Review Article

Does Alpha-lipoic Acid Supplement Regulate Blood Pressure? A Systematic Review of Randomized, Double-blind Placebo-controlled Clinical Trials

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Abstract

Although several animal and human studies have investigated the effect of alpha-lipoic acid (ALA) on blood pressure (BP), these findings are inconsistent. This systematic review of randomized clinical trials was conducted to summarize the evidence on the effect of ALA on BP. PubMed, SCOPUS, and Google Scholar databases were searched based on MESH term ("Thioctic acid" in combination with "Hypertension" and "Blood pressure") to identify related papers published up to December 2015. We summarized the results of the relevant studies in this review. In total, nine studies included in this review, seven parallel-designed trials and two crossover-designed trials. The results of parallel-designed studies are inconsistent. Five studies indicate no significant effects for ALA supplementation on BP, but two trials show effects on BP. Unlike parallel-designed trials, two crossover-designed trials have shown similar results and both report no effect for ALA on BP. Several studies investigated the effect of ALA on BP. Most of the papers show no significant effect for supplementation and the studies have shown that associations are limited. However, these findings are limited and there is a need for further and more accurate researches to be clarified.

Keywords: *Alpha-lipoic acid, diastolic blood pressure, hypertension, systolic blood pressure, thioctic acid*

Introduction

Hypertension as a noncommunicable disease is one of the major health problems worldwide.[1,2] On average, about 1 in 3 adults in the developing countries is suffering from high blood pressure (BP).[3] High BP is estimated to cause 6% of deaths worldwide.[4] People with high BP are at risk for stroke, heart disease, and kidney failure.[5-8] Clinical and experimental evidence have shown that an increased production of reactive oxygen species is related to certain diseases of the cardiovascular system including high BP.[9] Oral supplementation with antioxidants may be an inexpensive and useful alternative treatment for high BP.[10-12]

Alpha-lipoic acid (ALA) or thioctic acid is an eight-carbon, sulfur-containing compound. It works as a cofactor in the multienzyme complexes that are responsible for the oxidative decarboxylation of α-ketoacids.[13] A general agreement exists about the antioxidant properties of ALA, which is thought to function by clearing free radicals directly, chelating metallic ions, enhancing intracellular glutathione (GSH), and activating endogenous antioxidant systems.[14,15] Besides the antioxidant properties of ALA, nitric oxide synthesis can be increased by ALA, which may improve endothelial function.[16] Several animal[17-19] and human[20-22] studies investigated the effect of ALA on BP and some introduced it as a potential BP regulator. To the best of our knowledge, there is no systematic review in this field; moreover, the results of studies are contradictory. Therefore, we scrutinize the issue in this study to clarify unknown aspects.

Methods

We performed a systematic review of randomized, double-blind, placebo-controlled clinical trials, which evaluated the effect of ALA on BP.

Search strategy

A systematic search for relevant publications was done using PubMed, SCOPUS, and Google Scholar databases.

How to cite this article: Mohammadi V, Dehghani S, Askari G. Does alpha-lipoic acid supplement regulate blood pressure? A systematic review of randomized, double-blind placebo-controlled clinical trials. Int J Prev Med 2017;8:33.

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Access this article online

Website: www.ijpvmjournal.net/www.ijpm.ir

DOI: 10.4103/2008-7802.206138

Quick Response Code:

Two authors (Vida Mohammadi and Sirous Dehghani) independently searched English and non-English papers published up to December 2015 using "Lipoic acid," "Thioctic acid" in combination with "Hypertension" and "Blood pressure."

We found 313 papers, but after reading the titles and abstracts, some of them were excluded based on our exclusion criteria: Investigating molecular and biochemical aspects or animal studies, open-label, single-blind, single group, or nonrandomized trials. Eligible studies were scanned based on their title, abstract, and their major aims in the first step and related studies were assessed based on their full texts. We also checked references of related studies to extract relevant studies. Finally, we selected nine articles, which had our inclusion criteria (randomized, double-blind, placebo-controlled clinical trials which investigated the effect of lipoic acid on BP) for systematic review. Figure 1 shows the pathway we went through for selecting final articles.

Results

In total, nine studies included in the present review; seven with the parallel and two with the crossover design. The articles, reviewed in this paper, are summarized in Table 1.

