Review Article

Effect of L-arginine on immune function: a meta-analysis

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L-arginine plays an important role in immune regulation by affecting the immune response and inflammation. This meta-analysis was performed to assess whether L-arginine supplementation could improve the outcomes of immune function, and to evaluate the safety of L-arginine supplementation. Four databases (PubMed, EMBASE, Web of Science, the Cochrane Library) for all randomized controlled trials investigating the effects of supplementation with L-arginine published from 1966 to September 2013 were searched. The quality of controlled trials was assessed with the Jadad method. Meta-analyses were performed with fixed- or random-effects models according to heterogeneity of studies. Data from 11 trials involving 321 patients were enrolled. Meta-analysis showed that the L-arginine supplement group had a significantly greater $CD4^+$ T-cell proliferation response (MD 5.03; 95% CI 1.11, 8.95; $p<0.05$), and that the incidence of infectious complications was lower (OR 0.40; 95% CI 0.17, 0.95; $p<0.05$) than control.

Key Words: L-arginine, nitric oxide, immune, cytokines, meta-analysis

INTRODUCTION

The biological functions of L-arginine (L-Arg) may extend beyond its basic nutritional functions as an amino acid.[1-4] For example, arginine improves the body's defence against gastric carcinoma by increasing IgA, IgM, $CD4^+$ and the CD4/CD8 ratio.[5,6] Previous clinical studies have demonstrated that L-Arg in critical illness is associated with reduction in the inflammatory response, infection rate and length of hospital stay.[7-9] Moreover, Kirk et al[10] conducted a randomized, double-blind controlled study among elderly over age 65 supplementing free arginine (19 g/d, two weeks), and suggested that L-Arg could increase the levels of hydroxyproline and total protein, improve the lymphocyte reaction, and increase the serum insulin-like growth factor (IGF-1) levels. Based on a series of animal and human trials, L-Arg's basic mechanisms of immune regulation may have a close connection with the role of nitric oxide synthase (NOS) and the nitric oxide (NO) mediated signal pathways.[11,12] However, some arginine enriched trials did not achieve statistical significance. For instance, Sodergren et al[13] investigated the effect of L-Arg on patients undergoing major upper gastrointestinal surgery by assessment of the inflammatory and immune response, and changes in clinical outcome, which had no statistically significant change in primary end-points. Furthermore, it also had be proved that providing preoperative immunonutrition to the patients undergoing major gastrointestinal surgery, the addition of arginine, an ingredient that was expected to have an additional positive effect on immune function,had no influence.[14] So there is still considerable controversy in the efficacy of L-Arg on immune function. Therefore, the aim of this study was to conduct a meta-analysis of those randomized controlled trials (RCTs) which had investigated the effects of L-Arg supplementation on immune function published from 1966 to September 2013, to assess the evidence for an L-Arg immune modulatory function.

METHODS

Study selection

We systematically searched 4 databases [PubMed (http://www.pubmed.com), EMBASE (http://www.embase.com), Web of Science (http://apps.webofknowledge.com), The Cochrane Library (http://www.thecochranelibrary.com)] for all clinical trials investigating the effects of supplementation with L-arginine ("arginine," "Arg," "L-Arg" "immunonutrition," "immune nutrition," "im

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mune nutrition supplement" and their variants) on immune function ("immune," "immunity," "immunization," "immunize," "immuno," "cellular immunity," "cell-mediated immunity," "immunometabolic" and their variants) published from 1966 to September 2013. References from the extracted articles and reviews were also consulted to complete the data bank. When multiple articles for a single study were present, we used the latest publication and supplemented it, if necessary, with data from the most complete or updated publication.

Studies were included if 1) they were the randomized controlled trials (RCTs) with parallel controlled design; 2) data related to supplementation of L-arginine were available; 3) the association of L-arginine with immune function was specifically evaluated; 4) the supplementation of L-arginine was the only difference between the treatment group and the control group; and 5) specific outcomes were mentioned. We excluded studies if 1) they were not randomized designs; 2) outcomes about immune function were not specifically mentioned; and 3) they did not report an adequate statistical analysis.

