Review

L-arginine effect on inflammatory mediators: A systematic review of randomized controlled clinical trials

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Abstract: L-arginine is an important factor in several physiological and biochemical processes. Recently, scientists studied L-arginine effect on inflammatory mediators such as C-reactive protein (CRP), tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). We conducted a systematic review on randomized controlled trials assessing L-arginine effect on inflammatory mediators. We searched data bases including Google scholar, ISI web of science, SCOPUS, and PubMed/Medline up to April 2019. Randomized clinical trials assessing the effect of L-arginine on inflammatory mediators in human adults were included. Our search retrieved eleven articles with 387 participants. Five articles were on patients with cancer and 6 articles were on adults without cancer. L-arginine was applied in enteral form in 5 articles and in oral form in 6 articles. Eight articles were on both genders, two articles were on women, and one article was on men. L-arginine could not reduce inflammatory mediators among patients with and without cancer except one article which indicated that taking L-arginine for 6 months decreased IL-6 among cardiopathic nondiabetic patients. Our results indicated that L-arginine might not be able to reduce selected inflammatory mediators, but for making a firm decision more studies are needed to be conducted with longer intervention duration, separately on male and female and with different doses of L-arginine.

Keywords: L-arginine, C-reactive protein, Tumor necrosis factor-α, Interleukin-6, Inflammatory mediators, Nitric oxide, IL-6

Introduction

L-arginine is synthesized from glutamate endogenously and is a semi-essential amino acid. L-arginine is an important factor in several physiological and biochemical processes, including urea cycle, hormones synthesis and secretion, detoxification of lactate (LAC) and ammonia [1]. L-arginine is also a substrate for nitric oxide (NO) production (Figure 1) [2].

NO is a small molecule that penetrates easily across cell membranes and is synthesized in a variety of tissues. It means that NO can affect several diseases and vital biological processes [3]. Decreased amount of NO as an endothelium-dependent vasodilation can predict cardiovascular diseases independently of other risk factors. Nitric oxide has a regulatory role in the cardiovascular system, such as vascular structure, cell-cell interactions in blood vessels, and vascular tone [4].

Since NO is an important regulator of vascular homeostasis and L-arginine is its precursor, scientists assess L-arginine effect on prevention and treatment of cardiovascular disease. There is a growing evidence of L-arginine effect on type 2 diabetes [5], hypertension [6], hypercholesterolemia and atherosclerosis [7]. Previous articles have indicated that L-arginine has beneficial effects over insulin sensitivity and endothelial function both in type 2 diabetes mellitus patients and healthy individuals [8, 9].

Furthermore, experimental studies have indicated that L-arginine supplementation reduces mRNA expression of inflammatory cytokines [10], and in vitro studies suggested that NO donors can prevent the expression of pro-inflammatory genes by nuclear transcription factor (NF B) inhibition [11]. Recent studies assessed a relationship between atherosclerosis and inflammation and suggested that increased concentration of inflammatory mediators can reduce the activity of nitric oxide synthase and increase chronic intravascular inflammatory process and may cause coronary vascular disease (CVD) [12, 13].

Recently scientists studied L-arginine effect on inflammatory mediators such as C-reactive protein (CRP), tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). High concentration of pro-inflammatory mediators such as TNF-α can increase IL-6 secretion. IL-6 is a messenger cytokine and is secreted by smooth muscle cells and macrophages. IL-6 can increase CRP concentration and cause increased concentration of other inflammatory mediators, which contributes to CVD. It has been suggested that, although IL-6 mostly considered as a pro-inflammatory

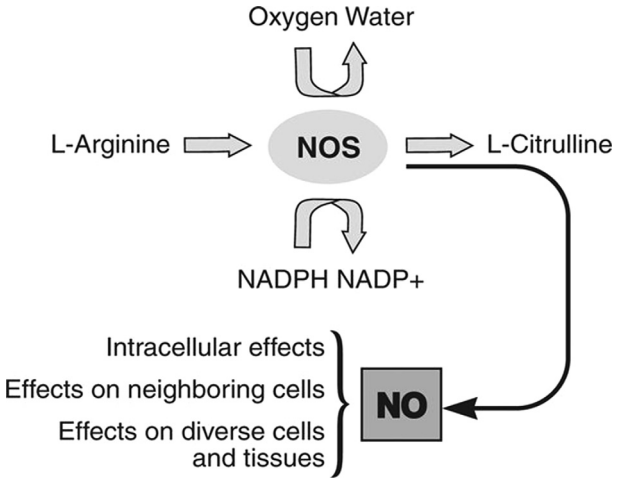

Figure 1. Production of nitric oxide. NADPH, nicotinamide adenine dinucleotide phosphate; NO, nitric oxide; NOS, nitric oxide synthase.

cytokine, it also has many regenerative and anti-inflammatory activities such as inhibiting TNF-α and IL-1 production [14].

