Arginine in type II diabetes

Clinical applications

By Heidi Fritz MA, ND

INTRODUCTION

L-arginine is an amino acid with profound effects on cardiovascular function. As the precursor to nitric oxide (NO), L-arginine affects endothelium dependent vasodilation, blood pressure, and select chemical mediators of atherosclerosis (Boger 2008). The insulin potentiating effects of arginine have also been well established in both healthy and sick populations when administered intravenously (Boger 2008, Wascher 1997). The combined insulin sensitizing and vasodilating effects of arginine may offer an additive benefit among diabetics, since this population is commonly affected by vascular disease leading to several types of complications including impaired kidney function, retinopathy, peripheral vascular disease, limb ischemia and diabetic ulcers, and erectile dysfunction in addition to characteristic glucose dysregulation. This paper examines the evidence for uses of arginine in patients with type 2 diabetes or insulin resistance syndromes.

PHYSIOLOGY

Arginine can be synthesized de novo in the body: citrulline is formed from glutamine, glutamate and proline in the enterocyte, and this is converted to arginine in the kidney (Wu 2009). Despite this, arginine is conditionally essential in situations of poor nutrition or in preterm infants since plasma levels are heavily dependent upon dietary intake (Appleton 2002, Wu 2009). The arginine content of dietary protein ranges from 3-15% (Boger 2008). Approximately 50% of ingested arginine is converted to ornithine by the arginase enzymes in the gut, and most of the remaining portion is delivered to the liver where it is used in the hepatic urea cycle to detoxify ammonia (Appleton 2002, Boger 2008, Wu 2009). A small amount, however, is used directly for NO production by nitric oxide synthase (NOS) as demonstrated by radioisotope labeling studies (Boger 2004).

In addition to its conversion to ornithine and urea, arginine is metabolized by four other major pathways once it has reached the cell. These are shown in Figure 1. Arginine can be converted to 1) creatine 2) agmatine 3) arginyl-tRNA, a precursor for protein synthesis, and 4) nitric oxide (Wu 2009). Ornithine is further converted to proline, a component of collagen, which may be of importance for wound healing and tissue repair (Arana 2004). Arginine's substrate role for the nitric oxide synthase (NOS) enzymes neuronal NOS (nNOS), inducible NOS (iNOS), and endothelial NOS (eNOS) is of most relevance for cardiovascular applications (Boger 2008).

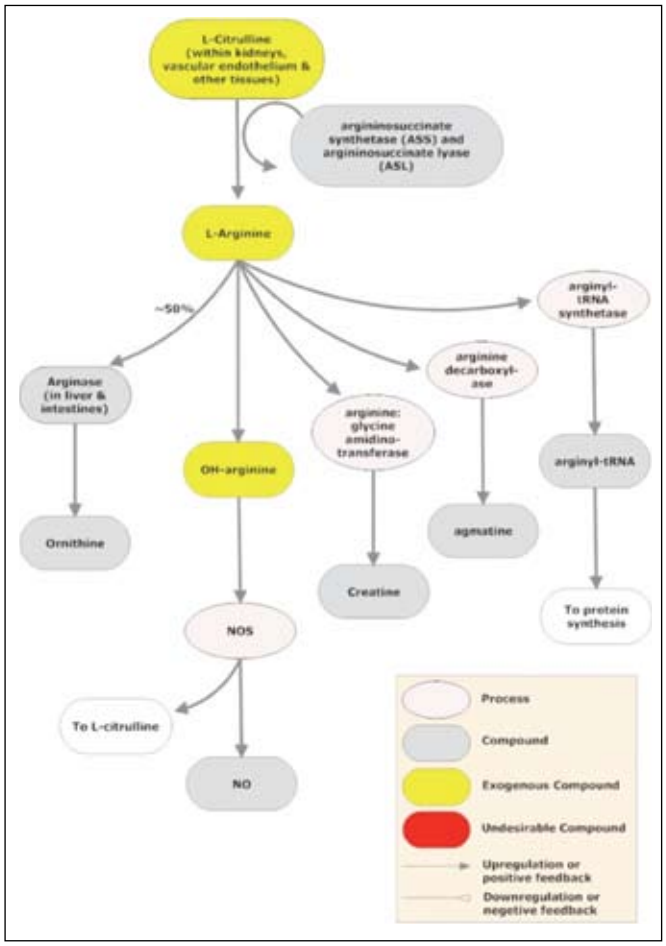

Figure 1. Arginine Metabolism

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Table 1. Effects on Insulin Sensitivity in Patients with Diabetes or Insulin Resistance

