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Review Article

The Use of L-arginine Supplements for Cardiovascular Disease and Related Disorders is Questionable

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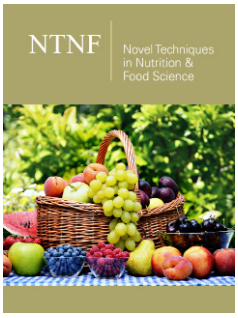

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Abstract

Purpose: L-arginine supplementation has been tested as a treatment for various conditions related to cardiovascular disease, but with mixed results. This article reviews the research findings related to the effects of L-arginine supplementation on the cardiovascular system of individuals with cardiovascular disease and related disorders.

Design/methodology/approach: Research and review articles were identified through the search engines Google Scholar, PubMed and ScienceDirect. Main key words included L-arginine, supplementation, nitric oxide, cardiovascular disease, hypertension, endothelia dysfunction, atherosclerosis, and exercise capacity.

Findings: Supplementation of L-arginine for short periods of time has been found useful in treating cardiovascular diseases including hypertension, atherosclerosis, coronary heart disease, heart failure, peripheral vascular disease and type 2 diabetes, but efficacy requires very high daily dosages ranging from 6 to 24g per day. However, prolonged supplementation with L-arginine generally has not been found to effectively treat cardiovascular related abnormalities, and under some conditions it has been found to be harmful.

Originality: This review provides insight into the efficacy of using L-arginine as a treatment for cardiovascular disease and related abnormalities. While short-term supplementation appears to provide some beneficial effects, its long-term use is highly questionable and could have adverse consequences. Therefore, careful consideration should be given before using L-arginine as a supplement to treat cardiovascular related diseases.

Keywords: L-arginine; Nitric oxide; Cardiovascular disease; Atherosclerosis; Endothelial dysfunction; Hypertension; Exercise

Introduction

L-Arginine is a proteinogenic, conditionally essential amino acid. It is involved in various metabolic pathways including the synthesis of creatine, L-ornithine, L-glutamate, and polyamines, and protein degradation by the ubiquitin-proteasome pathway [1]. One of its most important functions, however, is serving as substrate for the production of nitric oxide (NO) via the nitric oxide synthases (NOS) [2]. There are three isoforms of the NOS enzyme with nNOS or NOS-1, the isoform found in neuronal and muscle tissue, the first to be identified. The second isoform identified was iNOS or NOS-2. This isoform is inducible in a wide range of cells and tissues, most notably in immune cell. The third isoform identified was eNOS or NOS-3, which was found in vascular endothelial cells. Although there are some structural differences among these NOS enzymes, in their active form they are homodimeric and require the coenzymes NADPH, FAD, and FMN as well as heme iron, tetrahydrobiopterin, and oxygen [3].

The importance of NO cannot be overstated. However, research indicates that NOS activity declines by approximately 50% from ages 20 to 45 [4]. This decline has been associated with many metabolic disorders including, hypertension, cardiovascular disease, type 2 diabetes, kidney complications and sarcopenia to name but a few [5,6]. Because of its significant influence throughout the body, means of increasing NO production have been investigated including increasing the availability of its substrate, L-arginine.

The research related to increasing NO secretion by L-arginine supplementation has primarily focused on improving cardiovascular health and skeletal muscle function and performance. Research suggests that infusion or short-term oral supplementation of L-arginine might be useful in the treatment of hypertension, endothelial dysfunction, coronary heart disease, heart failure, and peripheral vascular disease [7-10]. However, not all research studies have demonstrated positive effects of L-arginine supplementation. In fact, a number of studies, particularly long-term studies, have demonstrated no beneficial effect of L-arginine supplementation for patient populations with underlying cardiovascular abnormalities, and some studies have actually found that L-arginine supplementation can cause significant adverse events.

This article is a review of the research findings related to the effects of L-arginine supplementation on the cardiovascular system of individuals with cardiovascular disease and related disorders. While research findings suggest that high dosages of L-arginine supplementation for short periods of time might be beneficial, it appears that long-term supplementation is likely to be counterproductive and may have severe consequences.

Methods

Research and review articles were identified and ascertained from the search engines Google Scholar, PubMed and ScienceDirect. Keywords that were used in the search included L-arginine, supplementation, nitric oxide, cardiovascular disease, hypertension, endothelia dysfunction, atherosclerosis and exercise. With few exceptions, research articles reviewed were limited to human clinical trials or meta-analyses.

