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## The impact of L-Arginine supplementation on disorders associated with obesity

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### Abstract

**Introduction:** L-Arginine (2-amino-5-guanidinovaleric acid) is a conditionally essential amino acid and a natural constituent of dietary proteins, serving as a precursor for the synthesis not only of proteins, urea, polyamines, proline, glutamate and creatine. This amino acid is a substrate for nitric oxide production, an endogenous messenger molecule involved in a variety of endothelium mediated physiological effects in the vascular system.

**State of knowledge:** The evidence suggests supplementation of L-Arginine may have a positive impact in conditions associated with obesity - type 2 diabetes, atherosclerosis or hypercholesterolaemia. The L-Arginine intake improves insulin sensitivity and may improve lipid profile reducing triglyceride serum levels. As a precursor for nitric oxide synthesis, a molecule involved in a variety of physiological effects in the vascular system, L-Arginine can have a positive impact on the cardiovascular system.

**Conclusions:** The evidence suggests that the L-Arginine may improve lipid profile reducing triglyceride serum levels. L-Arginine could be used as a strategy to improve endothelial function in the selected group of patients. Careful studies are necessary to assess its safety profile, determine under which conditions L-Arginine supplementation is appropriate and when it is undesirable. Attention should be focused to markers of oxidative stress and blood pressure stability.

**Keywords:** L-arginine, cardiovascular disease, metabolic disorder, insulin resistance, obesity

### Introduction

Obesity is caused by a chronic imbalance in energy metabolism, namely a greater energy intake than energy expenditure. This metabolic disorder has continued to increase worldwide at an alarming rate in the past decade and affects both adults and children, being one of the major public health problems due to its effects on morbidity, mortality, and healthcare costs.

[1]. Overweight and obesity is closely associated with many diseases. Insulin resistance, a common feature of visceral obesity, is a fundamental aspect of the aetiology of type 2 diabetes and is associated with a wide array of other pathophysiological sequelae including hypertension, hyperlipidemia and atherosclerosis [2].

Body mass index (BMI) is a universally recognized parameter for classifying obesity - The World Health Organization defines overweight as a BMI of 25.0 to 29.9 kg/m<sup>2</sup> and obesity as a BMI of  $\geq 30.0$  kg/m<sup>2</sup>. Over 1.9 billion adults worldwide were overweight, and more than 650 million adults were obese in 2016 [3]. The prevalence of obesity and the tremendous costs of its treatment necessitate the search for new alternative nutritional means. Effective methods of intervention aimed at inhibiting the development of insulin resistance and disorders of the lipid metabolism in people with adipose tissue excess are intensively sought.

L-Arginine (2-amino-5-guanidinovaleric acid) is a conditionally essential amino acid and a natural constituent of dietary proteins, serving as a precursor for the synthesis of proteins, urea, polyamines, proline, glutamate and creatine. Besides, in 1988 it was found that this amino acid is a substrate for nitric oxide production, an endogenous messenger molecule involved in a variety of endothelium mediated physiological effects in the vascular system. Nitric oxide synthase is an enzyme that converts L-arginine into nitric oxide, which functions to maintain vascular and adipocyte homeostasis [4]. Administration of L-arginine has been shown to improve endothelial function in animal models of hypercholesterolemia and atherosclerosis. Trials performed on the human population seem to support these results - Several long-term studies have been performed and found that oral administration of L-arginine can improve clinical symptoms of cardiovascular disease in man. The recognition of those links contributed to significant growth of interest in L-arginine in the treatment and prevention of cardiovascular system conditions [5].

In humans, several adipose tissue types are distributed throughout the body. Among these are white adipose tissue, which includes subcutaneous and visceral adipose tissue, and brown adipose tissue. Both types play an important role in regulating metabolism. White adipose tissue is the largest endocrine organ in the human body being able to secrete hormones as well as inflammatory molecules and having an important impact in multiple processes such as adipogenesis, metabolism and chronic inflammation [6].

