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Meta-analyses

A systematic review and meta-analysis of randomized controlled trials to evaluating the trend of cytokines to vitamin A supplementation in autoimmune diseases

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SUMMARY

Background & aims: Vitamin A is considered as a supplement that effect on autoimmune diseases. We aimed to systematically review the effect of vitamin A on cytokines in patients with autoimmune disease.
Methods: Two researchers searched Scopus and PubMed until May 2018. Researchers extracted data from 6 eligible published papers. Extracted data included the gene expression of the inflammatory and anti-inflammatory cytokines.
Results: Fixed effect analysis of the WMD (95% CI) of the changes in gene expression showed that gene expression of the inflammatory (IL-17, IFN-γ and T-bet) and anti-inflammatory (TGF-β and FOXP3) cytokines significantly decreased and increased due to vitamin A supplementation in patients with autoimmune (Multiple sclerosis and atherosclerosis) diseases.
Conclusions: Vitamin A supplementation effects on gene expression and may improve serum level of cytokines and clinical signs of autoimmune disease but there is no adequate evidence.

1. Introduction

Many *in vitro* and *in vivo* studies have shown that vitamin A is one of the most important micronutrients that can regulate immune system. It converts to retinoic acid in the liver under strong regulatory mechanisms. Retinoic acids (RAs) are active metabolites of vitamin A that connect to the retinoic acids receptors (RARs). There are the complex molecular mechanisms of the effect of vitamin A on regulation of immune cell activation. Vitamin A may effect on expression of pathogenic and regulatory cytokine genes [1].

On the other hand, some evidences have shown that insufficient intake of dietary vitamin A can lead to the immutability of the immune system to imbalance activation of pathogenic and regulatory T cells [2]. It is known that a recommended dietary allowance (RDA) for vitamin A for adult is 900 mcg/d (3000 IU/d) for men and 700 mcg/d (2310 IU/day) for women. Also. toxicity with vitamin A may occur with 500,000 IU/d supplementation, 100 times more than RDA, in adults [3,4].

Intake of vitamin A in developing countries such as Iran is lower than that is recommended and subclinical deficiency is common in recent years [5–7]. More than half of the vitamin A intake in western diet comes from animal source foods included meat, dairy products and fortified low fat food. However, in developing countries, vitamin A is obtained from pro-vitamin A (carotenoids) of Plant source foods with low bioavailability compared to retinol in animal source. Some practical methods for compensation subclinical deficiency in developing countries are fortifying plant foods or supplementation with vitamin A [8,9]. Retinyl palmitate (RP) is a dietary form of vitamin A in foods that is more practical to supplement [10,11].

Nowadays, the evaluation of the effect of vitamin A and its active derivatives, RAs, on inflammatory and autoimmune diseases is an interesting topic for researches [11]. The major probable mechanism of autoimmune and inflammatory diseases such as multiple sclerosis (MS), rheumatoid arthritis and atherosclerosis is the imbalance between proliferation or function of the pathogenic (Th1, Th17, Th9) and regulatory T cells (Th2, Treg) [1,12,13]. Th1 cells secrete

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interleukin-2 (IL), interferon gamma (IFN-γ), tumor necrosis factor beta (TNF-β). Th2 cells secrete IL-4, IL-5, IL-6, IL-10, IL-13, and transforming growth factor beta (TGF-β). So, cytokines are divided into two groups, pro-inflammatory and anti-inflammatory [2].

In the present study, we aimed to find all of randomized controlled trials (RCTs) that systematically studied the effect of vitamin A supplementation on cytokine genes expressions or cytokine serum levels in patients with an inflammatory and autoimmune disease.