Data extraction

From each study, we extracted information on first author, publication year, disease outcome, country of origin, method of outcome ascertainment, sample size, age, sex, daily dose of arginine, average study follow-up time, number of cases, type of nutrition support, unit of measurement, and corresponding 95% CIs, SEs, or exact *p* values. Because differences in study populations and design might cause variations in results, study-quality score was made by methodology quality accessment.[15] One point was given for each of these traits and a study-quality score that ranged from 0 to 5 for each investigation was calculated. Studies were categorized into those with low study-quality score (1-2 points) and those with a high study quality score (3-5 points), and no RCTs (0 point).

Data analysis

Data pooling was performed with the use of classical meta-analytic methodology, using the RevMan 5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration; http://ims.cochrane.org/revman/). $p<0.05$ was considered statistically significant. Data were extracted from the text, tables and figures of the original published papers. To include data from as many trials as possible, missing SD data for one trial were imputed from SD data from all other trials using the same measure.[16] When estimated the analysis indexes, relative risk (RR) or odds ratio (OR) was used as the effect size of the categorical variable, while the weighted mean difference (WMD) was used as the effect size of continuous variable. 95% CIs were calculated for each investigation and for each outcome variable. Before calculating the standardized mean effect for all trials, statistical heterogeneity test was evaluated by using the I^2 statistic (α=0.05), which assessed the appropriateness of pooling the individual study results. The I^2 value provided an estimate of the amount of variance across studies because of heterogeneity rather than chance.[17] And I^2 values of 25%, 50%, and 75% corresponded to low, moderate, and high levels of heterogeneity, respectively. If $p\geq0.05$, the heterogeneity was not substantial, that is there was low heterogeneity between the trials. Thus fixed-effects models were used, with Mantel-Haenszel method (M-H) weighting for combined statistics. If $p<0.05$, however, the heterogeneity was considered substantial, that is there was high heterogeneity between the trials. In this situation, subgroup analysis would be performed. If subgroup analysis could not remove the heterogeneity, combined results were conducted with random-effects models, which were inversed variance weighting or DerSimonian-Laird method (DSL) based on fixed-effects models. Moreover, a priori potential source of heterogeneity was publication bias. Possible publication bias was investigated by drawing a funnel plot to look for funnel plot asymmetry and meta-regression based on study size.[18]

In this meta-analysis, Bobbi et al[22] had various treatment groups, so the trial was separated to analyze according to different doses: 8.5 g/d group, 17 g/d group and control group in home 1 and home 2.

RESULTS

Characteristics of the studies

The initial search yielded 1297 potentially relevant references. After removing duplicates, reviews, animal trials and papers that were less related according to the titles and abstracts, there were 48 studies left. Then reading the full text of these studies and excluding the studies that were less related, 11 trials[19-29] met the inclusion criteria and were selected as appropriate for inclusion in this meta-analysis (Figure 1). The included trials were published between 1966 to September 2013. The characteristics of the selected trials are presented in Table 1. The sample size varied from 11 to 100, reaching a total of 321. Moreover, the average age of the patients varied from 18 to 92 y. Doses of L-arginine in the included studies ranged from 0.2 to 30 g/d (median dose was 15.1 g/d), and the treatment duration varied from 5 to 30 d. As for the 11 studies that evaluated immune function, 3 trials[19,24,29] investigated the effect of L-arginine on patients with abdominal tumour, and 2 trials[23,27] with head and neck cancer. The other 6 trials investigated the effect of L-arginine administration on patients with pressure ulcers,[22] HIV/AIDS,[20] burn,[26] ISS (injury severity score) of 20 or greater,[21] unstable angina undergoing angioplasty,[25] or the older people with vaccination against Streptococcus pneumonia.[28]

Serum albumin

One hundred and thirty-seven participants from four studies[19,22,26,27] were enrolled in the serum albumin (g/dL) analysis, the heterogeneity of which (I^2=37%, p=0.15, χ^2=9.45) was acceptable, so the fixed-effects model was used. There was statistically significant difference between treatment and control group (MD -0.10; 95% CI -0.16, -0.05; $p<0.05$), from which we could draw the conclusion that L-arginine had no more difference in changing the serum albumin than control group (Figure 2).