Tumour necrosis factor alpha (TNF $\alpha$ ) was initially assumed to be produced by adipocytes. However, the stromo-vascular fraction of adipose tissue, including endothelial cells, macrophages and leukocytes, seems to have higher TNF $\alpha$  production than adipocytes by itself. TNF $\alpha$  is thought to increase insulin resistance and cause dyslipidemia through suppression of adiponectin production. Furthermore, TNF $\alpha$  modulates insulin receptors through inhibition of tyrosine kinase activity, decreasing their insulin sensitivity [7]. The nitric oxide generated from L-arginine by the endothelial nitric oxide synthase activity is responsible for the endothelium-dependent vasorelaxation response. Endothelial dysfunction is an early marker of atherosclerosis and is often defined as the impaired release of nitric oxide by the endothelium. Excessive activity of TNF- $\alpha$  increases this impaired endothelial function in obese patients, reduces activity of nitric oxide synthase and activates the chronic intravascular inflammatory process, which may explain accelerated progression of atherosclerosis [8]. In summary, chronically elevated concentration of TNF- $\alpha$  probably plays an important role in the complex pathogenesis of insulin resistance, diabetes and hypertension.

### **State of knowledge**

Understanding of the mechanism involved in the development of complications associated with overweight and obesity is crucial to identify new therapeutic options. Moreover, the potential benefits of the use of L-arginine are not only limited to obesity management support. The evidence suggests it may have a positive impact in other conditions associated with obesity - hypertension, type 2 diabetes, atherosclerosis or hypercholesterolaemia. Although there is a lack of research assessing the potential of L-arginine supplementation in patients treated for obesity, the available evidence about its impact seems to be promising [9].

### **Animal models**

On the basis of animal studies, L-Arginine has beneficial effects on adipocyte metabolism and has been shown to reduce weight and white fat mass while increasing brown fat and skeletal muscle mass. Such experiments are still lacking in humans.

A study performed by Clemmensen et al. investigated the effects of L-Arginine to mice on an array of physiological parameters. Experimental group of mice receiving L-arginine supplementation was maintained on a low-protein diet. During the follow-up, their body composition, appetite regulation, glucose tolerance, insulin sensitivity and energy expenditure were evaluated. A significant reduction in epididymal white adipose tissue was observed in L-Arginine supplemented mice compared with the control group. The L-Arginine supplemented animals were hyperphagic, corresponding to a highly significant decrease in feed efficiency, as body weight developed in a similar pattern in both experimental groups. Glucose homeostasis experiments revealed a major effect of L-Arginine supplementation on glucose tolerance and insulin sensitivity. Dietary L-Arginine supplementation substantially affects an array of metabolic-associated parameters including a reduction in white adipose tissue, hyperphagia, improved insulin sensitivity and increased energy expenditure in mice fed a low-protein diet [10].

Results of another pre-clinical study demonstrate that dietary arginine supplementation was highly effective in reducing the gain of major white fat pad in diet-induced obese rats. High-fat feeding induced oxidative stress in rats, compromised nitric oxide synthesis and impaired insulin action. Arginine supplementation enhanced glucose disposal, reduced serum glucose concentrations, and augmented antioxidative capacity, as reported for chemically induced diabetic rats and Zucker diabetic fatty rats - a genetically obese animal model of type II diabetes with a defect in the leptin receptor. The mass of skeletal muscle was greater in both low- and high-fat fed rats in response to arginine supplementation. Such an anabolic effect of arginine was achieved independently of changes in serum concentrations of insulin. These beneficial effects of dietary arginine supplementation can result from both improved insulin sensitivity in skeletal muscle and an increase in its mass. The results of the study demonstrated that dietary arginine supplementation reduced white fat gain, increased skeletal-muscle mass, decreased serum concentrations of glucose and triglycerides, and improved insulin sensitivity in diet-induced obese rats [11].

