Complementary Therapies in Medicine 47 (2019) 102226

Contents lists available at ScienceDirect

Complementary Therapies in Medicine

journal homepage: www.elsevier.com/locate/ctim

Effect of L-arginine supplementation on C-reactive protein and other inflammatory biomarkers: A systematic review and meta-analysis of randomized controlled trials

Behzad Nazarian[a], Ezatollah Fazeli Moghadam[a], Omid Asbaghi[a], Mohammad Zeinali Khosroshahi[a], Razieh Choghakhori[b], Amir Abbasnezhad[a,*]

[a] Nutritional Health Research Center, Lorestan University of Medical Sciences, Khorramabad, Iran
[b] Razi Herbal Medicines Research Center, Faculty of Medicine, Lorestan University of Medical Sciences, Khorramabad, Iran

ARTICLE INFO

Keywords:
L-arginine
Inflammatory biomarkers
C-reactive protein
interleukin-6
TNFα
Meta-analysis

ABSTRACT

Objectives: We carried out a systematic review and meta-analysis of randomized controlled trials (RCTs) to assess the effect of L-arginine on inflammatory biomarkers including C-reactive protein (CRP), interleukin-6 (IL-6) and TNFα.

Methods: A systematic search was carried out in PubMed, Embase, Scopus, Cochrane library databases and ISI web of sciences to retrieve the RCTs which examined the effect of L-arginine supplementation on inflammatory biomarkers up to October 2019, with no language and time restriction. Meta-analysis was performed using a random effects model, and I2 index was used to evaluate the heterogeneity.

Results: Search yielded 2452 publications. Eleven RCTs were eligible. Results indicated that L-arginine supplementation had no significant effect on inflammatory biomarkers including CRP, IL-6 and TNFα. However, when subgroup analysis was performed, we found that L-arginine supplementation increased CRP levels in subjects with ages > 60 years old, participants with baseline circulating CRP levels > 3 mg/dl, patients with cancer and when used in enteral formula.

Conclusion: Results of the present meta-analysis indicated that L-arginine supplementation increased the circulating concentrations of CRP in subjects with ages > 60 years old, subjects with higher levels of CRP, patients with cancer and when used in enteral formula. Therefore, L-arginine should be used with caution in these subjects. However, further well designed, large-scale studies are needed.

1. Introduction

Arginine is an amino acid naturally consumed in our diets, and is abundant in foods like meat and nuts.[1] Although, it is an unnecessary amino acid, animal studies have shown that it is necessary for the growth of young rodents.[2] It has been shown that arginine can prevent thymic involution and increase the number of lymphocytes.[3] In addition, arginine is essential for wound healing.[4] This evidence revealed that arginine became an essential amino acid in situations such as surgery or trauma.[5] Further investigations indicated that nitric oxide (NO)[4] was produced from arginine in endothelial cells.[6] The fact that l-arginine is a substrate for the production of nitric oxide has contributed to a significant growth of interest in investigating the role of l-arginine in the treatment and prevention of cardiovascular disease.[7] A great deal of evidence suggests the potential benefits of using l-arginine in patients with hypercholesterolemia, diabetes mellitus, high blood pressure and atherosclerosis.[8,9]

In addition, role of l-arginine in immune regulation has been shown in numerous studies. In 2014, a meta-analysis was carried out to evaluate whether l-arginine supplementation could improve the outcomes of immune function.[10] This mete-analysis concluded that l-arginine supplementation led to a significant greater CD4+ T-cell proliferation response, and the incidence of infectious complications was lower in the group with l-arginine supplementation.[10] Results of the studies assessed the effect of l-arginine on inflammatory biomarkers were contradictory. In 2009, a study by Lucotti et al.,[11] indicated that arginine supplementation reduced circulating levels of interleukin-6 (IL-6). Another study by Casas-Rodera et al.,[12] found that an arginine-enhanced

* Corresponding author at: Nutritional Health Research Center, Department of Nutrition, Lorestan University of Medical Sciences, Goledasht Blvd, PO Box: 6813833946, Khorramabad, Iran.
E-mail address: abbasnezhad.amir@lums.ac.ir (A. Abbasnezhad).

https://doi.org/10.1016/j.ctim.2019.102226
Received 23 September 2019; Received in revised form 22 October 2019; Accepted 23 October 2019
Available online 31 October 2019
0965-2299/

formula had no significant effect on IL-6, C-reactive protein (CPR) and TNFα in comparison to a standard polymeric formula. Due to the inconsistent results found in the literature, we carried out a systematic review and meta-analysis of randomized clinical trials (RCTs) to assess the effect of L-arginine on inflammatory biomarkers.

2. Materials and methods

2.1. Search strategy

We systematically searched PubMed, Embase, Scopus, Cochrane library databases and ISI web of sciences for RCTs assessing the effect of arginine supplementation on inflammatory biomarkers without any language and time restriction until October 2019. The following combination of keywords and MeSH terms were used in databases in titles and abstract: (Arginine OR L-arginine OR Arg OR L-Arg) AND ("Biological markers" OR inflammatory OR inflammation OR cytokines OR interleukin OR "tumor necrosis factor alpha" OR "C-reactive protein" OR hs-CRP) AND (Placebo OR "clinical trial" OR "controlled clinical trial" OR "randomized controlled trial"). Moreover, a manual search and reference lists check of all included studies, and related reviews were performed to identify further relevant articles (Supplementary File 1. Complete search strategy).