Effective L-arginine Supplementation

Positive effects of infusion or oral supplementation of L-arginine have been found in a number of clinical conditions including coronary artery disease, hypertension, heart failure, hypercholesterolemia, peripheral vascular disease and type 2 diabetes [7-11]. Even very high oral doses of L-arginine can result in vasodilation in young, healthy individuals [12], and improve flow-mediated endothelium-dependent vasodilation of healthy middle-aged and older populations [13].

Endothelial function

Numerous studies have been conducted to investigate the effects of L-arginine supplementation on endothelial function in individuals with various cardiovascular complications. For example, Adams and colleagues [7] investigated the effects of L-arginine in premature coronary artery disease patients. The patients, with an average age of 41 years, were provided 21g of L-arginine per day for 3 days. After treatment it was found that flow-mediated vasodilation was significantly improved in the brachial artery, and monocyte adhesion improved. Likewise, Clarkson et al. [11] found that hypercholesterolemic patients who received 7g of L-arginine three times per day for 4 weeks had improved endothelium-dependent forearm blood flow and dilation of the conduit arteries. In a long-term study, Lerman et al. [14] reported that after receiving 9g of L-arginine per day for 6 months, coronary artery disease patients showed substantial improvement in coronary artery response to acetylcholine infusion. Lerman et al. [14] substantiated this finding, but also observed that the improvement in coronary artery responsiveness was related to a decrease in plasma endothelin-1 levels, a strong vasoconstrictor.

Platelet and monocyte regulation

Damage to the endothelial lining of the arteries and arterioles is primarily responsible for abnormal vascular reactivity. Endothelial dysfunction originates with insufficient control over anticoagulant substances and vascular inflammation. With a decline in eNOS activity comes a decline in regulation of platelet function, increase in monocyte adhesion and migration, smooth muscle cell proliferation and advancement of atherosclerosis [15,16]. Positive outcomes related to control over platelets and monocytes have been noted following supplementation with L-arginine [17,18]. Wolf et al. [18] found that L-arginine supplementation normalized platelet aggregation in individuals who were hypercholesterolemic. Asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide synthase, is typically elevated in hypercholesterolemic patients. In this regard, Chan et al. [19] found that monocyte adhesiveness in this patient population was inversely correlated with the plasma L-arginine/ADMA ratio. Furthermore, oral administration of L-arginine for 12 weeks normalized the plasma L-arginine/ADMA ratio and lessened monocyte adhesiveness.

Hypertension

NO is of considerable importance to blood pressure regulation and limiting NO production due to a decline in eNOS activity has been linked to atypical blood pressure regulation. Numerous studies have demonstrated that blood pressures of hypertensive and pre-hypertensive individuals can be substantially reduced following elevations in NO by acute and chronic inorganic nitrate supplementation [20-23]. Likewise, L-arginine supplementation has been found to reduce blood pressure. L-arginine appears to be effective in lowering the blood pressure of patients with various metabolic disorders. For example, Facchinetti and colleagues [24] found that infusion of 20g/500ml daily for 5 day and then 4g per day orally for 2 weeks significantly lowered both systolic and diastolic blood pressure of patients with gestational hypertension. Similarly, women with polycystic ovary syndrome and elevated blood pressure due to their oral contraceptive were found to respond well to L-arginine supplementation [25]. This was demonstrated with a normalization of blood pressure and improved endothelium-dependent vasodilation. L-arginine supplementation was also found to improve the blood pressure and insulin resistance of type 2 diabetics [26]. Patients were placed on a hypocaloric diet and then randomly divided into two groups. One group received a placebo for 2 months.

The second group received a placebo for the first month and then L-arginine (3g three times per day) the second month. Systolic blood pressure remained unchanged in the placebo group, whereas in the L-arginine group it fell from 128±4 to 110±3mmHg, a 14% decline. Lucotti et al. [27] also found a substantial improvement in the blood pressure of type 2 diabetics when provided L-arginine

supplements (8.3g per day) during 21 days of a weight management program. In addition, four weeks of L-arginine supplementation was found to improve the arginine/ADMA ratio and lower the blood pressure of hypertensive patients with micro-vascular angina [10], and the blood pressure of primary mild hypertensive patients [28]. Finally, from the cumulative results of a meta-analysis, it was concluded that L-arginine supplementation lowers systolic and diastolic blood pressure by approximately 5mmHg and 2mmHg, respectively. However, it should be noted that the majority of the studies evaluated did not find blood pressure significantly lowered by L-arginine supplementation, although it was reduced to some degree in most of the studies [29].