Oral intake of L-arginine indicated contradictory effect on inflammatory mediators in clinical trials. Some randomized clinical trials (RCTs) revealed that oral consumption of L-arginine decreases inflammatory mediators' levels, while a small number of RCTs did not indicate any effect.

Since, there is not any systematic review regarding L-arginine effect on inflammatory mediators and trials which assessed L-arginine effect indicated controversial results we accomplished a systematic review in order to answer the question of whether L-arginine consumption affects the serum levels of TNF-α, IL-6, and CRP. Furthermore, patients with cancer have higher levels of inflammation and it is possible that participants with a higher baseline inflammation indicate more reductions through L-arginine therapy than others, therefore; we reported articles on patients with cancer and without cancer separately.

Material and methods

In order to find articles which assessed L-arginine effect on inflammatory mediators, an advance search was performed. Google scholar, ISI web of science, SCOPUS, and PubMed/Medline were searched up to April 2019 with following Mesh and non-Mesh key words: 'Tumor Necrosis Factor-alpha', 'TNF alpha', 'TNF-alpha', 'Tumor Necrosis Factor alpha', 'Tumor Necrosis Factor', 'Protein, C-Reactive', 'C Reactive Protein', 'CRP', 'C-Reactive Protein', 'IL-6', 'Interleukin-6', 'Interleukin 6', 'IL6', 'Arginine', 'L-Arginine', 'L Arginine', 'Arginine, L-Isomer', and 'Arginine, L Isomer'. We performed advance search using asterisks, quotation marks, Boolean operators and parentheses. Quotation marks, parentheses and asterisks were used to search the exact term, a group search term and all words derived from one key word respectively. For reading title and abstract of articles found by advance search, all articles were exported to EndNote software (reference manager software, version X6) and two authors (MH, SRM) read their title and abstracts separately. We resolved all discrepancies by group discussion. In order to find all relevant articles reference, the list of included RCTs were searched. In this study, we did not place any restriction on study design and publication time, but we just included English articles. The protocol was registered as PROSPERO (No. CRD42019134030).

Inclusion criteria

The following criteria were considered as inclusion criteria for articles in this meta-analysis: 1) Human studies; 2) Original articles; 3) Clinical trial articles; 4) Articles with randomization in trial design; 5) Articles taking L-arginine as intervention; 6) Articles taking L-arginine orally or in enteral form; 7) Articles which did not take any other amino acid or food supplement in control and intervention group; 8) Studies which assessed serum concentration of CRP or TNF-α or IL-6 as the outcome variables; 9) Articles that mentioned intervention duration of trials; 10) Articles with trials having clear tables that reported the concentration of TNF-α or IL-6 or CRP at the beginning and the end of intervention study.

Exclusion criteria

The following criteria were considered as exclusion criteria and articles which met them were excluded in spite of satisfying inclusion criteria: 1) Unclear figures and tables; 2) Absence of a control group; 3) Taking other interventions besides L-arginine in intervention subjects but not in placebo subjects; 4) Taking one dose of L-arginine; 5) Participants being under 18; 6) Written in a language other than English.

Data extraction

We extracted the following data from eligible RCTs for our systematic review and meta-analysis: article publication year; country where trial was performed; trial design; participants' gender and age; first author's name; number of participants in each group; number of men and women; subjects' diseases; L-arginine dose; kind of placebo; and intervention duration. In case of any discrepancy in extracted data, corresponding authors were consulted by MH for clarification.