2.2. Study selection

We included the articles that met the following criteria: 1) RCTs of oral or enteral supplementation of arginine; 2) trials which reported mean or median values in baseline and at the end of supplementation in intervention and control groups with standard deviations (SDs), standard error (SE), or 95% CIs. The exclusion criteria were as follows: 1) studies with no placebo group; 2) case-control, cross-sectional, cohort design, conference papers and review studies; 3) studies which used a combination of other vitamins and minerals, 4) studies conducted in animal models; 5) studies that were not available.

2.3. Data extraction

After removing duplicates, titles and abstracts of all studies were assessed independently by two reviewers (BN and OA) to find potentially relevant studies for full text evaluation. Finally, full text of the selected articles was reviewed to determine whether the article is qualified for inclusion. Any controversy was discussed and resolved with a third author (AA). Using standardized data collection form, following data were abstracted: last name of the first author, year of publication, country where the study was conducted, study design, sample size (intervention and control group), dosage of arginine (gr), treatment duration (days), type of arginine supplementation, mean and standard deviations (SDs) of inflammatory markers in both the intervention and control group at the baseline and at the end of the studies, and participants characteristics, including sex (M/F), mean age and BMI and health status.

2.4. Quality assessment

Jadad scale was used to evaluate the quality of included studies.[13] This scale assesses the quality of RCTs and includes random allocation (up to 2 points), double blinding (up to 2 points), and description of withdrawals and dropouts (up to 1 point). Studies with the scores of 3 and higher are generally considered as a high quality study.

2.5. Statistical analyses

All analyses conducted using STATA v.12 (Stata Corporation, College Station, TX, USA). Mean and standard deviation (SD) of variables change between baseline and post intervention was used in meta-analysis. When S.D of change was not reported, it was calculated using following formula: s.d. = square root [(s.d. pre-intervention)^2 + (s.d. post-intervention)^2 − (2R × s.d. pre-intervention × s.d. post-intervention)]. A correlation coefficient of 0.8 was assumed as R-value of the above-mentioned formula. A fixed effect model was used for the assessment of pooled effect size. When heterogeneity was presented, a random effect model was used. Subgroup analysis was performed based on dosage of arginine, duration of intervention, age, baseline serum CRP, type of the supplementation (oral or enteral formula), health status and jadad score to find sources of the heterogeneity. We performed the sensitivity analysis (metaninf analysis) by conducting one-study remove (leave-one-out) approach, to estimate the impact of each trial on the pooled effect size. Between-study heterogeneity was examined using Q test and I-square (I^2) test.[14] Funnel plots, Begg's and Egger's tests were used to assess the publication bias.

3. Results

3.1. Study selection

The first step of searching yielded 157, 349, 320, 233 and 1393 citations in PubMed, Cochrane Library, Web of Science, Embase, and SCOPUS, respectively. No study was found while searching the reference lists. Of these, 610 articles were excluded due to the duplication. The titles and abstracts of 1842 articles were reviewed. Of these, 1818 studies were excluded due to the following reasons: animal studies, reviews, quasi-experimental, supplementation with other ingredients and antioxidants, no placebo or control group, non-related studies. Therefore, full text of 24 studies assessed for the eligibility. Eventually, 11 articles were included in this meta-analysis (Fig. 1).

3.2. Study characteristics

All 11 studies [11,12,15–23] were RCTs. The intervention durations were from 5 to 180 days. Data are pooled from studies with 264 participants in the intervention group and 266 participants in the control group. Age range of the participants was 35.2 to 79.7 years old. Four studies were conducted in Spain, 1 in Iran, 1 in Japan, 2 in Poland, 2 in Germany and 1 in Italy. Ten studies were conducted on both genders, and 1 study enrolled only females. Basis on the jaded scale, 6 studies had good quality (≥3) and quality score of 5 studies were lower than 3 (Table 1). Supplementation dose of L-arginine was ranged from 0.8 g/day to 20 g/day. Four studies were conducted on healthy subjects [16,18–20] and other studies were conducted on patients with cancer, hypercholesterolemia, pressure ulcers and cardiopathic nondiabetic patients. Eight studies reported that L-arginine supplementation had no significant effect on CRP,[12,15–17,20–23] whereas, one study indicated a significant reducing effect of L-arginine on CRP.[18] Three studies found no significant effect of L-arginine supplementation on TNFα,[12,15,17] whereas, two studies found a significant reducing effect.[11,19] Three studies reported that L-arginine supplementation had no significant effect on IL-6,[12,15,17] whereas, one study indicated a significant reducing effect of L-arginine on IL-6.[11]

3.3. Publication bias and sensitivity analyses

Evaluation of publication bias by both the Egger's test and the Begg's test showed no evidence of publication bias (p = 0.66 and p = 0.85, respectively). Furthermore, funnel plots demonstrated no evidence of publication bias within the studies (Fig. 5). Results of the metaninf analysis indicated that the elimination of any studies did not alter the final results (Supplementary File 2).