Change of $CD4^+$ T-cell

There were seven studies[19,20,24,26,28,29] with 168 subjects that mentioned the change of $CD4^+$ T-cell between the L-

arginine and control group, but the heterogeneity among them was significant (I^2=59%, p=0.03, χ^2=12.1). Thus we performed a subgroup analysis, and the subgroups were divided by criteria whether the control group added other immunonutrition, except L-arginine. I^2 between subgroups was 0% (p=0.44, χ^2=0.60), but the total heterogeneity was still large. In this case, we used a random-effects model to analyze the data. There was a statistically significant difference between the L-arginine and control group (MD 5.03; 95% CI 1.11, 8.95; p<0.05), which meant L-arginine was more effective at $CD4^+$ T-cell proliferation than control group. From the funnel plot, it could be concluded that studies mentioned change of $CD4^+$ T-cell data rarely had publication bias with the symmetric figures (Figure 3, Figure 4).

Change of CD4/CD8 ratio

In the analysis for change of CD4/CD8 ratio, five studies[19,24,26,29] with 128 subjects were included, but the heterogeneity among them was significant (I^2=63%, p=0.04, χ^2=8.17). Consequently, we performed a subgroup analysis, I^2 between subgroups was 0% (p=0.70, χ^2=0.15), thus a random-effects model was used. There was no statistically significant difference between the L-arginine and control group (MD 0.17; 95% CI -0.48, 0.83; p>0.05), which meant the relative data were not enough to draw a conclusion. Moreover, the asymmetry funnel plot suggested possible publication bias existed between studies mentioned change of CD4/CD8 ratio (Figure 5, Figure 6).

Infectious complications

Four studies,[19,21,23,27] 156 subjects included, evaluated the effect of L-arginine supplementation on infectious complications (including pneumonia, abdominal abscess, fasciitis, bacteremia, septic shock, septic coagulopathy, wound infections and urinary tract infections), and the analysis suggested that L-arginine is more effective in reducing infectious complications than control group (OR 0.40; 95% CI 0.17, 0.95; p<0.05). The heterogeneity of infectious complications (I^2=0%, p=0.94, χ^2=0.39) was acceptable, therefore, we used the fixed-effects model to analyze the data, in which the reduced incidence of infectious complications in the L-arginine group as compared with control group was significant (Figure 7).

Length of hospital stay

Three studies[19,21,23] with 85 subjects mentioned the length of hospital stay. I^2 between studies was 2% (p=0.36; χ^2=2.04), thus a fixed-effects model was used. There

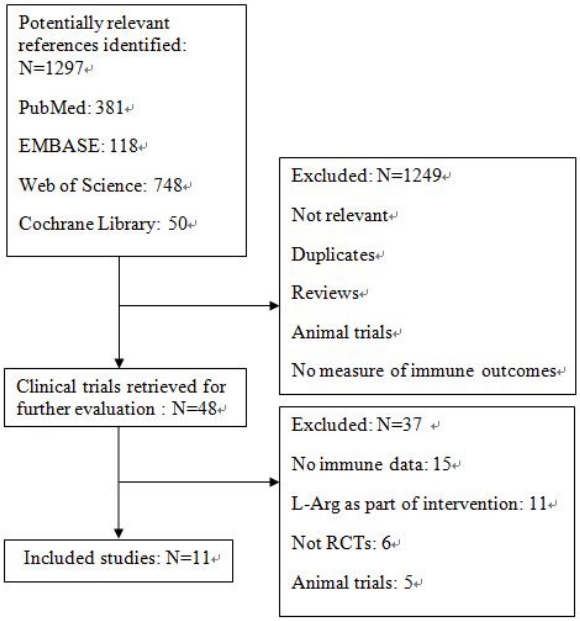

Figure 1. Flow diagram of trial selection process resulting from systematic search