2. Methods

2.1. Search strategy

The PRISMA guidelines for systematic review and meta-analysis have been designed for the current study [14] (Fig. 1). Two independent researchers (SB and ZM) systematically searched two databases of Scopus and PubMed until September 2018. We have recorded relevant publications in English using the keywords including text words and Mesh within the following concepts:

1) Outcomes: Interleukin, Cytokine, IFN, Interferon, TGF, Transforming Growth Factor, TNF, Tumor Necrosis Factor
2) Interventions: Vitamin A, Retinol, ATRA, Retinoic acid, Retinyl palmitate
3) Studies: Controlled clinical trial, Randomized, Randomized controlled trial, Randomly, Trial, NOT Animals

2.2. Selection criteria

Two researchers (SB and NF) independently reviewed all articles by title and abstract to include eligible studies and disagreements resolved by third one (Mh H). If articles reported inadequate data, information was requested by email. Furthermore, if duplicated data were reported in studies, only the one with higher quality was included. At the end, the references of all included articles were cross checked to find probably missing publications. Articles were included on the following inclusion criteria and exclusion criteria:

Inclusion criteria:

1) Designed in a randomized controlled trial (RCT)
2) Participant with any age, gender and race
3) Patients with autoimmune and inflammatory diseases
4) Supplementation of vitamin A for intervention and placebo for control group with any dose
5) Evaluating the serum or supernatant level or gene expression of the cytokines

Exclusion criteria:

1) Studies designed in case report, letter, comment, short communication, and review, and not animal, *in vitro* or ecological studies.
2) Inappropriate control group

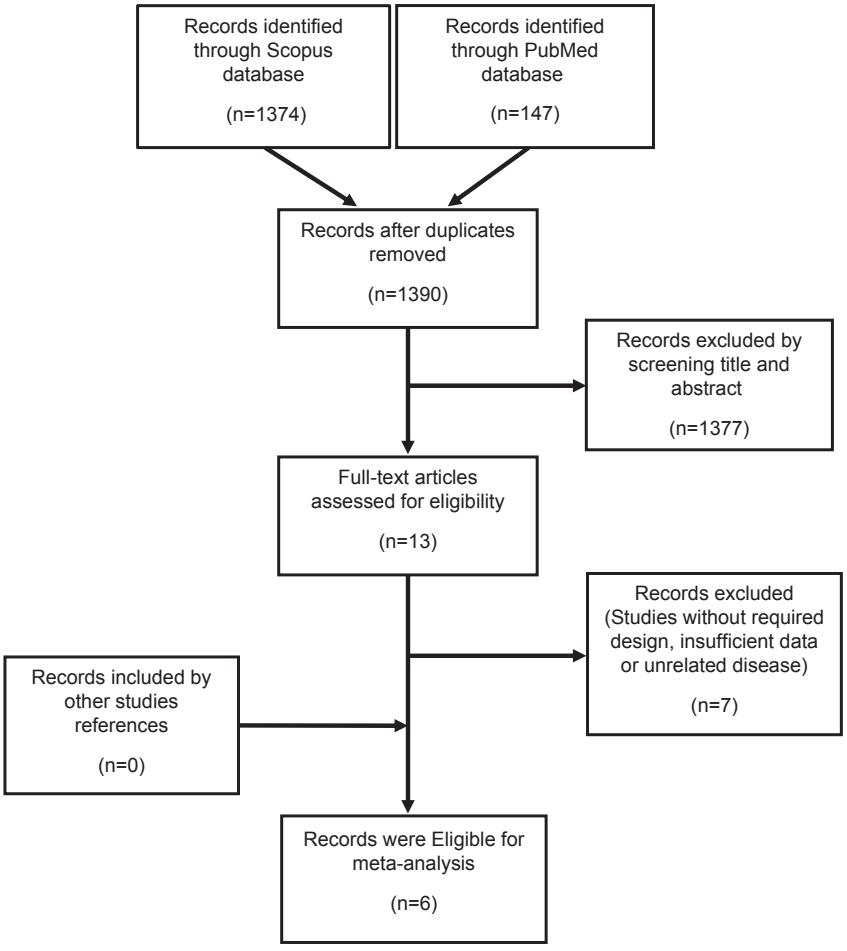

Fig. 1. The Flow diagram of study.

2.3. Data extraction and quality assessment

Three authors (SB, ZM and NF) reviewed the full text of each selected eligible article and extracted relevant data. They also assessed the quality of studies, independently. Any disputes are resolved by negotiation. Information was extracted with the following items:

1) General information: author, year, country, sample size
2) Predefined criteria: the type of disease, the form and amount of supplement, the duration of supplementation, the dietary intake of vitamin A
3) The key results of intervention: the number of participants in each group, the mean and SD of changes in the serum cytokine level measured by ELISA or changes in the expression of cytokine gene, measured by RT-PCR technique (Tables 1 and 2).