3.4. Meta-analysis

Results of the meta-analysis of 9 trials indicate that L-arginine

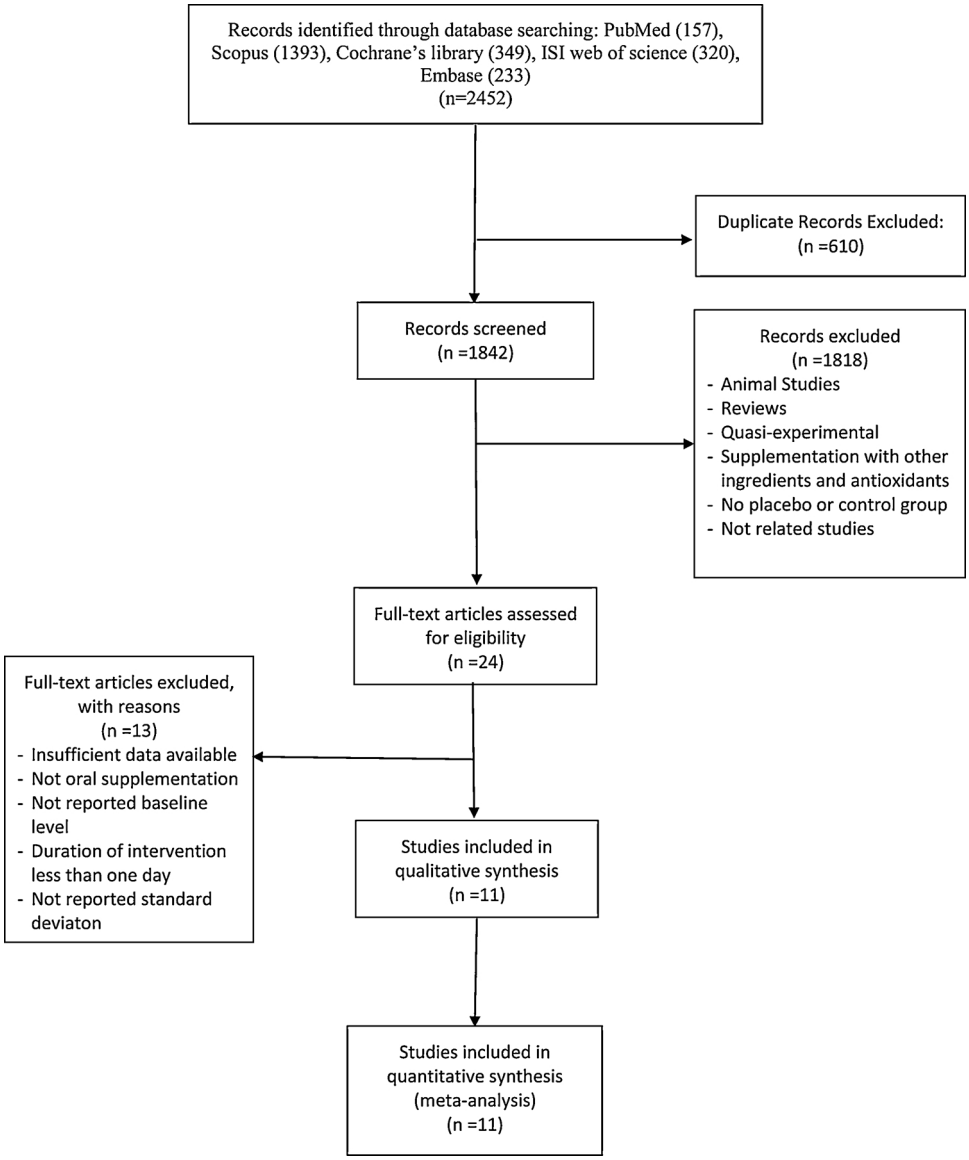

Fig. 1. Flowchart of the study selection for inclusion in the systematic review.

supplementation had no significant effect on serum levels of CRP (weighted mean difference (WMD) and 95% confidence interval (CI) with random effects model analysis: 0.04 mg/dl (-0.04, 0.11), $p =$ 0.31) (Fig. 2). As Fig. 3 indicates, L-arginine supplementation had no significant effect on serum levels of IL-6 (WMD and 95% CI with random effects model analysis: -0.25 pg/ml (-7.48, 6.98), $p =$ 0.94). Results of the meta-analysis of 5 trials indicate that L-arginine supplementation had no significant effect on serum levels of TNFα (WMD and 95% CI with fixed effects model analysis: -0.07 pg/ml (-0.61, 0.47), $p =$ 0.63) (Fig. 4). There was a low level of heterogeneity for CRP (I2 = 56.5%, $p =$ 0.006) and moderate level of heterogeneity for IL-6 (I2 = 74.6%, $p =$ 0.003) between included studies. Heterogeneity was not significant for TNFα (I2 = 39.2%, $p =$ 0.144). Results of the subgroup analysis indicated that L-arginine supplementation had no significant effect on CRP in subgroups of trial duration and L-arginine dose (Table 2). Furthermore, results of the subgroup analysis demonstrated that L-arginine supplementation significantly increased circulating levels of CRP in subgroups of enteral formula, participants with ages > 60 years old, baseline circulating CRP levels > 3 mg/dl and in patients with cancer (Table 2).

4. Discussion

To our best knowledge this is the first meta-analysis assessing the effect of L-arginine supplementation on inflammatory biomarkers. Results of the present systematic review and meta-analysis indicated that supplementation of L-arginine had no significant effect on inflammatory biomarkers including CRP, IL-6 and TNFα. However, when subgroup analysis performed, we found that L-arginine supplementation had an increasing effect on CRP in subjects with ages > 60 years old, participants with baseline circulating CRP levels > 3 mg/dl, patients with cancer and when used in enteral formula.

Evidence suggest the relationship between arginine and immune function.[10] Previous research has reported that availability of arginine is necessary for the function and proliferation of immune cells such as T-cells.[1] T lymphocytes need arginine for their biological functions such as expression of the T-cell receptor (TCR) complex, development of memory and proliferation.[24] In the deprivation of arginine, number of TCRs on the cell membrane decrease to 25% of basal level.[1] Arginine is essential for the ζ-chain peptide which is an important component of TCR complex.[25] Although, the exact mechanisms by which arginine depletion reduces T-cell proliferation have not been well known, it has

Table 1
Characteristics of the selected studies included in this meta-analysis.