Cardiovascular disease and exercise capacity

Raising NO levels by pharmacological or nutrient supplementation has been found to have a profound positive effect on exercise capacity in healthy individuals and those with cardiovascular disease. Therefore, it is not surprising that elevating endogenous NO production with L-arginine supplementation has been found to improve exercise capacity in coronary disease patients, and those with healed myocardial infarction [30,31]. Moreover, oral L-arginine supplementation (8g/d) was found to improve endothelium-dependent vasodilation in patients with heart failure, and this beneficial effect was additive with exercise training [32]. In addition, L-arginine supplementation has been found to produce greater pain-free exercise and total walking distance in peripheral vascular disease patients [33] and improve forearm blood flow, walking distance, and subjective symptoms in patients with chronic heart failure [34]. More recently, Doutreleau et al. [31] reported that chronic supplementation of L-arginine (6g/d twice a day for 6 weeks) delayed the ventilator threshold and reduced blood lactate levels during exercise of heart failure patients suggesting supplementation could result in a great aerobic work capacity.

Ineffective L-arginine Supplementation

As presented, there are a number of research studies that suggest L-arginine supplementation could be of benefit to individuals with cardiovascular disease or heart failure. However, not all research studies support these findings. In fact, there are numerous research studies that have found no benefit of L-arginine supplementation as it relates to cardiovascular disease, myocardial function or exercise capacity. More importantly, several of these studies indicated that the long-term supplementation of L-arginine could have significant harmful effects.

Endothelial function

Schulman et al. [35] started evaluation of 153 patients with stable coronary artery disease at 3 to 21 days after their first myocardial infarction. Patients were randomly assigned to receive 3g of L-arginine 3 times per day for 6 months or a placebo. Vascular function was not improved by L-arginine supplementation. Arterial compliance, pulse pressure, and pulse wave velocity were similar between placebo and L-arginine treated patients. The 6-month vascular properties of patients 60 years or older were also similar between L-arginine and placebo groups. Blum et al. [36] also reported that adding 9g of L-arginine supplementation per day to standard anti-ischemic therapy had no effect on levels of NO, flow-mediated brachial artery dilation or blood flow in 30 patients with stable coronary heart disease.

In a study to determine the effect of 2 weeks of L-arginine supplementation on the plasma L-arginine/ADMA ratio in men with stable angina, L-arginine supplementation increased the ratio by 60%. However, despite the increase in the L-arginine/ADMA ratio there was no reduction in oxidative stress or improvement in endothelial function [37]. Similarly, L-arginine infusion did not augment acetylcholine-mediated forearm blood flow in hypertensive participants [38] or improve the vascular reactivity of patients with peripheral artery disease after 6 months of oral supplementation [39].

Jahangi et al. [40] carried out a comprehensive evaluation of endothelial function in coronary artery disease patients after L-arginine or L-arginine plus creatine supplementation. They found that 4 days of supplementation with either supplement had no effect on brachial artery diameter, blood flow, reactive hyperemia, flow-mediated dilation, or nitroglycerin-mediated dilation. Even after adjusting for covariates such as tobacco use or previous stroke, vascular function was not improved by supplementation. Finally, in a study in which a meta-analysis was used to evaluate the effect of L-arginine supplementation in individuals with cardiovascular disease, obesity, or diabetes, L-arginine was found not to improve post-ischemia hyperemia [41].

Platelet and monocyte regulation

As previously discussed, Blum et al. [36] found that 9g of arginine per day for 28 days produced no effect on flow mediated dilation of the brachial artery, but they also found that it had little effect on the cell adhesion molecules E-selectin, intercellular adhesion molecule-1 or vascular cell adhesion molecule-1. Similar results were reported by Abdelhamed et al. [42] while studying the effects of L-arginine on patients with hypercholesterolemia. After oral supplementation of L-arginine for two weeks, there were no improvements noted in endothelial function, platelet aggregation or soluble levels of E-selectin or P-selectin. Wolf et al. [18] also evaluated platelet function in hypercholesterolemic subjects. The patients were randomized in a double-blind fashion to receive placebo or 8.4g per day of L-arginine. After 2 weeks of treatment with L-arginine, platelet reactivity was modestly reduced, but the reduction was not statistically significant.

Hypertension

Although a number of studies suggest that blood pressure can be lowered significantly with L-arginine supplementation, there are an equal number of studies that have failed to demonstrate this effect. For example, Neri et al. [43] enrolled 80 pregnant women with mild chronic hypertension and randomized them into two groups. One group received a placebo and the other group received an L-arginine supplement. After 10 to 12 weeks of treatment there was no difference in blood pressure between groups. Similar results

were also found by Adams et al. [7], who investigated the effects of L-arginine in patients with premature coronary artery disease. Using a placebo-controlled, crossover experimental design, the patients (N=10 men) were provided 7g of L-arginine 3 times per day or placebo for 3 days, with a washout period of 10 days. No changes were seen in blood pressure, endothelium-independent dilatation of the brachial artery, heart rate or fasting plasma lipid levels.