We used the Jadad scale to evaluate the quality of studies. The quality was considered poor (1–3 score) or high (4–5 score) based on scale guide, respectively [15].

2.4. Data synthesis and statistical analysis

In this study, ZM and FF used the fixed-effect analysis to calculate weighted Mean Differences (WMD). P-value <0.05 was considered statistically significant. Despite the determination of predefined criteria at the beginning, there were only two studies for each analysis, so we were not able to apply sub-group analysis. All statistical analyses were performed by STATA, version 12.0 (STATA Corp, College Station, TX).

3. Results

3.1. Study selection

We found 1521 articles via Scopus and PubMed search in initial search. A total of 1390 articles were screened by title and abstract after removing duplicated studies. After excluding 1377 articles according to inclusion and exclusion criteria, only 13 ones were retrieved for full text review. No other potentially eligible publications were found by reviewing the cited references of included articles. Six studies were focused on cytokine serum levels, but all of them were excluded after full text retrieval due to non-appropriate diseases and intervention [16–21]. Seven studies investigated the gene expression of the cytokines. After excluding 1 studies due to not adequate supplementation [22], only 6 ones met our inclusion criteria to systematic review and meta-analysis [23–28].

3.2. Study characteristics

All articles were done in Iran and used Retinyl Palmitate (RP) (25,000 IU) form of vitamin A as supplementation. Three of the included articles focused on MS [24,27,28] and 3 one's atherosclerosis [23,25,26]. According to the same methods and common data reported in such as sample size, age, gender and BMI of participants, dietary vitamin A intake and vitamin A supplementation duration; it seems that all of them were derived from two protocol studies [11]. Characteristics of the included studies are briefly outlined in Table 1.

3.3. Meta-analysis

Vitamin A supplementation significantly reduced the gene expression of pro-inflammatory cytokines including IL-17, IFN-γ and T-bet. Based on a fixed effect analysis, the WMD (95% CIs) of the gene expression changes were [79/237 patients, MD −2.173 (−3.427, −0.918CI) p = 0.001] for IL-17, [79/237 patients, MD −0.855 (−1.479, −0.231CI) p = 0.007] for IFN-γ, [79/237 patients, MD −0.972 (−1.393, −0.552CI) p = 0.000] for T-bet (Figs. 2–4) (Table 3). In contrast, the gene expression of anti-inflammatory cytokines including TGF-β and FOXP3 was increased in response to vitamin A supplementation (p value < 0.05). Fixed effect analysis resulted in WMD (95% CIs) of [79/237 patients, MD 4.760 (3.268, 6.252CI) p = 0.000] for TGF-β and [79/237 patients, MD 3.986 (2.814, 5.157CI) p = 0.000] for FOXP3 gene expression changes (Figs. 5 and 6) (Table 3).

4. Discussion

In present study, 7 studies were excluded in final step because of inappropriate disease and target population: Recurrent Furunculosis [16], acne vulgaris [22], healthy Women [18], obese women [19], enteric pathogen infections [17], pre-term infants [20] and pre-school children [21].

Table 1
Characteristics of included studies.