Author (year)	Country	Participants	sex	BMI	Age	Study design	Sample size in supplement/ placebo group	Dose of arginine	Duration day	Jaded score	Outcome
Daniel de Luis (2005)	Spain	Head and neck cancer	F/M	24.3 ± 2.1	61.1 ± 10.8	R/B	14/15	enteral diet with arginine (12.5 gr)	6	3	CRP IL-6 TNFα
Gerhild I. Böger (2007)	Germany	Healthy elderly subjects	F/M	25.16 ± 22.17	59.6 ± 16.2	R/DB/CS	15/15	Arginine (3 gr)	21	2	CRP
Gerhild I. Böger (2007)	Germany	Healthy elderly subjects	F/M	25.1 ± 22.74	54.5 ± 28.4	R/DB/CS	13/13	Arginine (3 gr)	21	2	CRP
P. Casas-Rodera (2007)	Spain	Oral and laryngeal cancer	F/M	NR	57.2 ± 7.95	R	14/15	enteral diet with arginine (0.81 gr)	7, 14	1	CRP IL-6 TNFα
Daniel de Luis (2008)	Spain	Head and neck cancer	F/M	24.7 ± 3	60.9 ± 10.6	R	18/23	enteral diet with arginine (17 gr)	5	1	CRP IL-6 TNFα
Pietro Lucotti (2009)	Italy	Cardiopathic nondiabetic	F/M	NR	64.5 ± 6.7	R/DB/PC	16/14	Arginine (6.4 gr)	180	3	IL-6 TNFα
Mohammad Alizadeh (2012)	Iran	Premenopausal women with central obesity	F	NR	35.2 ± 5.61	R/DB/PC	17/17	Arginine (5 gr)	21, 42	4	CRP
P. bogdanski (2012)	Poland	Simple obesity	F/M	38.3 ± 3.6	42.4 ± 5.4	R/PC	30/30	Arginine (9 gr)	90	1	TNFα
Joanna Suliburska (2013)	Poland	Simple obesity	F/M	36.4 ± 3.8	42.3 ± 5.6	R/DB/PC	44/44	Arginine (9 gr)	180	4	CRP
Daniel de Luis (2014)	Spain	Head and neck cancer	F/M	24.9 ± 3.2	64.6 ± 11.4	R/B	42/40	enteral diet with arginine (20gr)	10	2	CRP
Melanie Bähr (2014)	Germany	Hypercholesterolemic	F/M	26.3 ± 3.1	NR	R/DB/CS	24/24	Arginine (1.6 gr)	28	5	CRP
Hideharu Yamanaka (2017)	Japan	Pressure ulcers	F/M	18.4 ± 1.7	79.7 ± 7.5	R	17/16	Arginine (2.5 gr)	14, 28	3	CRP

R, randomized; B, blinded; PC, placebo-controlled; CS, crossing-over; DB, double-blinded; CRP, C-reactive protein; ADMA, asymmetric dimethyl arginine; IL-6, interleukin 6; TNFα, tumor necrosis factor alpha; NR, Not reported.

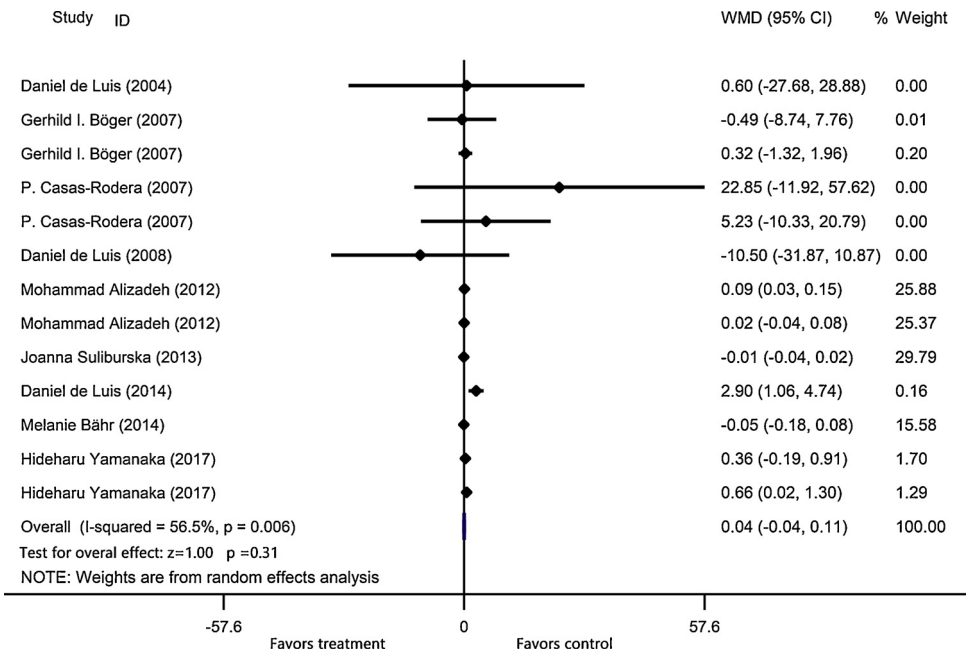

Fig. 2. Forest plot of the random-effects meta-analysis of the effect of L-arginine supplementation on C-reactive protein.

been reported that in the absence of arginine, the cell cycle of stimulated T- lymphocytes was stopped in the G_0-G_1 phase.[26,27] Moreover, there is an impaired production of cytokines by T lymphocytes in the absence of arginine.[28] Although, the role of L-arginine in immune function has been shown, results of the trails which assessed the effect of L-arginine supplementation on inflammatory biomarkers were inconsistent. Casas-Rodera et al., De Luis et al., and Böger et al.,[12] found that arginine had no significant effect on inflammatory biomarkers such as IL-6, CPR or TNFα, whereas, Lucotti et al.,[11] indicated that arginine supplementation had reducing effect on circulating levels of IL-6. Present meta-analysis indicated that L-arginine supplementation had no significant effect on inflammatory biomarkers including IL-6, CRP and TNFα. It should be noted that, the diversity of comorbidities in the included studies was very high. There are patients with diseases such as cancer, hypercholesterolemia, pressure ulcers and cardiovascular diseases, which have different origins that can influence the results. Therefore, this result is not conclusive, and further studies are needed.