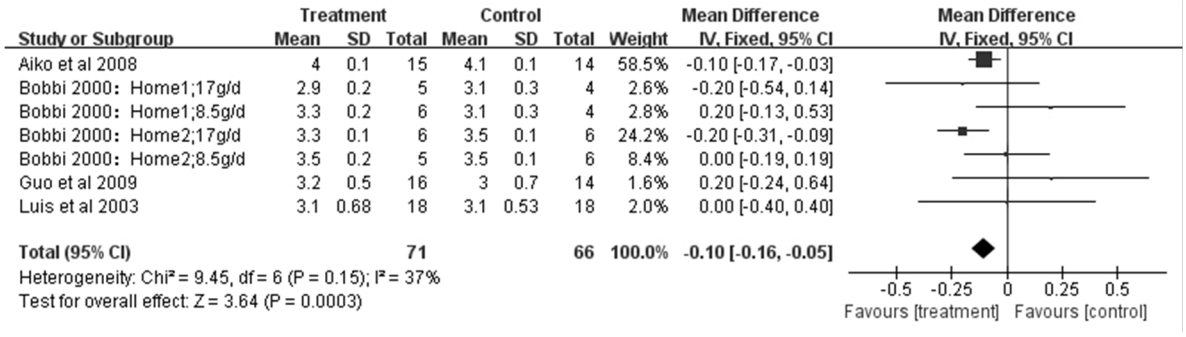

Figure 2. Forest plot of serum albumin between treatment and control group: fixed-effects model

Table 1. Characteristics of the trials included in the meta-analysis, by year of publication

Author	Year	Country	Type of diseases	Age (y)	Sex (M/F)	Type of nutrition support[†]	No. of subjects (treatment/control)	Daily dose of arginine (g)	Duration (d)	Design[‡]	Study-quality score
Daly et al [24]	1988	USA	Gastrointestinal malignancies	52-74	24/6	EN	30 (16/14)	25	7	R,DB,P	4
Bobbi et al [22]	2000	USA	Pressure ulcers	72-92	10/22	EN	32 (11,8.5g/d;11,17g/d;10)	8.5/17	28	R,DB,P	5
Schuerenet al [23]	2001	USA	Head and neck cancer	59±12	19/13	EN	32 (17/15)	12.5	9	R,DB,P	5
Barbara et al [20]	2002	USA	HIV/AIDS	18-64	9/2	EN	11 (6/5)	19.6	14	R,DB,PC	5
Luis et al [27]	2003	Spain	Head and neck cancer	59.6±10.9	2/34	EN	36 (18/18)	12.5	20	R,DB,PC	5
George et al [25]	2004	Israel	Unstable angina undergoing angioplasty	59-72	23/6	EN	29 (13/16)	6	30	R,P	3
Betty et al [21]	2005	USA	ISS[§] of 20 or greater	18-65	17/7	EN	24 (13/11)	30	14	R,DB,PC	5
Moriguti et al [28]	2005	Brazil	Older people with vaccination against streptococcus pneumoniae	60-91	13/16	EN	29 (15/14)	15	28	R,P	3
Zhou et al [29]	2007	China	Hepatocellular carcinoma	31-77	38/18	TPN	39 (21/18)	25	6	R,B,P	4
Aiko et al [19]	2008	Japan	Esophageal cancer	58-66	26/3	EN	29 (15/14)	0.2	7	R,P	3
Guo et al [26]	2009	China	Burns	30-52	21/9	EN	30 (16/14)	8.5	14	R,B,P	4

[†]EN: enteral nutrition; TPN: total parenteral nutrition. [‡]B: blind; DB: double-blind; P: Parallel; PC: placebo-controlled; R: randomized. [§]ISS: Injury Severity Score.