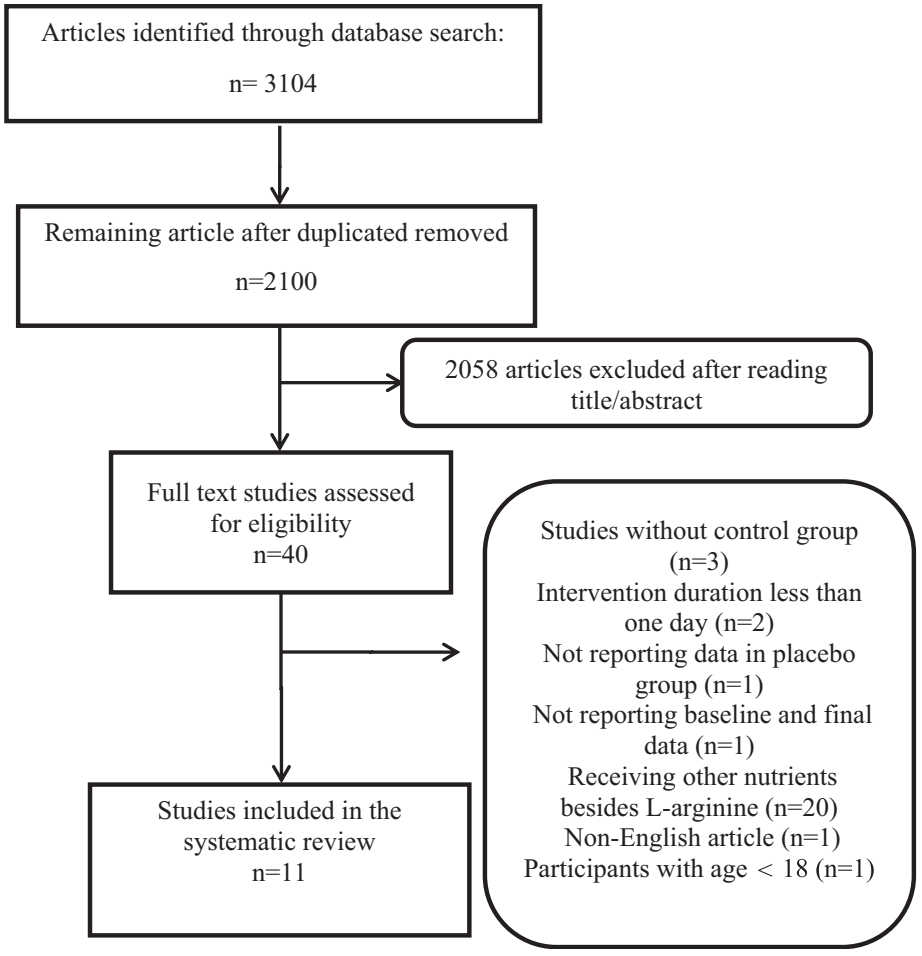

Figure 2. Flow diagram of database searches and study selection.

Quality assessment

For assessing the quality of articles, Delphi checklist was used and articles were scored on a scale of nine (rigorous) to zero (very poor) [15]. Delphi items are: I) Was the method of randomization performed? II) Was the method of randomization concealed? III) Were the groups similar at baseline? IV) Were both inclusion and exclusion criteria considered? V) Were the assessors blinded? VI) Were the care providers blinded? VII) Were the patients blinded? VIII) Were measures of variability and point estimates included? IX) Was intention to treat analysis conducted?

Results

By searching electronic data bases, we found 3104 articles. All articles were exported to EndNote software and 1004 articles were duplicated. After reading titles and abstracts, 2058 articles were excluded and 40 articles remained for full text reading and considering inclusion and exclusion criteria. Considering inclusion and exclusion criteria, 11 RCTs and 29 RCTs were removed because of following reasons: RCTs without control group (n = 3), intervention duration less than one day (n = 2), not reporting data in placebo group (n = 1), not reporting baseline and final data (n = 1), receiving other nutrients besides L-arginine (n = 20), non-English article (n = 1), and participants under 18 (n = 1) (Figure 2). L-arginine was taken in enteral form in 5 articles [16–20] and orally in 6 articles [21–26] with the treatment duration between 5 days to 24 weeks. Eight articles were on both genders [16–20, 23–25] and one article was on male [26] and two articles were on female [21, 22]. Since inflammation in patients with cancer is higher than patients without cancer, we separately reported L-arginine effect on patients with and without cancer (Table 1).