During immune stress, a subset of myeloid cells enters the lymphoid organs and peripheral tissues, and suppresses the immune responses.[24] These myeloid suppressor cells (MSCs) can control the activity of T-cells by two enzymes, including nitric oxide synthase (NOS), and arginase 1.[24,29] NOS generates NO from arginine, and arginase I metabolizes arginine to ornithine and urea, which depletes the milieu of arginine.[1] Following immune stress such as trauma and sepsis, the activation of MSCs depletes arginine from the surrounding environment.[30] As discussed, arginine is essential for the proliferation and cytokines production of T-cells.[1,24] One of the inflammatory biomarkers which increases during immune stress is CRP.[31] CRP is a part of the innate immunity that can activate the classical complement pathway.[32,33] Its serum level rises and falls more rapidly than other immune biomarkers,

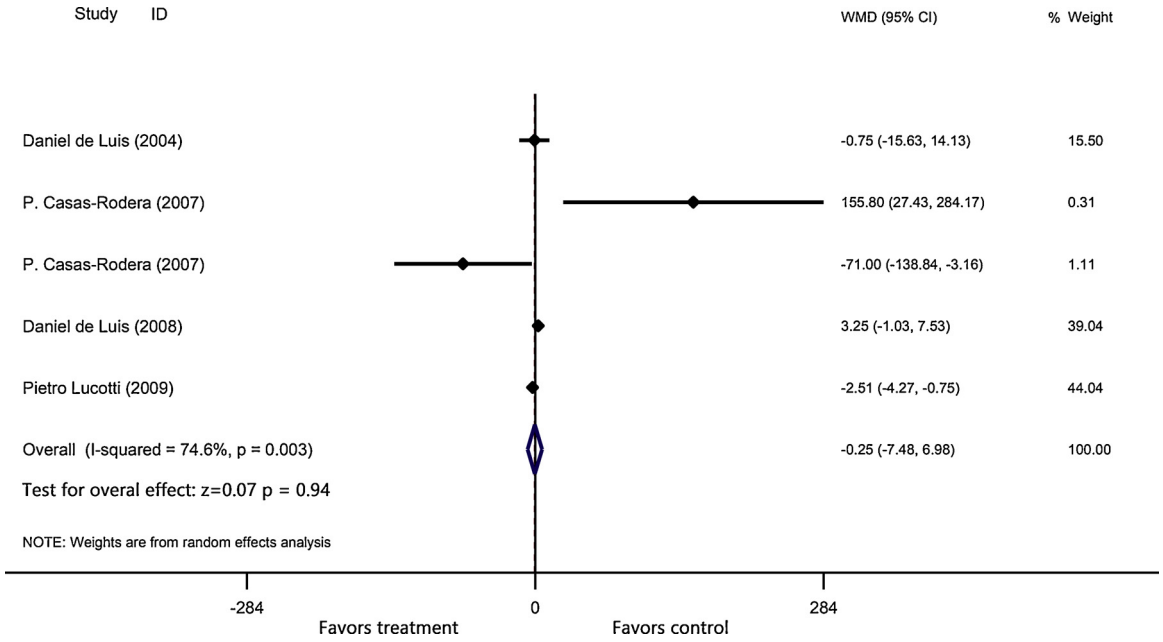

Fig. 3. Forest plot of the random-effects meta-analysis of the effect of L-arginine supplementation on interleukin-6.