The effect of L-arginine supplementation has also been studied on the blood pressure of patients with peripheral artery disease and hypercholesterolemia. Patients with peripheral artery disease were provided 24g of L-arginine per day for 8 weeks with no improvement of either systolic or diastolic blood pressure [13]. Patients with hypercholesterolemia were provided 7g of L-arginine three times per day for 4 weeks or placebo. Although endothelium dysfunction was improved, there were no differences in blood pressure noted within or across treatment groups [11]. In a rather unique study, West et al. [44] investigated the effects of L-arginine supplementation on the blood pressure of hypercholesterolemic patients while they were under stress conditions. They provided the patients 12g of L-arginine per day for 3 weeks and found that diastolic blood pressure was significantly lowered when the subjects were under mental or physical stress, but systolic blood pressure was unaffected.

The effects of L-arginine supplementation on healthy normotensive men have also been investigated. Ast et al. [28] found that 4 weeks of supplementation with either 6g or 12g of L-arginine led to a non-significant decrease of systolic and diastolic blood pressure. Likewise, Adams et al. [17] reported that 7g of L-arginine provided 3 times per day for 3 days did not lower the blood pressure of normotensive, young, healthy men or improve endothelial-dependent dilation.

Cardiovascular disease and exercise capacity

Peripheral vascular disease significantly limits physical activity and work capacity due to limited muscle blood flow secondary to reduce NO production. Therefore, Wilson et al. [39] investigated the effects of long-term L-arginine supplementation on NO production, vascular reactivity and functional capacity in this patient population. Patients were randomly assigned to receive either 3g of L-arginine per day or placebo. Surprisingly, after 6 months of treatment, improvement in walking distance was found to be significantly better in the placebo group than the L-arginine group. Furthermore, flow-mediated dilation and systemic NO production were not improved by L-arginine supplementation.

In another study, the exercise capacity of men with obstructive coronary artery disease and stable angina were studied before and after 1 month of L-arginine supplementation (15g per day) or placebo. Symptom-limited standard Bruce protocol exercise tests were performed along with time to 1mm ST depression, and time to onset of symptoms. Improvement in exercise time was noted in both the L-arginine-supplemented and placebo groups, but there was no difference found between groups. Likewise, there were no group differences for changes in rate pressure product, time to 1mm ST depression or time to onset of symptoms [37]. These findings are supported by the study of Kanaya et al. [45], who reported that infusion of L-arginine in chronic heart disease patients had no effect on indices of exercise capacity including peak oxygen consumption, anaerobic threshold and exercise time. Similar results have also been noted in patients with hypercholesterolemia [46].

There is also little evidence that L-arginine supplementation will improve aerobic exercise endurance in healthy individuals [47,48]. For example, Sunderland et al. [48] supplemented 18 trained endurance cyclists with 6g of L-arginine twice a day for 4 weeks. Post treatment results revealed L-arginine supplementation had no effect on maximal oxygen consumption or ventilator threshold.

Adverse Effects of L-arginine Supplementation

Review of adverse events

In addition to the evidence that L-arginine supplementation may be ineffective in treatment of cardiovascular disease and heart failure, there is also evidence that prolonged use of high dosages may have negative consequences. For example, Schulman et al. [35] investigated the long-term effects of L-arginine supplementation on coronary heart disease patients starting within a few days following their first myocardial infarction. Patients (N=153) were randomly assigned to receive 3g of L-arginine three times per day or placebo. After 6 months of treatment there were 12 clinical events in the L-arginine group verses 7 in the placebo group. Clinical events included death, myocardial infarction and hospitalization for heart failure. More disturbing was the death of 6 patients in the L-arginine group compared with no deaths in the placebo group. The study was terminated after 6 months. The adverse effects of long-term L-arginine supplementation have also been noted in patients with peripheral vascular disease. Wilson et al. [39] reported that administering 3g of L-arginine 3 times per day for 6 months resulted in functional capacity being attenuated in patients receiving L-arginine. Also, neither measures of vascular function nor systemic NO production were improved by L-arginine supplementation. It was observed that plasma ornithine levels were increased with L-arginine treatment, suggesting that intestinal arginase may have been induced and caused development of tolerance to L-arginine supplementation.

