -82.461, -27.427, p <0.0001). The pooled effect of age was significant (p=0.000).

The fixed-effect of vitamin D supplementation on anti-TG was assessed in 4 studies Figure 2. The results of our meta-analysis proposed that the level of anti-TG was not decreased significantly after intervention compared to control or baseline subjects (WMD: -0.903 IU/mL, 95% CI: -2.208, 0.401, p = 0.175). In this part of our analysis there was a negligible heterogeneity (I^2=26.5%).

Discussion

In this systematic review and meta-analysis,

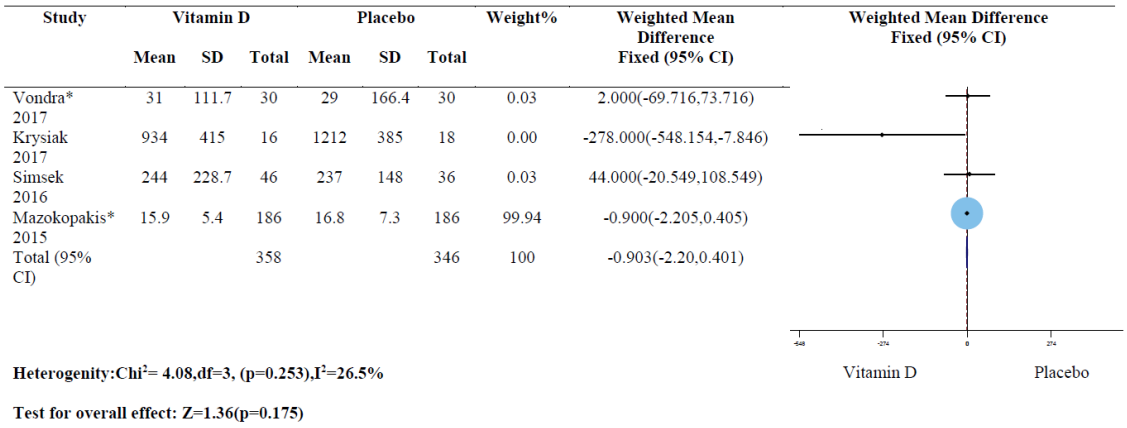

Figure 2. Comparisons of vitamin D supplementation versus placebo on serum Anti-TG

we summarized published evidence from 8 clinical trials which investigated the effects of vitamin D supplementation on thyroid autoantibodies including Anti-TPO and anti-TG [19, 22, 29, 30, 32-34]. The main finding of the review was that the serum level of anti-TPO did not significantly decrease at the end of the intervention although in age, sex, study population, baseline serum levels of vitamin D and anti-TPO, dose and duration of treatment and quality of publications subgroups. Vitamin D could reduce mentioned parameter noticeably as this effect seems to be dose-dependent, in fact subgroup analysis suggested that doses of ≤1000 IU and durations of ≤2 months did not reach to lower effects of vitamin D supplementation. Also this effect was weaker in female patients in comparison to trials with both sexes. Additionally, in subjects with baseline serum levels of vitamin D > 25 nmol/L and anti-TPO < 500 IU/mL , vitamin D administration had not significant influences (p = 0.075 and p = 0.479 , respectively). Serum level of anti-TG had no considerable changes in vitamin D-treated group compared with placebo.

Vitamin D deficiency or insufficiency is common in AITD patients [36]. Vitamin D directly regulates T lymphocyte functions by suppressing the proliferation of Th1 cells and enhancing the number of Th2 cells [37]. Vitamin D also inhibits the production of IL-2, IL-5, IFN-γ, and TNF-α, and increases the production of IL-4 and transforming growth factor in Th2 cells, additionally increasing the numbers of CD4+/CD25+ T-regulators cells (Tregs) which produce IL-10, therefore they block the development of Th1 and inhibit the secretion of IL-17 by the T-effectors [38]. As regards animal studies, evidences have shown that vitamin D decreases the severity of symptoms and reduces the Th1 response in experimental autoimmune encephalomyelitis and collagen-induced arthritis and consequently prevents clinical diabetes and pancreatic lesions in the non-obese diabetic mice model [39]. Also, animal models have proposed a preventive impact of vitamin D in experimental autoimmune induced thyroiditis [40] and vitamin D deficiency developed persistent hyperthyroidism in BALB/c mice [41].