Design	Outcomes	Ref
RDBPCT, n=30 Patients without a history of diabetes but with insulin resistance secondary to recent CABG, randomized to receive arginine or placebo in addition to standard meds Arginine 6.4g/d x 6mo	1. Improved blood glucose throughout and at the end of OGTT in the treatment group c/t the placebo group (p<0.05 and p<0.01) 2. ↑ insulin sensitivity (p<0.05) 3. ↓ fasting glucose from 103.9 to 96.6 mg/dL in the treatment group, which was significant when c/t change in the placebo group (p<0.05)	Lucotti 2009
RDBPCT, n=25 Patients with unmedicated type 2 diabetes and who were also treated with a hypocaloric diet and exercise program. Arginine 8.3g/d x 21d	1. Both groups had a significant decrement in whole body weight and fat mass (FM), but the arginine group had a significantly greater reduction in FM (P <0.05) and in waist circumference (P< 0.0001) c/t placebo. 2. Arginine showed a lean tissue sparing effect: In the arginine group, FM accounted for 100% of the total weight loss without any changes in fat free mass (FFM), whereas in the placebo group the loss of FM was 57% and the loss of FFM was 43% of the total weight loss. 3. Metabolic parameters improved in both groups, but the following improved significantly more with arginine therapy: a. systolic (P<0.0001) and diastolic blood pressure (P<0.0002) b. fructosamine (P<0.02) c. insulin (P<0.04) d. homeostasis model assessment (HOMA) index = decrease was almost twice that of the placebo group (P<0.02). 4. Daily glucose profiles improved significantly more in the arginine group (P<0.0001) and this was due to a near normalization of post prandial glucose.	Lucotti 2006
RDBPCT, n=12 Patients with type 2 diabetes Arginine 9g/d x 1mo	1. The arginine group had decreased endogenous glucose production 29% as measured by the euglycemic clamp procedure (p<0.05 c/t placebo) although there was no overall decrease in blood glucose. 2. Glucose disposal during the euglycemic clamp increased 34% in the arginine group (p<0.05).	Piatti 2001

Key: ADMA assymetrical dimethylarginine; c/t compared to; CABG coronary artery bypass graft; FFM fat free mass; FM fat mass; OGTT oral glucose tolerance test; RDBPCT randomized double blind placebo controlled trial. Note: All trials administered arginine orally unless otherwise stated.

NITRIC OXIDE (NO)

In the cardiovascular system, NO is produced by endothelial cells in response to the force of flowing blood in order to regulate vascular tone and structure as well as cell-cell interactions between platelets, white blood cells, and the vessel wall (Boger 2008). In addition to vasodilatorty effects, NO exerts anti-atherosclerotic effects through inhibition of signaling pathways such as NF- B that lead to vascular smooth muscle cell proliferation and monocyte activation and adhesion (Martina 2008). Arginine supplementation has been found to increase levels of cGMP, the second messenger in the NO signaling pathway, by more than 50% (Lucotti 2009).

The activity of NOS is inhibited under certain conditions including hyperglycemia. Giugliano (1997) reported that acute hyperglycemia increased blood pressure, and decreased peripheral blood flow in humans, which was reversible by intravenous arginine. The effect of arginine was negated by use of a NOS inhibitor, suggesting that hyperglycemia reduces nitric oxide synthesis and that intravenous arginine can overcome this (Hunyh 2002). Additionally, inflammation and injury cause upregulation of arginase activity and consequent diversion of arginine to ornithine and proline, resulting in a relative deficiency of arginine available for NOS (Reid 2007, Wu 2009). These factors provide further support to the idea that supplementation of arginine may be of particular benefit in diabetes.

ASSYMETRIC DIMETHYLARGININE

Assymetric dimethylarginine (ADMA) has been proposed as a novel marker of cardiovascular risk (Boger 2006, 2008). ADMA is an endogenously produced competitive antagonist

of NOS, and is thus capcable of decreasing NO production and causing a relative deficiency of arginine in local tissues (Boger 2005). Elevated ADMA levels are common in several conditions associated with cardiovascular disease including type 2 diabetes, insulin resistance, preeclampsia, hypertension, and coronary artery disease, and have been shown to predict cardiovascular outcomes and mortality (Boger 2006, Lu 2003, Nijveldt 2003, Zoccali 2001). It has been suggested that ADMA antagonism may explain the observation that supplementation with arginine benefits cardiovascular outcomes even among patients that do not have an absolute arginine deficiency (Boger 2005). For instance, Lucotti (2009) showed that arginine supplemenation improved endothelial function while lowering ADMA by 27%. Interestingly, exercise has also been shown to reduce ADMA levels (Mittermayer 2005).