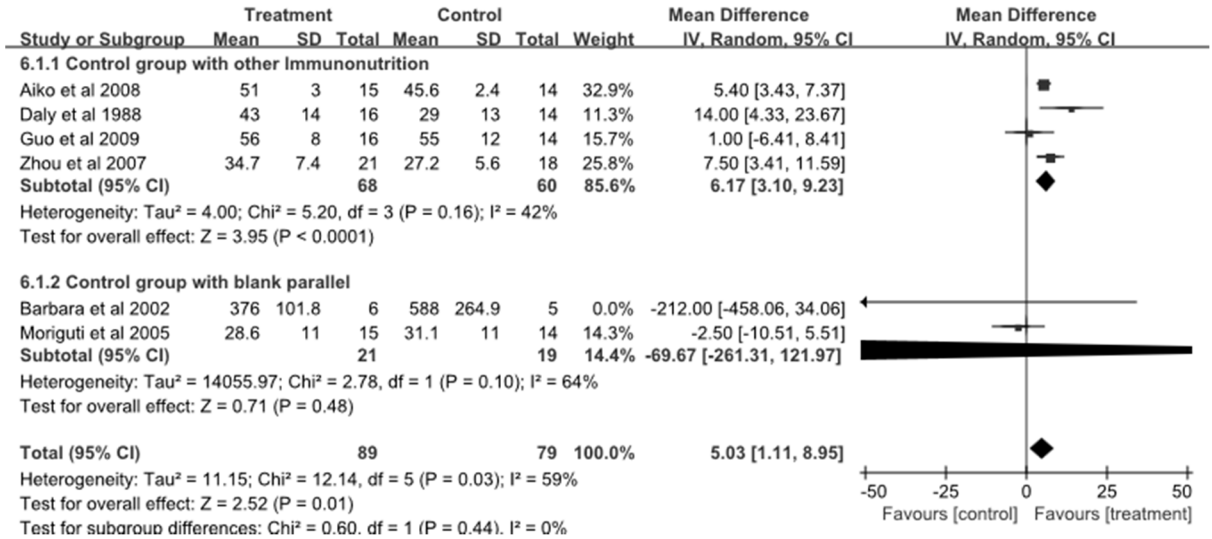

Figure 3. Forest plot of change of $CD4^+$ T-cell between treatment and control group: subgroup analysis with random-effects model

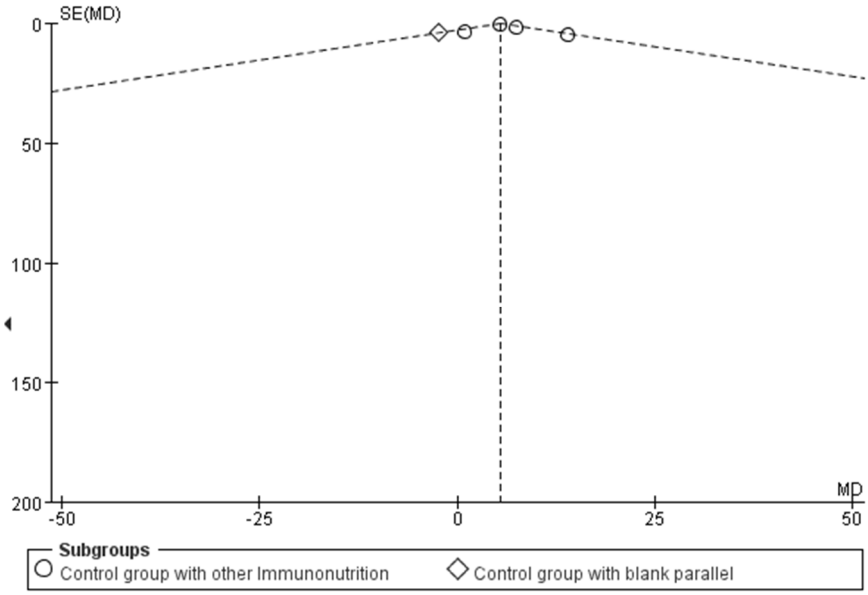

Figure 4. Funnel plot of studies mentioned change of $CD4^+$ T-cell between treatment and control group. Dotted lines are pseudo 95% CIs. The studies were mainly symmetrically distributed at the top of the plot. This indicates studies mentioned change of $CD4^+$ T-cell data rarely had publication bias.