We did a systematic review and meta-analysis to investigate the relationship between serum 25(OH) D levels and AITD [42]. Several observational studies have proposed that those with AITD present lower vitamin D levels [38, 43, 44] as vitamin D serum level was inversely associated with risk of HT. On the other hand, another studies revealed that there is no significant relation between vitamin D insufficiency or deficiency and AITD or HT incidence in children, adolescence, premenopausal women and the elderly [15, 45-48]. Regarding anti-TPO titers, cross-sectional studies have confirmed that higher vitamin D status is inversely linked to presence of anti-TPO [49-52]. Although another study has denied this association which reported no relationship between vitamin D and anti-TPO levels [16-18, 44, 53]. Most clinical trials have suggested that vitamin D supplementation could reduce the level of anti-TPO [22, 23, 30, 31] while several lines of evidence fit with our results which showed administrating of vitamin D did not have any considerable effect on anti-TPO [19, 32]. Although serum changes of anti-TG were not

noticeable in two trials [19, 31], other studies proposed a significant of vitamin D supplementation on serum anti-TG [22, 34].

Our finding showed that vitamin D supplementation could reduce the serum levels of anti-TPO in subjects but the heterogeneity of pooled effect was 77.1%. Therefore subgroup analysis was done to detect of the potential sources of heterogeneity. The subgroup analysis based on sex suggested that anti-TPO level in intervention group was decreased in mixed-sex trials although this reduction was negligible in female studies. A possible explanation for gender difference in the response to vitamin D is related to differences in the amount of body fat and/or its distribution [54, 55]. Generally, the percentage of body fat in women is higher than men therefore vitamin D as a fat soluble vitamin may potentially be insulated more in adipose tissue of women [56, 57].

Moreover, results showed that vitamin D dosage less than 1000 IU/Day did not improve noticeably the level of anti-TPO. A clinical trial suggested that a dose of near 1000 IU/Day of vitamin D did not improve vitamin D deficiency and cytokine profile in IBD and MS patients , as an immune disease [58]. Additionally, reduction of the annualized relapse rate in MS was observed in clinical trials with daily doses of 5000 to 10000 IU and serum vitamin D was remained stable in patients receiving low doses of vitamin D supplements [59, 60]. Also, several studies suggested the immunologic activity of vitamin D in SLE is observed after at least 3 month treatment [61-63] which is consistent with our results on immunological factors.

Similar to other meta-analyses, our review has several limitations. Firstly, the present meta-analysis has focused only on papers published in English; the ones that reported in other languages may affect the present results. Secondly, included trials were heterogeneous regarding population characteristics, study design, and supplementation properties. Nevertheless, the impact of heterogeneity on estimated effect sizes was minimized by choosing a random-effects mode of analysis. Additionally, one included study was blinded and in other studies detailed information about random sequence generation was not reported.

Conclusion

In conclusion, the present meta-analysis of clinical trials suggests no significant effect of vitamin D supplementation in lowering thyroid autoantibodies; anti-TPO and anti-TG. However, the results should be interpreted with caution because of the evidence of heterogeneity. Further studies, especially with larger sample size and high quality studies, are needed to confirm the effectiveness of vitamin D supplementation on anti-TPO and anti-TG levels.

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SS-b designed the initial idea of this work, which was further developed by MS. MS, NS and ZA independently done the literature search and screening; SS-b, MS and ME analyzed data; MS and HT wrote the manuscript; SS-b revised the manuscript. All authors read and approved the final manuscript.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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