CLINICAL EVIDENCE

Glucose metabolism

Based on a handful of studies, oral arginine appears to exert modestly beneficial effects on glucose metabolism. (see Table 1). L-arginine has been shown to decrease fasting blood glucose, improve glucose control during the oral glucose tolerance test (OGTT), increase insulin sensitivity, increase glucose disposal, and decrease endogenous glucose production in patients with type 2 diabetes or insulin resistance (Lucotti 2009, Piatti 2001). When administered in addition to diet and lifestyle interventions, arginine was able to augment the benefit derived from treatment on reductions in fat mass and waist circumference, insulin levels, daily glucose profile (consisting of several measures throughout the day), and post-prandial glucose (Lucotti 2006). Intravenous arginine has also been shown to significantly improve insulin sensitivity (Wascher 1997), but this route of administration is not the focus of the present review.

CARDIOVASCULAR FUNCTION IN DIABETES

Arginine has consistently been shown to improve endothelial function, lower systolic and diastolic blood pressure, and improve markers of atherosclerosis (Lucotti 2009, Lucotti 2006, Piatti 2001, Wascher 1997). Arginine improved endothelial function and hemodynamics as measured by flow mediated dilation of the brachial artery by 50%; increased reactive hyperemia by 31%, decreased the inflammatory and pro-atherosclerotic markers such as fibrinogen, IL-6 and MCP-1; reduced ADMA levels 27% and increased the arginine-to-ADMA ratio 116% compared to baseline; and reduced systolic blood pressure by up to 18 points (Huynh 2002, Lubec 1997, Lucotti 2009, Martina 2008, Piatti 2001, Regensteiner 2003). Arginine also increased the post-exercise decrease in systolic blood pressure to double that of placebo, 22 versus 11 points ($p<0.05$) (Lucotti 2006).

DIABETIC ULCER AND PERIPHERAL VASCULAR DISEASE (PVD)

Arginine benefits conditions of compromised peripheral circulation due to its vasodilatory effects. Topical arginine has been shown to increase blood delivery and temperature in the feet of patients with diabetes (Fossel 2004); local applications of arginine have also been shown to improve healing of diabetic ulcers, and may have averted the need for amputations in one study (Arana 2004, Steed 1995) (see Table 2). Arginine reduced healing times and increased extent of healing among patients with peripheral vascular disease and foot ulcers when given orally in combination with other vasodilating substances and/ or stem cell therapy plus antioxidants (Napoli 2008, Pepe 1999). The activity of arginine in healing of ulcers may be due to both its vasodilatory effects as well as its ability to be converted to proline, an important component of collagen and extracellular matrix. Arginine 2.5g in addition to propionyl-L-carnitine 250mg, and nicotinic acid 20mg for twelve weeks has been shown to benefit erectile dysfunction associated with diabetes, as assessed by International Index of Erectile Function (IIEF5) questionnaire, $p<0.05$ compared to placebo (Gentile 2009). No benefit was found for use in peripheral neuropathy (Jude 2010).

POLYCYSTIC OVARY SYNDROME (PCOS)

Arginine supplementation has been shown to offset the hypertension promoting effects of the birth control pill used in the treatment of PCOS (Battaglia 2010). Arginine in conjunction with NAC was also able to improve ovarian and menstrual function as well as insulin sensitivity in PCOS patients (Masha 2009). weight loss without any changes in fat free mass (FFM), whereas in the placebo group the loss of FM was 57% and the loss of FFM was 43% of the total weight loss.

CLINICAL CONSIDERATIONS

Arginine appears to be most useful when used in conjunction with dietary and lifestyle interventions, as it is able to augment the benefit derived from these therapies. Arginine can also be considered for the management of hypertension in patients with diabetes and may be useful for the treatment of certain diabetic complications including peripheral vascular disease causing limb ischemia or ulcers, and erectile dysfunction. In women with PCOS, arginine appears to be beneficial in preventing elevations in blood pressure associated with the birth control pill, and may also increase the number of ovulatory cycles.