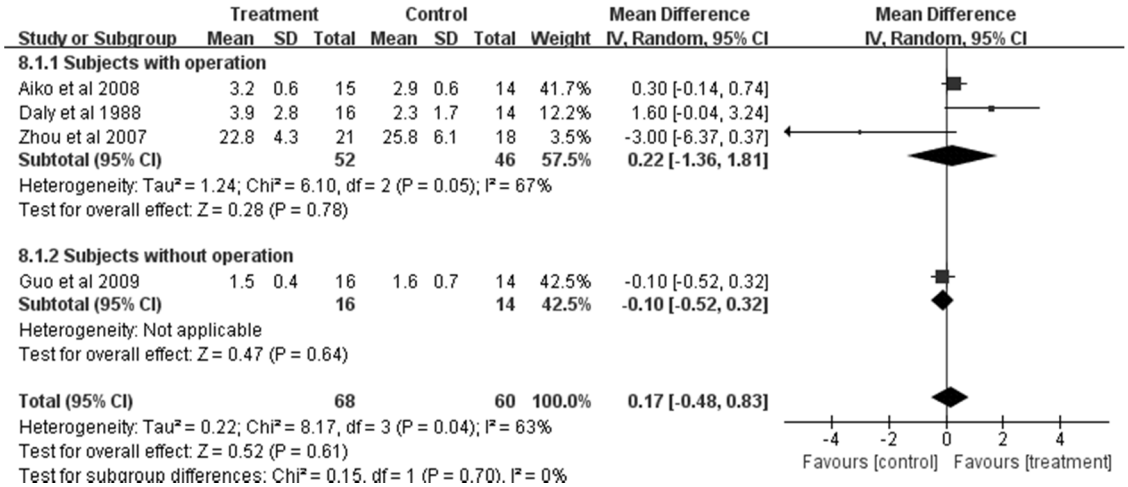

Figure 5. Forest plot of studies mentioned change of CD4/CD8 ratio between treatment and control group: subgroup analysis with random-effects model

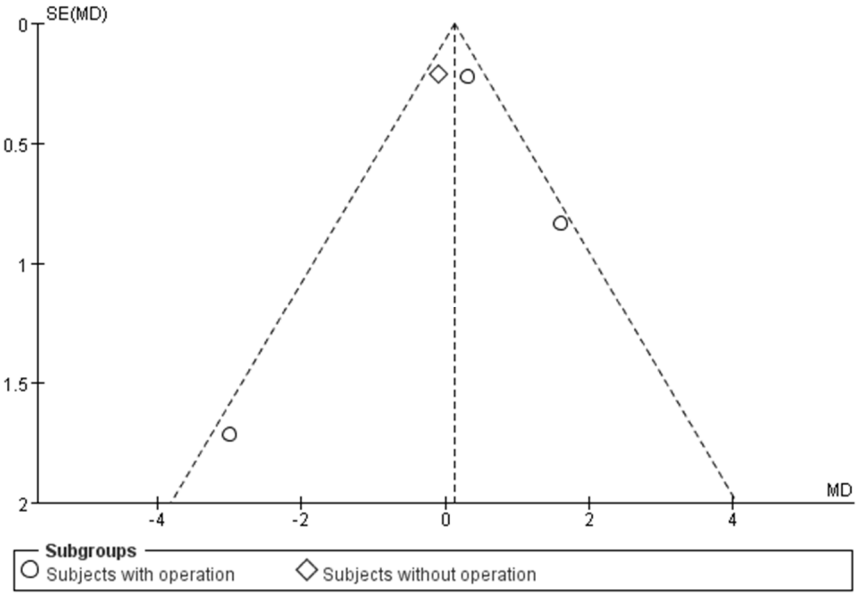

Figure 6. Funnel plot of studies mentioned change of CD4/CD8 ratio between treatment and control group. Dotted lines are pseudo 95% CIs. The asymmetry funnel plot suggested possible publication bias existed between studies mentioned change of CD4/CD8 ratio, which was associated with the significant heterogeneity.