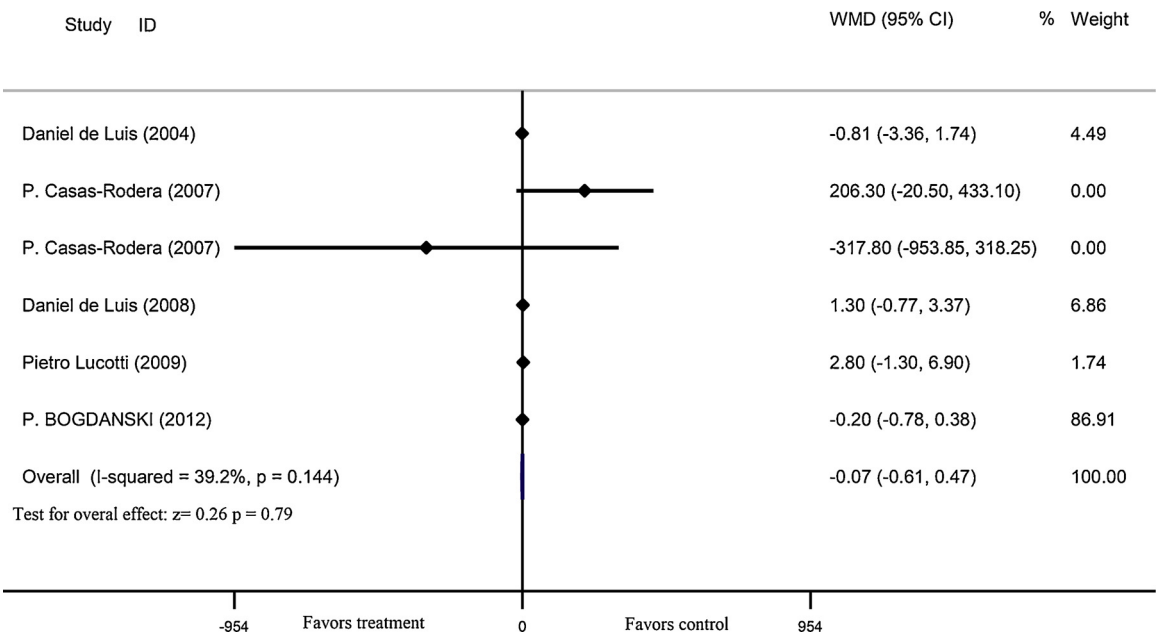

Fig. 4. Forest plot of the fixed-effects meta-analysis of the effect of L-arginine supplementation on TNFα.

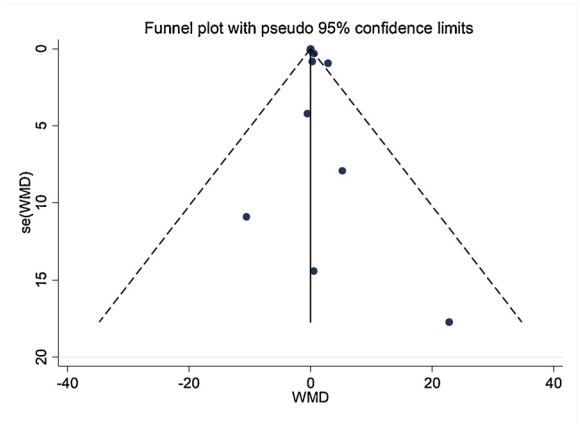

Fig. 5. Funnel plot of the studies included.

which make it an advantageous biomarker to follow clinical status of a disease and response to a particular treatment.[34,35] Prospective epidemiological studies indicated that CRP is a useful marker to predict the incident of cardiovascular diseases, and sudden cardiac death.[36,37] It has been well documented that pro-inflammatory cytokines such as IL-6 and TNFα are the main stimuli of CRP synthesis in the liver.[27,34] These pro-inflammatory cytokines are secreted by activated T-cells during the immune stresses.[38,39] Results of the present met-analysis indicated that L-arginine supplementation had an increasing effect on CRP in participants with higher concentrations of CRP (> 3 mg/dl). As the starvation of arginine reduces the activity of T lymphocytes, its higher concentrations can increase the activity of these immune cells.[1] Animal studies suggested that arginine could have beneficial effects on the functions of T lymphocyte like cytokines production under conditions of stress.[40,41] Therefore, it can be speculated that in stress conditions with higher levels of CRP, L-arginine supplementation could increase the activity of immune cells, and subsequently increase the circulating

Table 2
Subgroup analysis of the effect of L-arginine supplementation on CRP level.

	No	WMD (95%CI)	P Within Group	P Heterogeneity	I^2
Method of supplementation					
Enteral formula	5	2.88 (1.07, 4.69)	< **0.001**	0.57	0.0%
Oral	8	0.02 (-0.02, 0.08)	0.33	0.03	53.4%
Trial duration (day)					
≤21	9	0.42 (-0.13, 0.98)	0.13	0.11	38.4%
< 21	4	−0.00 (-0.05, 0.05)	0.98	0.15	43.5%
Arginine dose (gr)					
≤3	7	0.20 (-0.14, 0.56)	0.24	0.20	29.7%
< 3	6	0.03 (-0.04, 0.11)	0.38	< 0.001	73.7%
Age (year)					
≤60	7	0.02 (-0.02, 0.08)	0.29	0.09	44.5%
< 60	5	0.83 (0.02, 1.64)	**0.04**	0.09	48.9%
Baseline circulating CRP (mg/dl)					
≤3	8	0.02 (-0.02, 0.08)	0.33	0.03	53.4%
< 3	5	2.88 (1.07, 4.69)	< **0.001**	0.57	0.0%
Health status					
Cancer	5	2.88 (1.07, 4.69)	< **0.001**	0.57	0.0%
Non-cancer	8	0.02 (-0.02, 0.08)	0.33	0.03	53.4%
Jaded score					
≤3	9	0.69 (0.10, 1.27)	**0.02**	0.27	19.3%
< 3	4	0.02 (-0.03, 0.07)	0.47	0.02	67.9%

CI, Confidence Interval; CRP, C-Reactive Protein; WMD, Weighted Mean Differences.

levels of CRP.

Moreover, we found that L-arginine supplementation could increase the CRP levels in older participants (> 60 years old) and in patients with cancer. Based on previous investigations, serum CRP levels are associated with variables such as age.[42,43] Population-based studies have reported that there is a direct correlation between age and serum levels of CRP.[42] In addition, previous studies indicated that increased concentration of CRP is associated with increased risk of cancer of any type.[44] Epidemiologic studies reported that increased concentrations of CRP are correlated with poor prognosis in patients with different cancers.[44] As discussed in previous paragraph, L-arginine can increase the CRP concentrations in subjects with higher levels of CRP. Thus, it can be assumed that due to the higher levels of CRP in older subjects and in patients with cancer, arginine supplementation could increase the CRP levels in these subjects. Furthermore, we found that L-arginine increased the concentration of CRP when used in enteral formula. It is noteworthy that all the studies which included in this meta-analysis and assessed the effect of L-arginine added to the enteral formula, were conducted on patients with cancer.