Possible reasons for adverse events

There are a number of possible reasons for L-arginine supplementation to be ineffective or to cause adverse events. First, studies that have demonstrated improvements in cardiovascular function and blood pressure with L-arginine supplementation have required dosages of 6 to 24g of L-arginine per day [29,49]. Such high levels of L-arginine over time could induce increased expression of arginase, which metabolizes L-arginine to urea and ornithine [50]. Therefore, an increased expression of arginase could reduce availability of L-arginine as substrate for eNOS and reduce NO production. It has also been found that over expression of arginase due to chronic supplementation of L-arginine can accelerate endothelial cell senescence, increase adhesion molecule

expression, cause uncoupling of eNOS and lower NO production [51]. This of course can lead to a reduced vascular reactivity and propagation of atherosclerosis and coronary heart disease.

It should be noted that enhanced arginase activity has been implicated in a number of medical conditions such as endothelial dysfunction, atherosclerosis, hypertension, type 2 diabetes, and pulmonary hypertension [52-56]. Second, high L-arginine levels have been found to inhibit dimethylarginine dimethylaminohydrolase, the enzyme responsible for ADMA metabolism to L-citrulline [57]. As previously discussed, ADMA is a competitive inhibitor of eNOS. Decreasing the L-arginine/ADMA ratio lowers eNOS activity and has been associated with vascular dysfunction, reduced renal function, hypertension and heart disease [58].

Third, supplementing with high concentrations of L-arginine creates a methylation demand, resulting in an increase in L-homocysteine accumulation [59]. Hyperhomocysteinemia is associated with increased risk of coronary artery disease, atherosclerosis, hypertension and stroke [60-63]. Furthermore, hyperhomocysteinemia is associated with elevated ADMA levels owing to the ability of homocysteine to inhibit dimethylarginine dimethylaminohydrolase [64].

Fourth, cardiovascular disease, hypercholesterolemia, type 2 diabetes and other metabolic disorders can result in the uncoupling of eNOS [5,6]. This uncoupling is primarily caused by a reduction in intracellular tetrahydrobiopterin availability secondary to oxidative stress, elevated levels of homocysteine, aging and inadequate nutrition [65,66]. Tetrahydrobiopterin is a necessary cofactor involved in the eNOS reaction. When unavailable, eNOS changes its functional profile from oxidizing L-arginine and generating NO to reducing molecular oxygen to superoxide anions [51,61,65,67]. Superoxide anions can scavenge NO to form peroxynitite and also lead to the production of other reactive oxygen species [5,6]. Aside from removing NO by superoxide anion scavenging, the free radicals generated can increase oxidative stress further damaging the endothelium and creating a vicious cycle [59]. Supplementing with high concentrations of L-arginine will only exacerbate this situation.

Conclusion

The infusion or oral supplementation of L-arginine has been found to improve vascular reactivity, blood pressure, platelet and monocyte function, and exercise capacity in patients with hypertension, heart failure, peripheral vascular disease, and other metabolic complications. However, the amount of L-arginine required to be efficacious is relatively high, between 6 to 24g per day. Moreover, the durations of these studies have been limited, for the most part, to only 3 days to 6 weeks in length. Conversely, there are a number of studies that do not support the use of L-arginine supplementation for improvement in cardiovascular related diseases and indicate that under some conditions L-arginine supplementation could cause an adverse event. This is particularly true for studies of long duration.

There are several possible explanations for the ineffectiveness of prolonged, high dose supplementation of L-arginine. These include the development of tolerance to L-arginine due to over expression of arginase. Increasing the activity of arginase could rapidly metabolize L-arginine and lower its availability as substrate for eNOS. High dosages of L-arginine could also inhibit dimethylarginine dimethyaminohydrolase, the enzyme responsible for metabolizing ADMA. A reduction in ADMA metabolism could affectively decrease the L-arginine/ADMA ratio and result in eNOS inhibition. The supplementing of high concentrations of L-arginine can also increase methylation demand inadvertently raising the homocysteine level, which is associated with increased risk of developing atherosclerosis, hypertension, coronary heart disease and other cardiovascular complications.

Finally, cardiovascular disease and other metabolic disorders are associated with an uncoupling of eNOS, converting it from a NO generating enzyme to a free radical generating enzyme. Providing high concentrations of L-arginine to an uncoupled eNOS would therefore increase oxidative stress imparting more damage than repair in the vascular system. These findings bring into question the feasibility of using L-arginine supplementation long-term to treat cardiovascular disease and related conditions. Because of the possible contraindications associated with long-term use of L-arginine, it is also prudent to question its use in other nutritional supplements.

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