Parallel-designed studies

Mohammadi *et al*.[20] assessed the effect of ALA supplementation on systolic blood pressure (SBP) and diastolic blood pressure (DBP) in male patients with chronic spinal cord injury. They prescribed 600 mg ALA for 12 weeks and then compared within and between groups' changes. A significant reduction was observed within ALA group and between groups' differences were significant for both SBP and DBP. In another study,[23] on healthy women, 0.3 g/day ALA for 10 weeks, made no significant difference between or within groups. In 2011, Koh *et al*.[24] investigated the effects of 20-week 1800 and 1200 mg ALA supplementation on BP in an obese or overweight individual with hypertension, diabetes mellitus, or hypercholesterolemia and reported no significant effect for supplementation with both doses. Lukaszuk *et al*.[25] in a trial on twenty type 2 diabetic patients assessed the effect of 600 mg R-lipoic acid for 91 days. They found no differences between groups for SBP and DBP.

In another parallel-designed trial, the effect of 300 mg ALA supplementation was tested in type 2 diabetic patients by Mazloom *et al*.[22] They found a significant reduction in SBP and DBP within ALA group after 8 weeks intervention. Sola *et al*.[26] in 2004 reported that 4-week prescription of 300 mg/day ALA plus irbesartan cannot cause a significant reduction in BP compared with control group (irbesartan + placebo) in metabolic syndrome participants. In a randomized, double-blind placebo-controlled multicenter trial, noninsulin-dependent diabetes mellitus patients were randomly divided into two groups, receiving a daily oral dose of 800 mg ALA (n = 39) or placebo (n = 34) for 4 months. No significant difference in SBP and DBP between or within groups was observed.[27]

In general, the results of parallel-designed studies are inconsistent. Five studies indicate no significant effects for ALA supplementation on BP,[23-27] but two trials on chronic

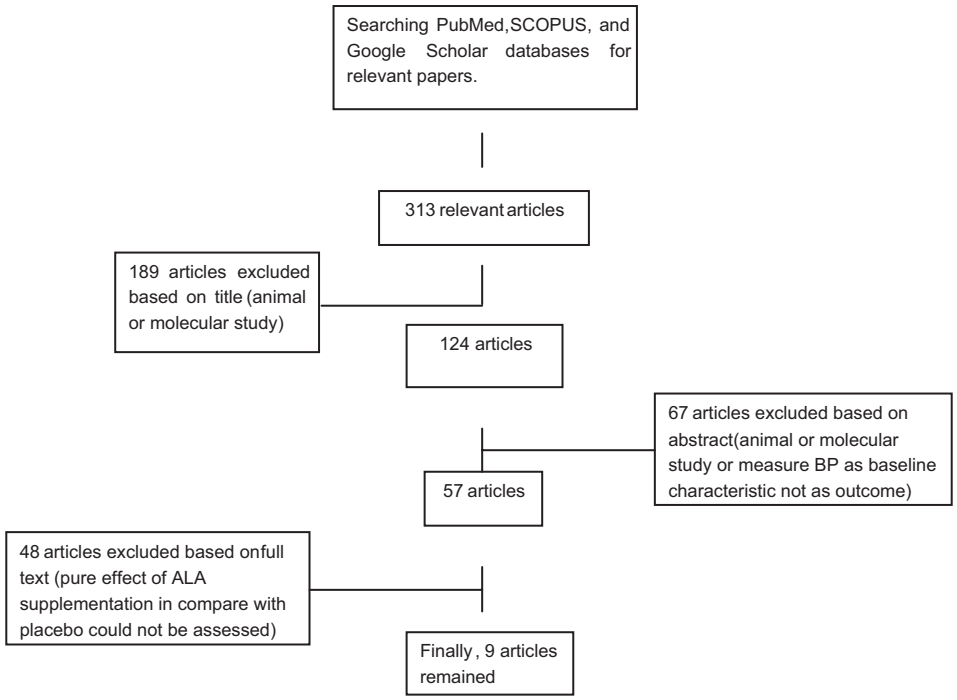

Figure 1: A summary of how articles have been selected. ALA=Alpha-lipoic acid, BP=Blood

Table 1: Characteristics of eligible randomized, double-blind placebo-controlled clinical trials included in this review