L-arginine effect on inflammatory mediators among subjects with cancer

Five articles assessed L-arginine effect among patients with cancer [16–20]. Four articles were on patients with oral and laryngeal cancer [17–20] and one article was on patients

Table 1. Randomized controlled trial studies included in the systematic review and meta-analysis

Code Author (year) (country)	Subjects and gender	Age (mean ± sd)	RCT	Intervention	Placebo	Duration (wk)	Variables	Results	Score
1 Alizadeh, M. Iran 2012 (24)	Women with Central Obesity N:34 F = 34	36.6 ± 8.6	Randomized, double-blind, placebo-controlled trial	Hypocaloric diet enriched in legumes + L-arg 5 g/day	Hypocaloric diet enriched in legumes	6 weeks	CRP[1]	CRP did not change in intervention group	4
2 Blum, A Maryland 1999 (25)	Healthy Postmenopausal Women N = 10 F = 10	55 ± 5	randomized, double-blind, crossover study	9 g/day L-Arg	Not mention	4 weeks	CRP	CRP did not change	4
3 Bogdanski, P Poland 2012 (26)	subjects with simple obesity N = 60 M[2]:31 F[2]:29	43.8 ± 8.2	Randomized clinical trial	9 g/day L-Arg	microcrystalline cellulose	12 weeks	TNF-α[1]	Non-significant tendency in decreasing TNF-α.	6
4.1 Boger, G. I. 2007 Germany (27)	Elderly subjects with high ADMA N = 15 M:11 F:4	59.6 ± 16.26	single-blinded, randomized, 3-period crossover trials	Simvastatin 40 mg/day; L-arginine 1.5 g twice a day	Simvastatin 40 mg/day	3 weeks	CRP	CRP did not change in both groups	4
4.2 Boger, G. I. 2007 Germany (27)	Elderly subjects with low ADMA N = 13 M:5 F:8	54.5 ± 8.4	single-blinded, randomized, 3-period crossover trials	Simvastatin 40 mg/day; L-arginine 1.5 g twice a day	Simvastatin 40 mg/day	3 weeks	CRP	CRP significantly deceased in intervention group with no significant changes between groups	5
5 Casas-Rodera, P Spain 2007 (19)	Patients with oral and laryngeal Cancer N = 30 M:28 F:2	59.67 ± 9.07	Randomized clinical trial	Enteral nutrition formulas with 0.81 g L-Arg per 100 ml	Standard enteral nutrition	2 weeks	IL-6[1], CRP, TNF-α	IL-6, CRP, and TNF-α did not change in both groups	7
6 de Luis, D Spain 2014 (20)	Head and neck cancer non diabetic Patients N = 82 F: 10 M: 72	65.5 ± 12.2	Randomized, double-blind, clinical trial	Enteral nutrition supplemented with a high dose of L-arginine (20 g per day)	Isocaloric, isonitrogenous enteral formula without L-arginine.	10 days	CRP	CRP did not change in both groups	5
7 de Luis, D Spain 2005 (21)	Head and neck cancer patients N = 29 F = 5 M = 14	60.7 ± 11.6	Randomized clinical trial	Eternal nutrition fortified by L-arginine 12.5 g/day	Eternal nutrition without L-arginine	6 days	IL-6, CRP, TNF-α	IL-6 and CRP significantly decreased in both groups, TNF-α did not change in both groups	3

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Table 1. (Continued)

Code Author (year) (country)	Subjects and gender	Age (mean ± sd)	RCT	Intervention	Placebo	Duration (wk)	Variables	Results	Score
8 de Luis, D. A Spain 2003 (22)	head and neck cancer patients N = 36 F:2 M:34	63.1 ± 12.7	Randomized clinical trial	Eternal nutrition fortified by L-arginine 0.6 g/100 ml	Eternal nutrition without L-arginine	5 days	IL-6, CRP, TNF-α	CRP significantly decreased in both groups, IL-6 and TNF-α did not change in both groups	7
9 Lucotti, P 2009 Italy (28)	Cardiopathic nondiabetic patients after an aortocoronary bypass N = 30 M:28 F:2	65 ± 10	Randomized, double-blind, clinical trial	6.4 g/day L-arginine	Not mention	24 weeks	IL-6 and TNF-α	IL-6 decreased significantly in intervention group, but TNF-α concentration did not change	4
10 van Bokhorst-De Van Der Schueren, M. A. Netherlands 2001 (23)	Severely malnourished head and neck cancer patients N = 32 M:19 F:13	60 ± 8	Double-blind, randomized trial	Arginine-supplemented preoperative and postoperative tube feeding (12.5 g/day)	Standard preoperative and postoperative tube feeding	7 days	IL-6 and TNF-α	IL-6 and TNF-α did not change in both groups	5
11 West, S. G France 2004 (29)	Middle-age men with hyper- Cholesterolemia N = 16 M:16	45 ± 7.9	Randomized, double-blind, crossover design	4 g/d for 2 day, 8 g/d for 3 day, and 12 g/d thereafter	Microcrystalline cellulose	3 weeks	CRP	CRP did not significantly change in intervention group	4