Present systematic review and meta-analysis has several strengths. We included RCTs which examined complementary endpoints, providing a comprehensive review on this topic. This review is based on an up to date literature search from a large number of databases and included 11 studies. Present study has also several limitations. First, we did not limit the systematic search to a particular disease, which led to an increase in heterogeneity. However, by subgroup analysis, heterogeneity decreased in some of the subgroups. Second, although we conducted a comprehensive search of the electronic literature, there might be studies that have not been included. Finally, the small sample size of the individual studies limits the strength of the conclusion of the present meta-analysis, however, we hope this study will be helpful for future studies.

In conclusion, present meta-analysis indicated that L-arginine supplementation had no significant effect on inflammatory biomarkers including IL-6, CRP and TNFα. Further analysis indicated that supplementation of L-arginine could increase the circulating levels of CRP in subjects with ages > 60 years old, participants with baseline circulating CRP levels > 3 mg/dl, patients with cancer and when used in enteral formula. Therefore, arginine supplement should be used with caution in these subjects. However, further well designed, large-scale studies are needed to fully determine the effect of L-arginine on inflammatory biomarkers.

Authorship

AA and BN designed the study. BN and OA reviewed and selected the articles. MZK and BN extracted needed data from articles. AA and BN performed data analysis and interpretation. AA and RC drafted the manuscript. EFM revised the article for important intellectual content.

Funding

No source of funding to declare.

Declaration of Competing Interest

The authors report no conflict of interests.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ctim.2019.102226.

References

1. Popovic PJ, Zeh III HJ, Ochoa JB. Arginine and immunity. *J Nutr.* 2007;137(6):1681S–1686S.
2. Wakabayashi Y, Yamada E, Yoshida T, Takahashi H. Arginine becomes an essential amino acid after massive resection of rat small intestine. *J Biol Chem.* 1994;269(51):32667–32671.
3. Barbul A, Rettura G, Levenson SM, Seifter E. Arginine: a thymotropic and wound-healing promoting agent. *Surg Forum.* 1977;28:101–103.
4. Kavalukas SL, Barbul A. Nutrition and wound healing: an update. *Plast Reconstr Surg.* 2011;127(Suppl 1):38s–43s.
5. Morris Jr SM. Arginine: beyond protein. *J. Clin. Nutr.* 2006;83(2):508s–512s.
6. Hibbs Jr JB, Taintor RR, Vavrin Z, Rachlin EM. Nitric oxide: a cytotoxic activated macrophage effector molecule. *Biochem Biophys Res Commun.* 1988;157(1):87–94.
7. Hibbs Jr J. Synthesis of nitric oxide from L-arginine: a recently discovered pathway induced by cytokines with antitumour and antimicrobial activity. *Res Immunol.* 1991;142(7):565–569.
8. Boger RH. L-Arginine therapy in cardiovascular pathologies: beneficial or dangerous? *Curr Opin Clin Nutr Metab Care.* 2008;11(1):55–61.
9. Cable DG, Celotto AC, Evora PR, Schaff HV. Asymmetric dimethylarginine endogenous inhibition of nitric oxide synthase causes differential vasculature effects. *Med Sci Monit.* 2009;15(9):Br248–Br253.
10. Kang K, Shu XL, Zhong JX, Yu TT. Effect of L-arginine on immune function: a meta-analysis. *IFIC J. Clin. Nutr.* 2014;23(3):351–359.
11. Lucotti P, Monti L, Setola E, et al. Oral L-arginine supplementation improves endothelial function and ameliorates insulin sensitivity and inflammation in cardiopathic nondiabetic patients after an aortocoronary bypass. *Metab Clin Exp.* 2009;58(9):1270–1276.
12. Casas-Rodera P, Gomez-Candela C, Benitez S, et al. Immunoenhanced enteral nutrition formulas in head and neck cancer surgery: a prospective, randomized clinical trial. *Nutr Hosp.* 2008;23(2):105–110.
13. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials.* 1996;17(1):1–12.
14. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ: Br Med J.* 2003;327(7414):557.
15. de Luis DA, Arranz M, Aller R, Izaola O, Cuellar L, Terroba MC. Immunoenhanced enteral nutrition, effect on inflammatory markers in head and neck cancer patients. *Eur J Clin Nutr.* 2005;59(1):145–147.
16. Boger GI, Rudolph TK, Maas R, et al. Asymmetric dimethylarginine determines the improvement of endothelium-dependent vasodilation by simvastatin: effect of combination with oral L-arginine. *J Am Coll Cardiol.* 2007;49(23):2274–2282.
17. De Luis DA, Aller R, Izaola O, et al. Efecto de una fórmula enteral enriquecida en arginina sobre los marcadores inflamatorios en pacientes con tumores de cabeza y cuello. *Med Clánica.* 2009;132(2):49–52.
18. Alizadeh M, Safaeiyan A, Ostadrahimi A, et al. Effect of L-arginine and selenium added to a hypocaloric diet enriched with legumes on cardiovascular disease risk factors in women with central obesity: a randomized, double-blind, placebo-controlled trial. *Ann Nutr Metab.* 2012;60(2):157–168.
19. Bogdanski P, Suliburska J, Grabanska K, et al. Effect of 3-month L-arginine supplementation on insulin resistance and tumor necrosis factor activity in patients with visceral obesity. *Eur Rev Med Pharmacol Sci.* 2012;16(6):816–823.
20. Suliburska J, Bogdanski P, Szulinska M, Pupek-Musialik D, Jablecka A. Changes in mineral status are associated with improvements in insulin sensitivity in obese patients following L-arginine supplementation. *Eur J Nutr.* 2014;53(2):387–393.
21. de Luis D, Izaola O, de la Fuente B, Aller R. Effect of l-arginine supplementation on insulin resistance and adipocitokines levels in head and neck cancer non diabetic patients after surgery. *icion hospitalaria.* 2014;30(4).
22. Bahr M, Fechner A, Kiehntopf M, Jahreis G. Consuming a mixed diet enriched with lupin protein beneficially affects plasma lipids in hypercholesterolemic subjects: a randomized controlled trial. *Clin Nutr.* 2015;34(1):7–14.
23. Yamanaka H, Okada S, Sanada H. A multicenter, randomized, controlled study of the use of nutritional supplements containing collagen peptides to facilitate the healing of pressure ulcers. *J Nutr Intermed Metab.* 2017;8:51–59.
24. Bronte V, Serafini P, Mazzoni A, Segal DM, Zanovello P. L-arginine metabolism in myeloid cells controls T-lymphocyte functions. *Trends Immunol.* 2003;24(6):302–306.
25. Backstrom BT, Milia E, Peter A, Jaureguiberry B, Baldari CT, Palmer E. A motif within the T cell receptor alpha chain constant region connecting peptide domain controls antigen responsiveness. *Immunity.* 1996;5(5):437–447.
26. Rodriguez PC, Quiceno DG, Ochoa AC. L-arginine availability regulates T-lymphocyte cell-cycle progression. *Blood.* 2007;109(4):1568–1573.
27. Abbaszadeh A, Darabi S, Hasanvand A, et al. Minocycline through attenuation of oxidative stress and inflammatory response reduces the neuropathic pain in a rat model of chronic constriction injury. *Iran J Basic Med Sci.* 2018;21(2):138–144.
28. Rodriguez PC, Quiceno DG, Zabaleta J, et al. Arginase I production in the tumor microenvironment by mature myeloid cells inhibits T-cell receptor expression and antigen-specific T-cell responses. *Cancer Res.* 2004;64(16):5839–5849.
29. Choghakhori R, Abbasnezhad A, Amani R, Alipour M. Sex-related differences in clinical symptoms, quality of life, and biochemical factors in irritable bowel syndrome. *Dig Dis Sci.* 2017;62(6):1550–1560.
30. Makarenkova VP, Bansal V, Matta BM, Perez LA, Ochoa JB. CD11b+/Gr-1+ myeloid suppressor cells cause T cell dysfunction after traumatic stress. *J Immunol.* 2006;176(4):2085–2094.
31. Castelli GP, Pognani C, Meisner M, Stuani A, Bellomi D, Sgarbi L. Procalcitonin and C-reactive protein during systemic inflammatory response syndrome, sepsis and organ dysfunction. *Crit Care.* 2004;8(4):R234–242.
32. Sjoberg AP, Trouw LA, McGrath FD, Hack CE, Blom AM. Regulation of complement activation by C-reactive protein: targeting of the inhibitory activity of C4b-binding protein. *J Immunol.* 2006;176(12):7612–7620 (Baltimore, Md : 1950).