### **Clinical studies**

A randomised double-blind placebo-controlled study was carried out by Suliburska et al. to answer the question of whether long-term L-arginine intake can influence mineral concentrations and to evaluate the changes in insulin resistance as well as lipid plasma levels. A study was conducted on 88 obese patients (BMI  $\geq 30$  kg/m<sup>2</sup>), who were randomly assigned to receive either 9g of L-arginine three times daily or placebo, for 6 months. The dosage was chosen as optimal for the patients, as it is nearly twice the amount of arginine found in average food rations in Poland. The study found that L-arginine supplementation resulted in significant increases in insulin sensitivity ( $\Delta 1.1$  mg/kg/min,  $P < 0.01$ ) and zinc levels ( $\Delta 1.5$   $\mu\text{mol/L}$ ,  $P < 0.001$ ). Moreover this study found that 6 months of treatment with L-arginine significantly increased zinc and decreased copper level in serum. In authors opinion, changes in the concentration of minerals under the influence of L-arginine in obese subjects can be linked to the impact of arginine on insulin secretion and the synthesis of nitric oxide. In this study, zinc concentration in the serum was positively correlated with insulin sensitivity in patients following treatment with L-arginine. Furthermore, decreased copper concentration accompanied by increased insulin sensitivity following L-arginine supplementation was observed. It can be assumed that this change in copper concentration might be caused by the influence of L-arginine on insulin status. Slightly decrease in body fat content has been reported, probably connected with increased insulin sensitivity and changes in zinc and magnesium levels [12]. Despite conducting numerous studies with similar results, the exact

effect and mechanism of action of L-arginine on carbohydrate metabolism disorders still cannot be determined. Studies often show various, contradictory results. However, the ones that can be spotted in the research most commonly and that show the greatest therapeutic potential of L-arginine are the improvement of insulin sensitivity, an increase of nitric oxide levels and vasodilation of vessels. In long-term use, L-arginine may also improve glucose tolerance and even reduce the risk of diabetes [13].

Several studies have examined the effect of oral L-Arginine supplementation on lipid profiles and inflammatory markers. However, findings are inconsistent in this regard. The systematic review and meta-analysis of 17 randomised-control trials was aimed to summarise and examine the effect of L-Arginine supplementation on lipid profiles and inflammatory markers. The analysis revealed that L-Arginine supplementation may indicate a reduction in triglyceride concentrations, but authors emphasise that evidence is not strong and the results should be interpreted with caution. Only several among analysed studies showed improved lipid metabolism after two to eight weeks of L-Arginine supplementation. No significant effect was observed for other lipid profiles nor the beneficial influence of L-Arginine supplementation on CRP and TNF $\alpha$ . Further trials in this field are required to confirm these results [14].

### **Side effects**

Chronic intake of high amounts of individual amino acid or its derivatives alters various biochemical pathways and cellular function. Arginine load may induce overstimulation of nitric oxide synthase and therefore hypotension due to nitric-oxide-mediated vasodilatation, which was observed in subjects receiving a large dose of L-Arginine intravenously. A serious problem with the use of this amino acid in therapy of cardiovascular disorders is that its beneficial effects disappear if it is given chronically - it is supposed to be linked with oxidative stress. Therefore, recommendations to increase L-Arginine intake should be aware of its negative interaction with blood pressure medications. The effects on tumour growth are unclear. The minor reported side effects are gastrointestinal distress, such as nausea and diarrhoea. Careful studies are necessary to determine under which conditions L-Arginine supplementation is appropriate and when it is undesirable. Attention should be focused to markers of oxidative stress and blood pressure stability [15].

### **Summary**

In summary, the evidence suggests that the L-Arginine may improve lipid profile reducing triglyceride serum levels. However, no significant effect was observed for other lipid profiles or inflammatory markers. L-Arginine could be used as a strategy to improve endothelial function in the selected group of patients. This has been evidenced by the results of studies performed on in vitro and in vivo models, as well as some clinical trials involving patients with metabolism disorders. Careful studies are necessary to assess its safety profile, determine under which conditions L-Arginine supplementation is appropriate and when it is undesirable. Attention should be focused to markers of oxidative stress and blood pressure stability. The mechanisms of regulatory effects of L-arginine on carbohydrate and lipid metabolism have not been fully understood and are currently under investigation.

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