[1]TNF-α: Tumor necrosis factor-alpha, CRP: C-reactive protein, IL-6: Interlukin-6.
[2]M: Male, F: Female.

with head and neck cancer [16]. Four articles reported TNF-α, IL-6 [16, 18–20] and CRP levels [16–19].

In a randomized trial, de Luis, D. A et al. [19] indicated that arginine-enhanced enteral nutrition cannot reduce IL-6 and TNF-α in patients with cancer while CRP decreased in intervention and control group. In this study, 36 patients with oral and laryngeal cancer were randomly assigned to two study groups. The mean age was 59.6 ± 10.9 years. There were 18 patients in the group I (enteral nutrition supplements with arginine) and 18 patients in the control diet group (isonitrogenous and isocaloric enteral formula). Intervention duration in L-arginine and control group was similar with an average of 9.6 ± 9 days. After intervention, CRP decreased in both groups and TNF-α and IL-6 did not change.

Casas-Rodera, P et al. [16] conducted a prospective, randomized clinical trial among patients with head and neck cancer. A total of 44 patients were randomly assigned to three groups: arginine-enhanced enteral formula (group I); standard polymeric enteral formula (group II), and RNA, arginine, and omega-3 fatty acids enhanced enteral formula (group III). The average duration of intervention was 14.5 ± 8 days and arginine-enhanced formula contained 810 mg L-arginine per 100 ml. Serum concentration of CRP, IL-6 and TNF-α were measured before and after the intervention and their results indicated that enteral nutrition fortified with L-arginine could not reduce serum concentration of CRP, IL-6 and TNF-α.

Another study was conducted among 29 patients with oral and laryngeal cancer in 2005 [18]. Fourteen patients

in intervention group received an enteral diet supplements with L-arginine and fifteen patients in control group received standard enteral formula. Intervention group received 12.5 g/day L-arginine for an average of twenty days and after intervention their results indicated that both formula decreased IL-6 and CRP without any changes in TNF-α levels.

In another article, de Luis et al. [17] reported that taking 20 g/day L-arginine could not reduce CRP concentration in patients with head and neck cancer. Eighty-two participants were randomly assigned to intervention and control group. Intervention group (n = 42) received enteral nutrition supplemented with L-arginine (20 gr/day) and control group (n = 40) received standard enteral nutrition for ten days. They measured CRP before and after intervention, and their results indicated that enteral nutrition supplemented with L-arginine did not reduce CRP among patients with cancer.

In a randomized clinical trial, van Bokhorst-de Van Der Schueren, M. A. et al. [20] assigned patients in three study groups: I) Eleven patients in no tube feeding, II) Seven patients in standard tube feeding, and III) Twelve patients in arginine supplemented tube feeding (12.5 gr/L). Patients in both tube feeding groups received almost 9 days of tube feeding. They measured IL-6 and TNF-α before and after intervention, and their result indicated that L-arginine did not change inflammatory mediators among their participants.

L-arginine effect on inflammatory mediators among subjects without cancer

Six RCTs assessed L-arginine effect on inflammatory mediators among participants without cancer [21–26] and L-arginine dose ranged from 3 mg/day to 12 g/day. Four articles measured CRP [21, 22, 24, 26], two articles measured TNF-α [23, 25], and one article measured IL-6 [25].

In a randomized, double-blind, crossover study by Blum, A et al. [22], ten postmenopausal women received L-arginine 9 gr or placebo daily for one month and treatment periods were separated by one month. Serum concentration of CRP was measured before and after supplementation, and their results indicated that taking L-arginine supplement could not reduce CRP concentration after one month.