Study	Location	Jadad score	Disease	Genes	Supplement	Duration[d]	Sample size of groups			vitamin A intake, RE/day[a]		P-value	BMI[c]		P-value
							Vit A	placebo	Control	Vit A[b]	placebo		Vit A[b]	placebo	
							Male/ Female	Male/ Female	Male/ Female						
Mottaghi [16] 2012	Iran	5	Atherosclerosis	TGF-β FOXP3	RP (25,000 IU)	4	8/8	8/7	5/7	256.3 ± 85.7	252.3 ± 88.6	0.57	29.1 ± 2.3	30.2 ± 5.3	0.56
Mottaghi [18] 2014	Iran	5	Atherosclerosis	IL-17 RORγt	RP (25,000 IU)	4	8/8	8/7	5/7	256.3 ± 85.7	252.3 ± 88.6	0.57	29.1 ± 2.3	30.2 ± 5.3	0.56
Sezavar [19] 2014	Iran	5	Atherosclerosis	IFN-γ T-bet	RP (25,000 IU)	4	8/8	8/7	5/7	256.3 ± 85.7	252.3 ± 88.6	0.57	29.1 ± 2.3	30.2 ± 5.3	0.56
Honarvar [17] 2013	Iran	5	MS	IL-17 RORc	RP (25,000 IU)	6	6/13	4/13	–	400.2 ± 132.4	358.0 ± 144.3	0.38	18.9 ± 2.5	20.4 ± 3.0	0.11
Saboor-Yaraghi [21] 2015	Iran	5	MS	TGF-β FOXP3	RP (25,000 IU)	6	6/13	4/13	–	400.2 ± 132.4	358.0 ± 144.3	0.38	18.9 ± 2.5	20.4 ± 3.0	0.11
Honarvar [20] 2016	Iran	5	MS	IFN-γ T-bet	RP (25,000 IU)	6	6/13	4/13	–	400.2 ± 132.4	358.0 ± 144.3	0.38	18.9 ± 2.5	20.4 ± 3.0	0.11

[a] Retinol equivalent.
[b] Mean±SD.
[c] Body Mass Index.
[d] Months.

Table 2
Results of studies.

Studies	Disease	Genes	Fresh PBMC (Diff of Δ CT between before and after supplementation)[a]			*P*-value	Fresh PBMC (Diff of Gene expression CT between before and after supplementation)[a]			*P*-value
			Vit A	Placebo	Control		Vit A[a]	Placebo	Control	
Mottaghi[16]	Atherosclerosis	TGF-β	−1.59 ± 1.46	−0.25 ± 1.06	−1.17 ± 1.03	0.013	4.61 ± 4.11	1.67 ± 2.04	2.96 ± 2.73	0.009
		FOXP3	−2.72 ± 1.33	0.62 ± 2.04	−1.90 ± 1.16	0.000	10.09 ± 8.70	1.93 ± 3.17	5.58 ± 6.09	0.000
Saboor-Yaraghi[21]	MS	TGF-β	−2.57 ± 0.91	0.30 ± 0.90	–	0.000	7.14 ± 4.36	0.98 ± 0.65	–	0.001
		FOXP3	−1.83 ± 1.09	0.79 ± 1.20	–	0.000	4.46 ± 2.58	0.77 ± 0.74	–	0.000
Sezavar[19]	Atherosclerosis	IFN-γ	0.66 ± 1.34	−0.50 ± 1.68	−0.22 ± 1.36	0.272[b]	0.85 ± 0.65	1.25 ± 1.36	1.73 ± 1.58	0.384[b]
		T-bet	2.38 ± 1.69	0.70 ± 2.52	0.01 ± 1.01	0.005	0.39 ± 0.52	2.17 ± 4.21	1.23 ± 0.85	0.005
Honarvar[20]	MS	IFN-γ	3.17 ± 1.30	0.42 ± 2.53	–	0.002	0.14 ± 0.10	1.95 ± 2.31	–	0.002
		T-bet	0.96 ± 0.94	−0.43 ± 0.86	–	0.000	0.62 ± 0.48	1.56 ± 0.78	–	0.000
Mottaghi[18]	Atherosclerosis	IL-17	1.81 ± 2.02	−0.07 ± 1.89	+0.11 ± 0.79	0.009	0.63 ± 1.06	2.03 ± 2.62	1.06 ± 0.6	0.020
		RORc	2.71 ± 1.79	−0.38 ± 2.53	+0.08 ± 1.18	0.000	0.29 ± 0.34	4.53 ± 7.53	1.29 ± 1.18	0.001
Honarvar[17]	MS	IL-17	2.40 ± 1.79	−1.27 ± 2.47	–	0.001	0.569 ± 1.30	5.42 ± 5.44	–	0.001
		RORγt	7.28 ± 2.73	0.80 ± 2.80	–	0.001	0.02 ± 0.04	1.42 ± 1.31	–	0.001

[a] Mean ± SD.
[b] Not significant.