Table 2. Treatment of Diabetes Complications

Design	Outcome	Ref
Peripheral Vascular Disease – Blood Flow		
RDBPC cross over trial n=16 patients with type 2 diabetes with decreased peripheral blood flow 12.5% L-arginine hydrochloride cream applied to feet 2x/d for 2wk	1. After 2wk of arginine, the temperature at the metatarsal area ↑from 82.0 to 86.9°F (P<0.0001) compared to baseline, and the temperature of the big toe rose similarly (P<0.0001). 2. Blood flow as measured by Doppler ultrasound at the metatarsal area ↑from 8.7 to 11.6 units (P<0.0001), and flow at the Achilles area had risen similarly (P<0.02).	Fossel 2004
Diabetic Foot Ulcer		
Non-randomized controlled trial n=22 patients with chronic diabetic foot ulcers and hyperglycemia. 11 patients each received usual care, or arginine therapy. 11 healthy patients served as controls and received no treatment. 10 mM L-arginine administered subcutaneously on the site of the wound every day	1. All eight patients treated with L-arginine who completed the study reached total wound healing, and the remaining three who dropped out of the study due to change of residence showed improvement ≥85% in terms of lesion size and histology. However, the group receiving usual care deteriorated over the course of the study, and some patients required amputations. 2. Dark ischemic tissue adjacent to the ulcer changed in color with L-arginine treatment, recovering similar characteristics to normal skin, which was associated with improvement in local blood circulation. 3. "L-arginine was a potentially successful treatment to prevent lower limb amputation and improve time of healing of chronic ulcer in diabetic patients."	Arana 2004
Controlled trial, n=20 patients with diabetic and non-diabetic occlusive PVD and trophic lesions of the lower limbs Oral ASA + Ginkgo biloba extract + arginine and magnesium OR ASA and conventional hemorheology	1. Experimental treatment reduced healing times for the trophic lesion compared to the control group, improved painful symptoms, and increased peri-lesional neoangiogenesis. 2. No significant differences on Doppler ultrasound or claudication.	Pepe 1999 [Abstr]
RDBPCT, n=65 diabetic patients with chronic full-thickness neurotrophic foot ulcer RGD peptide matrix gel containing arginine-glycine- aspartic acid OR saline solution was applied topically twice weekly for up to 10 weeks in addition to standard care.	1. The percentage of patients whose ulcers healed completely in the RGD peptide matrix group (35%; 14 of 40 patients) was over fourfold greater (P = 0.02) than that in the placebo group (8%; 2 of 25 patients). 2. By the study end point, 30 of 40 (75%) RGD peptide matrix patients had achieved > 50% ulcer closure compared with 12 of 25 (48%) placebo patients (P = 0.03).	Steed 1995 [Abstr]
Controlled prospective trial, n=18 patients with advanced PAD including intermittent claudication, resting pain, and chronic ulcers. Half of the patients had diabetes. An additional 18 patients who refused the experimental therapy were the control group. Autologous bone marrow stem cell therapy followed by daily oral administration of antioxidants vitamin E & C, and arginine 2g/d.	1. Ankle brachial index improvement > 0.1 was seen in 10 patients at 3 months and in 12 patients at 12–18 months. 2. Ischemic ulcers improved in 13 patients after 6–12 months. 3. Although two patients underwent amputation, the mean maximum walking distance significantly increased at 3 months and was sustained up to 18 months. 4. Among conservative patients, 10 underwent amputation in comparison with two BMC-treated patients (55.6 vs. 13.3%; P = 0.014).	Napoli 2008

The therapeutic dose of arginine ranges from 2-9g per day orally in divided doses, with one study using up to 30g over a 10 hour period (Huynh 2002). Due to the short half-life of oral arginine (<30min), it has been suggested that a sustained release formulation would increase the therapeutic efficacy of arginine supplementation however studies have shown benefit even without this type of timed release (Boger 2005). Topical administration can also be effective for treatment of diabetic ulcer and limb ischemia.

Shah (2008) performed a review of safety for L-arginine supplementation, finding an absence of

a systematic pattern of side effects. The observed safe level (OSL) for arginine supplementation is 20g daily in healthy adults. No serious adverse events were reported in the studies included above.

CONCLUSION

Arginine should be considered for the prevention of cardiovascular complications in patients with diabetes. Supplementation with arginine has been shown to benefit endothelial function, blood pressure, peripheral blood flow, limb ischemia, diabetic ulcer healing, erectile dysfunction, insulin sensitivity, and ovarian function, as well as augment weight loss induced by lifestyle change in patients with diabetes or PCOS.

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