In another randomized clinical trial, subjects with visceral obesity were assigned to L-arginine 9 gr/day or placebo for 3 months [23]. Sixty patients (male = 31 and female = 29) with age range from 30 to 60 without any additional risk factor for cardiovascular disease participated in this study. Serum concentration of TNF-α was measured before and after intervention, and according to their result taking 9 gr L-arginine daily for 3 months caused non-significant tendency to decrease TNF-α.

Boger, G. I et al. [24] performed a single-blinded, randomized, 3-period crossover trial on 28 elderly subjects with high and low level of asymmetric dimethylarginine (ADMA). Scientists believe that ADMA elevates in patients with cardiovascular risk factors including hypercholesterolemia, hypertension, hyperhomocysteinemia and diabetes. In this study, fifteen patients with highest ADMA and thirteen patients with lowest quartiles of the ADMA in a randomized order took L-arginine (3 g/day), simvastatin (40 mg/day), or a combination of L-arginine and simvastatin for 3 weeks with three weeks washout between each treatment. CRP serum concentration was measured before and after intervention, and their result indicated that CRP concentration was not significantly affected by simvastatin or L-arginine in both groups; however, treatment with the combination of simvastatin and L-arginine caused significant reduction in CRP among subjects with high ADMA.

The results of a randomized, double-blind, clinical trial showed taking 6.4 g/d L-arginine for 6 months could significantly reduce serum concentration of IL-6 [25]. In double-blind randomized parallel design, thirty cardiopathic nondiabetic patients with age 65 ± 10 were assigned to L-arginine group (n = 16) and placebo group (n = 14). Participant in intervention group took 3.2 g L-arginine 2 times a day after breakfast and lunch and patients in placebo group took identical placebo solutions for six months. IL-6 and TNF-α were measured before and after intervention, and their results showed significant reduction in IL-6 and no changes in TNF-α concentration.

There was a randomized, placebo-controlled, crossover study on sixteen hypercholesterolemia men with age 45 ± 1.9. Results indicated that taking 12 gr per day L-arginine for 3 weeks could not decrease serum concentration of CRP [26]. In this crossover study, L-arginine and placebo intake was gradually enhanced during the first week of intervention as follows: 4 g/d for 2 days, 8 g/d for 3 days, and 12 g/d thereafter; microcrystalline cellulose was taken as placebo. Since this study was a crossover, all participants received two treatments (3 weeks each) separated by a one-week washout. Serum concentration of CRP was measured before and after treatment, and results showed non-significant effect of L-arginine on CRP concentration.

Alizadeh et al. [21] investigated whether L-arginine or selenium could increase the effect of a hypocaloric diet enriched in legumes (HDEL) on cardiovascular risk factors in women with central obesity. A total of 84 premenopausal women with central obesity after a 2-week run-in period on isocaloric diet were randomly assigned to one of following groups: HDEL + L-arginine (5 g/day) + selenium

(200 μg/day), HDEL + placebo of L-arginine + selenium, HDEL + L-arginine + placebo of selenium and HDEL + placebo of L-arginine + placebo of selenium. Intervention duration in this study was 6 weeks and sample size was seventeen in each group. Serum concentration of CRP was measured before intervention, 3 weeks after intervention and 6 weeks after intervention. According to their results, HDEL significantly decreased CRP concentration in the first 3 weeks but it returned to basal concentration in the subsequent 3 weeks, and adding selenium and/or L-arginine did not change HDEL effect.

Discussion

Our article was the first systematic-review that summarized the results of articles which studied L-arginine effect on inflammatory mediators among patients with and without cancer. According to our results, L-arginine could not reduce inflammatory mediators among patients with and without cancer except one article which indicated that taking L-arginine for 6 months decreased IL-6 among cardiopathic nondiabetic patients.

New evidence suggests that perioperative nutritional supplements which have immune-nutritional additives might modulate the inflammation and immune response in vitro and in subjects with burns, trauma, or those with oncological surgery [27]. Nutrients such as omega 3 fatty acids, L-arginine, and RNA as a medicine can modulate the immune system; therefore, scientists fortified enteral formula for cancer patients with those nutrients to improve host immune defenses [28].