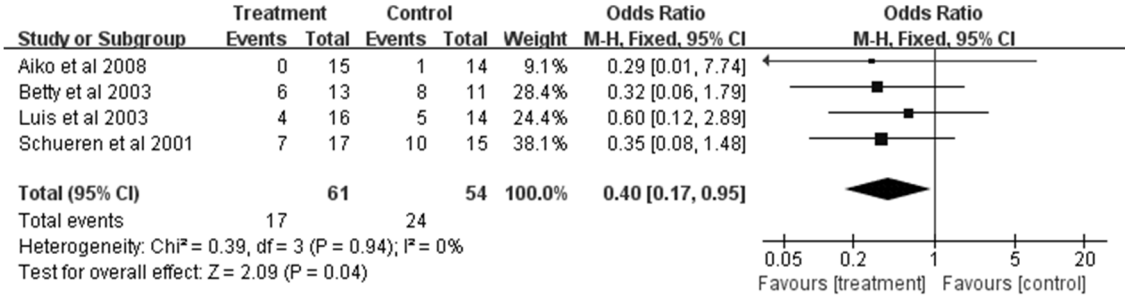

Figure 7. Forest plot of infectious complications between treatment and control group: fixed-effects model. M-H: Mantel-Haenszel test.

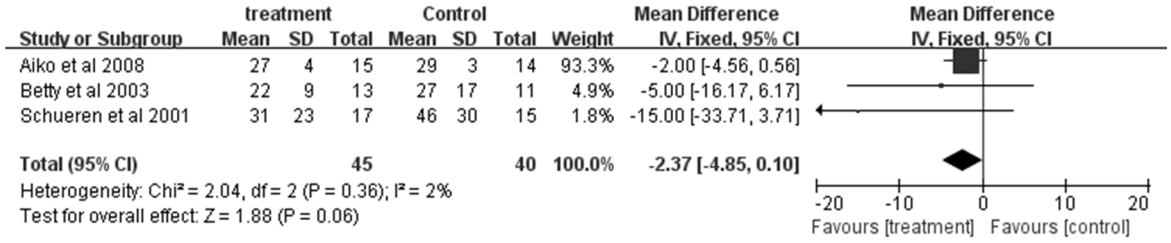

Figure 8. Forest plot of length of hospital stay between nutrition support group and control group: fixed-effects model

was no statistically significant difference between the L-arginine and control group in shortening the length of hospital stay than control group (MD -2.37; 95% CI -4.85, 0.10; $p>0.05$) (Figure 8).

DISCUSSION

Arginine-enhancing nutrition formulas have been found to be beneficial in animal and human trials.[30-34] There is little evidence, however, that arginine is responsible for these beneficial effects since the immune-enhancing diets contained other pharmacologically active components (eg omega 3 free fatty acids, RNAs, antioxidant vitamins). As one of semi-essential amino acids, L-arginine is synthesized by endothelial cells and excreted inurine.[35] In clinical studies, L-arginine supplementation enhanced nitrogen retention and protein synthesis in animals and in healthy human subjects, performing an active part in boosting immune function,[36-38] yet its basic mechanism of immune regulation remains poorly characterized. Although the metabolic fates of arginine are complex, the two major pathways involve the production of nitric oxide (NO) by nitric oxide synthase (NOS), and the production of ornithine by the enzyme arginase.[21] Studies suggested that L-arginine might be effective through the nitric oxide pathway.[39] Three isoenzymes, known as nitric oxide synthases (NOSs), produce nitric oxide: endothelial (eNOS), neuronal (nNOS), and inducible (iNOS). Of the three enzymes, nNOS and eNOS are calcium dependent;