First author/year	Study design	Sample size (male: female)	Study intervention duration	ALA dose	Participants note (intervention: placebo)	Participants note	Main findings
Mohammadi/2015[20]	Parallel	58 (58:0)	12 weeks	600 mg	28:30	Chronic spinal cord injury	Significant reduction in SBP and DBP within ALA group and between two groups
Huerta/2015[23]	Parallel	42 (0:42)	10 weeks	0.3 g	20:22	Overall healthy	No significant difference between or within groups
Rahman/2012[28]	Crossover	28 (NM)	8 weeks A 4-week washout	600 mg	28:28	T2DM with Stage I hypertension	No significant difference between groups
Koh/2011[24]	Parallel	228 (NM)	20 weeks	1800 or 1200 mg	82:73:73	BMI ≥30 or 27< BMI<30 plus hypertension, diabetes mellitus, or hypercholesterolemia	No significant difference between groups
Huang/2011[29]	Crossover	103 (63:40)	8 weeks A 4-week washout	1200 mg	103:103	Overweight/obese	No significant difference between groups
Lukaszuk/2009[25]	Parallel	20 (10:10)	91 days	600 mg R-lipoic acid	13:7	Type 2 diabetic	No significant difference between groups
Mazloom/2009[22]	Parallel	57 (NM)	8 weeks	300 mg	29:28	T2DM	Significant reduction in SBP and DBP within ALA group
Sola/2005[26]	Parallel	29 (11:18)	4 weeks	300 mg	15:14	Metabolic syndrome	No significant changes in blood pressure were noted in any of the study groups
Ziegler/1997[27]	Parallel	56 (NM)	4 months	800 mg	29:27	NIDDM	No significant difference between or within groups

BP=Blood pressure, SBP=Systolic blood pressure, DBP=Diastolic blood pressure, T2DM=Type 2 diabetes mellitus, BMI=Body mass index, NIDDM=Noninsulin-dependent diabetes mellitus, NM=Not mentioned, ALA=Alpha-lipoic acid

spinal cord injury males[20] and type 2 diabetic patients[22] reported significant effects for this antioxidant on both SBP and DBPs.

Crossover-designed studies

Rahman *et al*.,[28] in a crossover manner, evaluated the effects of quinapril plus 600 mg ALA or quinapril plus placebo in type 2 diabetes mellitus with Stage I hypertension. Intervention duration in each phase was 8 weeks and washout period was for a week in this study. Researchers reported no additional effects for ALA on SBP and DBP. In another study by Huang *et al*.,[29] no significant effects were observed for 1200 mg/day ALA on SBP and DBP in overweight and obese individuals. This study in intervention duration in each phase and washout period is like Rahman's study.

Unlike parallel-designed studies, these two crossover-designed studies have shown similar results and both report no effect for ALA supplementation on BP.

Discussion

In this systematic review of randomized, double-blind placebo-controlled clinical trials, we investigated the effect of ALA supplementation on BP. In this regard, we systematically reviewed the related parallel- and

crossover-designed trials. Based on the results of most of the papers, we concluded that ALA supplementation could not show a significant effect on BP.

Based on scientific evidence, ALA is a powerful antioxidant with both aqueous and lipid solubility and performance characteristics.[13,14] In addition, ALA can increase nitric oxide production and improve endothelial function, therefore affects BP.[21] Mohammadi *et al*.,[20] in their study on chronic spinal cord injury patients, reported a significant reduction in SBP and DBP within ALA group and in comparison with placebo. These findings can be explained by rising effect of the supplement on reduced GSH levels in tissues GSH peroxidase activity and nitric oxide production in endothelial cells.[13,14,30] Authors mentioned that a possible reason for the difference between their result and the other studies could be due to the inherent physical differences associated with these study participants.[20] Results of the other study,[22] with a significant effect of ALA on BP, can be explained through mentioned mechanism.

In contrast with cellular and molecular evidence, most eligible studies in this review could not observe a significant change in BP. This is important to take the limitations of these studies into account, including the sample size, the short period of the intervention, and low doses of ALA in some studies. The longest-term study has 20-week intervention duration,[24] and the shortest period of study is four weeks. ALA doses varied from 300 to 1800 mg/day. Target groups are diverse. In addition to all this, BP was not a main purpose in most of the articles[23,24] and authors did not describe their findings in the discussion. All of these can make it difficult to draw a conclusion. It seems a meta-analysis is needed for interpreting findings.

Acknowledgments

We thank all personnel of the Food Security Research Center.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Received: 10 Jan 16 **Accepted:** 27 Sep 16
Published: 11 May 17

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