L-arginine is an immune-nutrient used for improving wound complications among patients with head and neck cancer [29]. Evidence indicated that enteral nutrition, fortified with immunomodulatory nutrients including arginine, decrease postoperative complications and modulate immune function in different patients, such as those in the surgery of stomach and colorectum cancer [30], pancreatic surgery [31], head and neck cancer patients [32], and critically-ill patients [33]. Since immune-nutrients improve immune defenses through different mechanisms and procedures, combining different immune-modulating nutrients with L-arginine makes indicating the treatment effect of arginine difficult.

In our systematic review, we excluded articles which used enteral formulas supplemented with different nutrients including L-arginine. Our data base search results showed that enteral nutrition supplemented solely with L-arginine stimulates the release of anabolic hormones and accelerated wound healing, but could not reduce the concentration of IL-6, TNF-α, and CRP. In two studies, enteral nutrition in both intervention and control group decreased the serum levels of inflammatory mediators [18, 19]. According to other articles [34, 35] and our review results, enteral nutrition might be a good choice to attenuate the immunosuppression condition of critically-ill patients.

Our results regarding patients without cancer indicated that L-arginine could not reduce serum levels of inflammatory mediators except one article that used L-arginine for a longer intervention duration compared with other RCTs. The result of animal and in vitro studies suggested various benefits regarding L-arginine such as reducing atheroma formation [36], reducing platelet aggression [37], decreasing expression of endothelial cell adhesion molecules, and decreasing human monocyte adhesion to endothelial cells [38].

However, this systematic review did not indicate the beneficial influence of L-arginine supplementation on CRP, TNFα and IL-6, but there are reports revealing positive effect of L-arginine on inflammation. That evidence suggests that L-arginine produces protective effects on cardiovascular system by stimulating nitric oxide synthases (NOSs) in endothelial cells and suppressing cytokine gene expression [4, 39]. Cell culture experiments have indicated that NO donors can prevent the expression of pro-inflammatory genes by the inhibition of nuclear transcription factor (NF B) [11]. L-arginine deficiency causes NOSs inhibition and increases asymmetric dimethylarginine (ADMA) synthesis; therefore, it might induce inflammations in the arterial endothelium [40]. In one animal study also indicated that L-arginine supplementation might prevent cardiovascular disease by increasing endothelial nitric oxide synthase (eNOS) that is involved with regulating vascular function [41], but Rodrigues-Krause et al. summarized 13 studies regarding L-arginine effect on NO and ADMA and their results indicated that L-arginine supplementation was not associated with improvements in NO and ADMA responses compared to placebo [42]. Other evidence suggests L-arginine reduces inflammation and prevents cardiovascular disease by plasma advanced glycation end products reduction which are identified as pro-inflammatory compounds [43]. In one study indicated that L-arginine reduced inflammation by elevating the adiponectin levels [8]. It seems the mechanism of L-arginine for reducing inflammation is not clear and requires further investigations.

Our systematic review has the following strengths: first of all, results indicated that L-arginine might not decrease inflammatory mediators for a short period of intervention; therefore, our results will help scientists to design new RCTs. Secondly, we did not have any limitation on publication time. Thirdly, the result of advanced search method

indicated that this review is the first article that examined L-arginine effect on inflammatory mediators among patients with and without cancer. Fourthly, studies which used other amino acid and nutrients beside L-arginine in intervention group were excluded; therefore, confounding effects of other nutrients were excluded. The following items should be considered as limitations for this study: 1) A few articles measured L-arginine effect on inflammatory mediators; therefore, we could not conduct a meta-analysis on quantities results; 2) Since most articles did not report L-arginine effects on participants' clinical outcomes, they were not taken into account; 3) We could not indicate L-arginine effect on men and women, because separate studies on men and women were scarce.; 4) The effect of confounding factors such as medicine, nutrients intake, smoking, and physical activity were not clear, because studies did not have pertinent data; 5) We excluded non-English articles.

Conclusion

L-arginine might not be able to reduce IL-6, TNF-α, and CRP, but more studies are needed with longer intervention duration, separately on male and female and different doses of L-arginine. For making a firmer decision especially among patients with cancer future studies should control confounding factors, such as drugs, diet, lifestyle, nutritional status, and performance status.

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