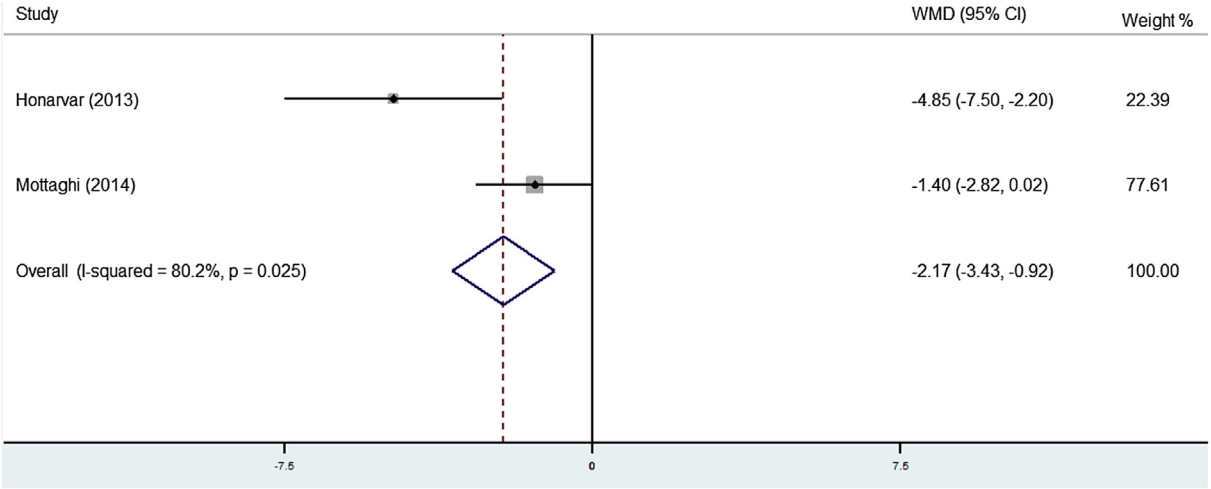

Fig. 2. IL17 gene expression was decreased.

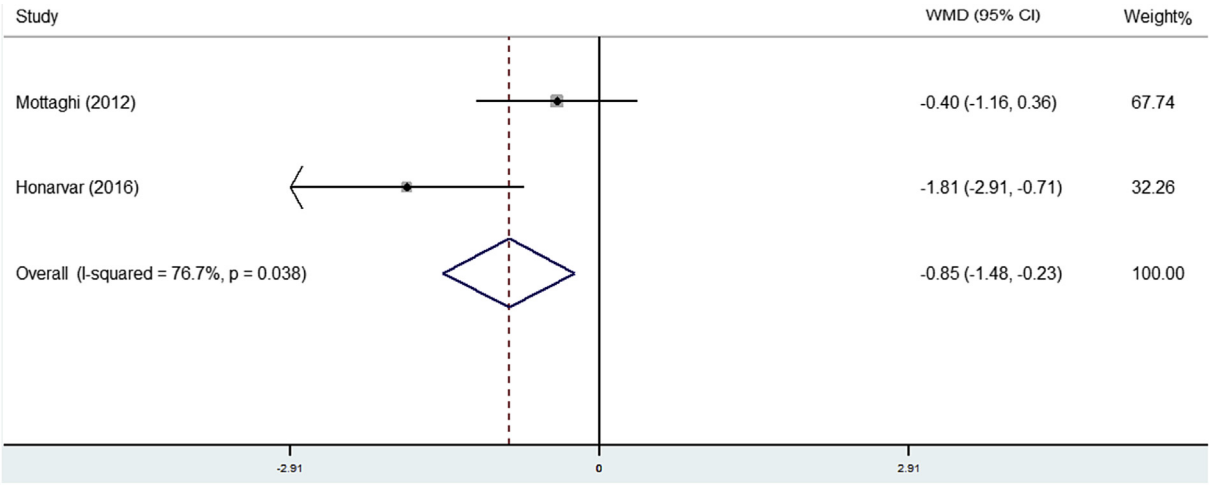

Fig. 3. IFN-γ gene expression was decreased.