33. Alipour M, Malihi R, Hosseini SA, et al. The effects of catechins on related risk factors with Type 2 diabetes: a review. *Prog Food Nutr Sci.* 2018;20(1):12–20.
34. Du Clos TW, Mold C. C-reactive protein: an activator of innate immunity and a modulator of adaptive immunity. *Immunol Res.* 2004;30(3):261–277.
35. Asbaghi O, Fouladvand F, Gonzalez MJ, Aghamohammadi V, Choghakhori R, Abbasnezhad A. The effect of green tea on C-reactive protein and biomarkers of oxidative stress in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. *Complement Ther Med.* 2019;46:210–216.
36. Ridker PM. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. *Circulation.* 2003;107(3):363–369.
37. Eslampour E, Ebrahimzadeh F, Abbasnezhad A, Khosroshahi MZ, Choghakhori R, Asbaghi O. Association between circulating irisin and C-Reactive protein levels: a systematic review and meta-analysis. *Endocrinol Metab (Seoul).* 2019;34(2):140–149.
38. Reinecker HC, Steffen M, Witthoeft T, et al. Enhand secretion of tumour necrosis factor-alpha, IL-6, and IL-1β by isolated lamina ropria monouclear cells from patients with ulcretive cilitis and Crohn's disease. *Clin Exp Immunol.* 1993;94(1):174–181.
39. Amani R, Abbasnezhad A, Hajiani E, Cheraghian B, Abdoli Z, Choghakhori R. Vitamin D3 induced decrease in IL-17 and Malondialdehyde, and increase in IL-10 and total antioxidant capacity levels in patients with irritable bowel syndrome. *Iran J Immunol.* 2018;15(3):186–196.
40. Choudhry MA, Haque F, Khan M, et al. Enteral nutritional supplementation prevents mesenteric lymph node T-cell suppression in burn injury. *Crit Care Med.* 2003;31(6):1764–1770.
41. Knoferl MW, Angele MK, Schwacha MG, Bland KI, Chaudry IH. Preservation of splenic immune functions by female sex hormones after trauma-hemorrhage. *Crit Care Med.* 2002;30(4):888–893.
42. Hughes A, Kumari M. Age modification of the relationship between C-reactive protein and fatigue: findings from understanding Society (UKHLS). *Psychol Med.* 2018;48(8):1341–1349.
43. Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW. C-reactive protein in healthy subjects: Associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? *Arterioscler Thromb Vasc Biol.* 1999;19(4):972–978.
44. Allin KH, Nordestgaard BG. Elevated C-reactive protein in the diagnosis, prognosis, and cause of cancer. *Crit Rev Clin Lab Sci.* 2011;48(4):155–170.