iNOS is calcium independent and is produced in response to cytokines and endotoxin signals.[40] Once induced, iNOS produces high levels of nitric oxide. Recently, Mao et al identified NO as a critical negative regulator of the NLRP3 inflammasome via the stabilization of mitochondria.[41] Moreover, studies have shown that NO can function as a double-edged sword on the immune system and the doses of the NO donating compounds are prime determinants of its effects in vivo.[25,42] Low doses of NO could improve tissue blood supply, reduce platelet adhesion, inhibit the inflammatory response, promote protein synthesis, accelerate wound healing and provide other beneficial effects. While high doses of NO might stimulate immune cells, they might at the same time induce a large number of inflammatory mediators and free radicals, and promote the inflammatory response, which in turn might aggravate tissue trauma. In addition, Ogilvie et al[43] showed that L-Arg could increase tumour cells from the G0 period to S period and different doses of L-Arg had different effects on cancer cells. Therefore, it is important to demonstrate whether L-arginine is effective in systemic immunity.

If the Th1-type cytokines (such as TNF-α, IL-1β and IFN-γ) secretion had a dominant advantage, then the iNOS activity predominated in the body; while Th2-type cytokines (such as IL-4, IL-10 and TGF-β1) would have a significant role in inducing activity of arginase.[44-46] In this meta-analysis, data of effect of L-arginine on immune function were extracted and analyzed, including serum albumin, change of $CD4^+$ T-cell and CD4/CD8 ratio, infectious complications, and length of hospital stay. Interestingly, the analysis showed the L-arginine supplement group had a significant change in the $CD4^+$ T-cell proliferation, however, the CD4/CD8 ratio was not statistically significant between the two groups. There was a significant heterogeneity among the included trials. Although we made a subgroup analysis, the total heterogeneity could not be eliminated. The asymmetry funnel plot suggested possible publication bias between the included trials. Furthermore, incidence of infectious complications was lower in the L-arginine group than control group with statistical significance, which proved the active effect of L-arginine on immune function in a sense. We have shown that patients with L-arginine supplementation had a shorter length of hospital stay than control, however, this was without statistical significance. This could have occurred on account of critical illness among the selected subjects,[19,21,23] which would need further verification in large-sample, multicenter RCTs.

The present meta-analysis has limitations. First, the 11 included trials all mentioned randomization and parallel control, but did mention blinding, which resulted in some trials' Jadad scoring relatively lower. Second, the sample sizes of individual trials were fairly small, which limited the capacity of randomization to minimize the potential influences of confounding factors. Third, among all the studies, the intervention methods were complex, including administration routes, type of nutrition support, duration and dosages. Fourth, the Jadad score of some trials[19,25,28] was only 3 but the total number of enrolled subjects was large, which would create uncertainty bias in this particular meta-analysis. Fifth, the parameter evaluations were different with each study making it difficult to review the required information.

In conclusion, L-arginine supplementation provides some improvements in immune function, but larger samples and multicenter RCTs are required for verification to offer further evidence of its clinical application.

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AUTHOR DISCLOSURES

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Review Article

Effect of L-arginine on immune function: a meta-analysis

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L-精氨酸对免疫功能的影响：一项 meta 分析

L-精氨酸通过影响机体免疫应答和炎症反应在免疫调节中发挥重要作用。本 meta 分析对补充 L-精氨酸是否可以改善机体免疫功能的结果进行了评估，同时对补充 L-精氨酸的安全性进行了评价。本文检索了四个数据库（PubMed, EMBASE , Web of Science, the Cochrane Library）中自 1966 至 2013 年 9 月发表的有关补充 L-精氨酸对免疫功能影响的所有随机对照试验。按照 Jadad 评分量表对纳入的随机对照研究进行方法学质量评定，并根据异质性检验的结果，选择使用固定或随机效应模型。最终 11 项试验（包括 321 名患者）被纳入本次研究。Meta 分析结果显示，与对照组相比，L-精氨酸组 $CD4^+$ T 细胞的增殖显著增加（MD 5.03; 95% CI 1.11, 8.95; $p<0.05$），且感染并发症的发生率降低（OR 0.40; 95% CI 0.17, 0.95; $p<0.05$）。

关键词：L-精氨酸、一氧化氮、免疫、细胞因子、meta 分析