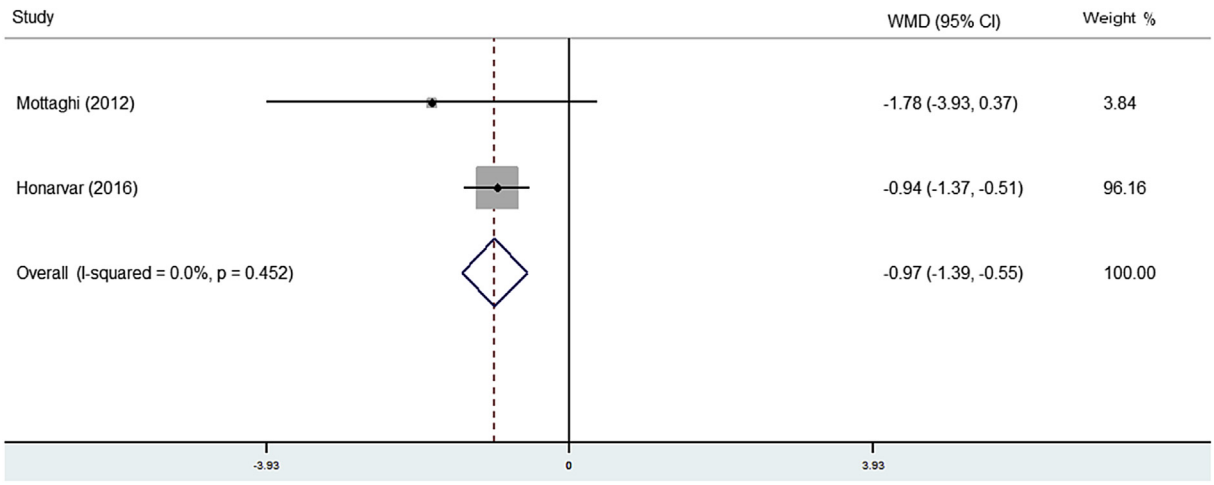

Fig. 4. T BET gene expression was decreased.

Table 3
Result of meta-analysis.

Studies	Name of genes	WMD Gene expression (95% CIs)	*P*-value
Mottaghi[16] and Saboor-Yaraghi[21]	TGF-β	4.760 (3.268, 6.252)	0.000
	FOXP3	3.986 (2.814, 5.157)	0.000
Sezavar[19] and Honarvar[20]	IFN-γ	−0.855 (−1.479, −0.231)	0.007
	T-bet	−0.972 (−1.393, −0.552)	0.000
Mottaghi[18] and Honarvar[17]	IL-17	−2.173 (−3.427, −0.918)	0.001

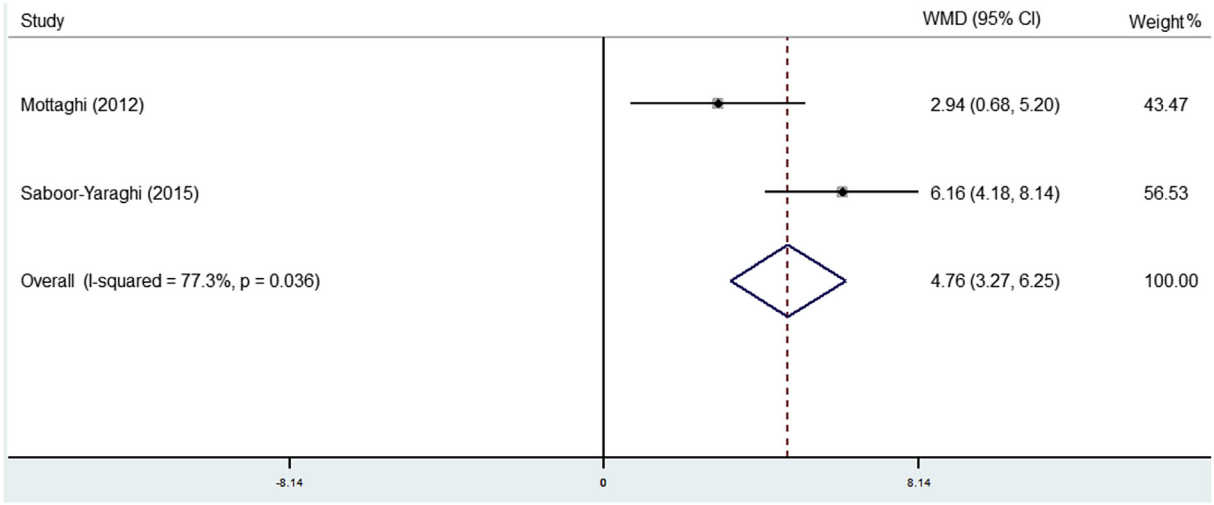

Fig. 5. TGF-β gene expression was increased.

Finally, we reviewed 6 eligible studies and analyzed their pooled data (Tables 1–3). These articles were derived from two large study protocols of Iran [11]. Three trials have evaluated the effect of vitamin A on patients with MS [24,27,28]. Each article in MS was investigated cytokines for 36 male and female patients. Three studies were done in 31 patients with atherosclerosis and evaluated the effect of vitamin A on cytokines in atherosclerosis as an autoimmune and inflammatory disease [23,25,26].

The results of the reviewed studies were homogeneous due to the use of the same supplement (RP) and the same dose (25,000 IU/d) and nearly the same time of supplementation (4–6 months). The evaluated gene expression of TGF-B, FOXP3, IFN-γ, T-bet, IL-17 is affected by RP supplementation and there are no data on serum levels of the cytokines.

The major hypothesis in these studies was that the dose of 25,000 IU/d of retinyl palmitate for 3–6 months can increase serum RA level in patients and significantly increase RA receptor gene expression. It seems the applied dose of vitamin A supplementation has pharmaceutical effects in addition to the recovery of vitamin A deficiency [29].

Multiple sclerosis is considered to be the most prevalent autoimmune and demyelinating disorder with no definite treatment that induces disabilities in young people [30]. We found strong evidence that shown pathogenic CD4+ T helper cells play a major

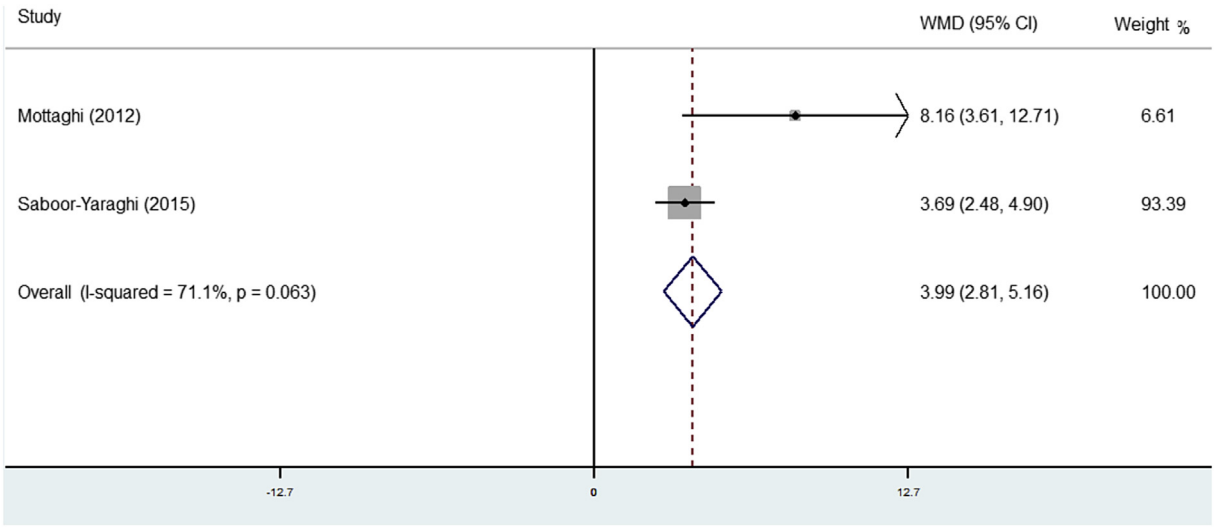

Fig. 6. Foxp3 gene expression was increased.

role in the pathogenesis of MS. Interferon gamma (IFN-γ) is an inflammatory cytokine secreted from Th1 cells and transforming growth factor beta (TGF-β) is an anti-inflammatory interleukin secreted from Th2 cells [31].

Forkhead box protein-3 (Foxp3) is a master and requisite transcription factor that presented on natural Treg (nTreg) cells that inhibit the activation of pathogenic CD8 and CD4 T cells, B and NK cells, dendritic cells and macrophages mediated by TGF-β. When nTreg cells do not work definitely, immune system deregulation and autoimmunity will happen [32,33].

Atherosclerosis is considered as a chronic inflammatory disease that arterial walls are affected by T lymphocytes that respond to oxidized LDL as an auto-antigen [34]. According to this hypothesis, the plaque inflammation in atherosclerosis has an autoimmunity trend, there is the concept of the protective role of Treg cells and Foxp3 in the organization of plaques [35,36].

Some studies have shown that Treg cell population is reduced in the blood of patients with atherosclerosis. This can be a target for treatment with some nutritional factors such as RAs, vitamin A active derivatives [37]. Retinoic acids can play crucial roles in suppressing autoimmunity by shifting the naïve T cells to the Treg lineage and away from the Th17 lineage. It is established that RAs stimulate histone acetylation at the promoter of Foxp3 and increase its transcription. On the other hand, RAs are as a cofactor for TGF-β that induce expression of Foxp3 [23,25,38].

Atherosclerotic lesions include T helper (Th) 1, Th2, Th17 cells and Treg. Th17 cells produce an inflammatory cytokine, IL-17. One of the major transcription factors that controls the differentiation of Th17 cells and collaborates with other transcription factors such as STAT3, STAT 4 is retinoid related orphan receptor-c (RORc) [39].

Vitamin A converts to active derivatives, RAs that can modulate the immune process in autoimmune disease such as type I diabetes, rheumatoid arthritis, multiple sclerosis and atherosclerosis. RAs suppress Th17 activity and development (IL17 production) with down-regulation of RORc and increase Foxp3 and TGF-β gene expression [38,40].

T-bet is a member of the T box group and a specific transcription factor for Th1 that controls the expression of IFNγ secreted from Th1 and natural killer (NK) cells. Therefore, T-bet induces Th1 production from naive T cells by activating the genetic programs of Th1 and inhibiting production of Th2 [41,42].

Different types of pathogenic Ths (th1, th2, and th17) are differentiated from naive CD4 T cells by expression of the transcription factors T-bet, GATA3, and RORγt, respectively. On the other hand, Treg cells are a lineage that induces anti-inflammatory cytokines identified by Foxp3, a X-linked transcription factor [43].

To the best of our knowledge, few studies have been shown the vitamin A supplementation cellular mechanism of the immune cells function and gene expression. Thus, in this study, we reviewed the effects of vitamin A supplementation on cytokine levels and gene expressions in patients with autoimmune disease.

Mottaghi et al. and Sezavar et al. showed significant differences in TGF-β, FOXP3, IFN-γ, T-bet, IL17, and RORc gene expression in fresh and PHA-activated PBMC between 3 groups (patients with atherosclerosis that were in vitamin A group and other patients in placebo group and healthy control group) [23,25,26]. Honarvar et al. and Saboor-Yaraghi et al. reported in other studies on patients with MS that there is a significant effect of vitamin A on the gene expression of TGF-β, FOXP3, IFN-γ, T-bet, IL17, and RORγt in Freshly Isolated PBMCs. These studies involved two groups of vitamin A and placebo without healthy control and they did not active PBMC with PHA [24,27,28].

Among the evaluated genes, there was no significant difference in IFN-γ gene expression in RP supplementation in patients with atherosclerosis. When data from studies were pooled in the current study, we observe a significant difference in this gene expression. There were some limitations in the included studies. Serum level and the gene expression of inflammatory cytokines can be affected by gender and BMI. Selected studies have not evaluated the relationships between them. However, they try to control confounding effects of gender and BMI on results.

In conclusion, we have found so little studies to systematically review the trial studies that evaluate the effect of vitamin A on autoimmune and inflammatory disease. It has shown that this field can be an interesting, required and neglected field to study. We emphasized that vitamin A can reduce the gene expression of inflammatory cytokines and increase the gene expression of anti-inflammatory cytokines.

Statement of authorship

SB and Mh H contributed to the study concept and design. SB, ZM and NF contributed to the acquisition. ZM and FF performed

analysis. Mh H and SB interpreted of the data and critically revised the manuscript.

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Conflict of interest

Authors announce that there was not conflict of interest in present study.

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