

IMPROVEMENT OF TEMPERATURE AND FLOW IN FEET OF SUBJECTS WITH DIABETES WITH USE OF A TRANSDERMAL PREPARATION OF L-ARGININE: A PILOT STUDY; OBSERVATIONS

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Circulatory impairment and its sequelae have long been known to be major complications of diabetes. It has been shown that in diabetes, the functionality of the endothelial nitric oxide (NO)/nitric oxide synthase (eNOS) system is impaired (1-3). NO is generated in the endothelium through the oxidation of the amino acid L-arginine by the enzyme eNOS. NO causes vascular smooth muscle to relax, resulting in increased blood flow. In addition to being a substrate of eNOS, L-arginine facilitates the dimerization of two identical subunits, forming a homodimer. The enzyme is only active in the dimerization. Under proper conditions, dimerization occurs rapidly, on a timescale of minutes. Once formed, the dimer is stable (4).

Subjects with diabetes have abnormally low levels of L-arginine (5) and elevated levels of the eNOS inhibitor asymmetric dimethylarginine (ADME) (6) in their plasma. Though the value of increasing L-arginine levels in cases of impaired circulation is now recognized, practical schemes for therapeutic use of L-arginine have

been elusive. In this pilot study, we sought to determine whether supplying L-arginine transdermally would improve vascular function of the feet in patients with diabetes as indicated by flow and temperature.

The study was designed as a double-blind, vehicle-controlled, two-period, crossover protocol with washout periods of 1 week.

Sixteen subjects were enrolled, and 13 completed the study (aged 56 [+ or -] 8 years).

After analyzing the data, it was clear that

the effect of L-arginine persisted throughout the washout periods (Tables 1 and 2). Because of this, except for the initial exposure of L-arginine virgin feet, the analysis was altered to determine the effect from cumulative exposure to L-arginine throughout the protocol. Flow was measured at the metatarsal and Achilles area using a Doppler flow meter (7), and temperature was measured at the metatarsal and big toe areas using an infrared thermometer. The active cream was a water-based moisturizing vehicle containing 12.5% L-arginine hydrochloride in a hostile

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biophysical environment comprised of high concentrations of choline chloride, sodium chloride, and magnesium chloride. The vehicle control was identical except that the L-arginine was omitted.

At the first visit, after baseline measurements were made each subject rubbed active cream (4 mg L-arginine/[cm.sup.2]) into one foot and vehicle into the other. After 30 min, measurements were made again. A 1-week washout period followed. Patients returned after the washout period and flow and temperature measurements were made. They were then randomly given either active or placebo cream and told to rub it into their feet in the morning and evening every day for 2 weeks.

At the end of 2 weeks, subjects returned and again measurements were made. A second 1-week washout period followed that third visit. At the end of that period subjects returned and measurements were made. They were given the crossover product and told again to rub it into their feet morning and evening for 2 weeks. The subjects returned for final flow and temperature measurements at the end of that period.

At the first visit, flow was increased at the Achilles area in the foot with active cream from 8.1 [+ or -] 3.3 to 11.5 [+ or -] 5.5 AU (P = 0.05) 30 min after application. In the foot that received placebo cream, flow failed to increase (8.1 [+ or -] 1.4 vs. 8.3 [+ or -] 2.2 AU). Furthermore,

at the last visit the temperature at the metatarsal area had risen from the initial value of 82.0 [+ or -] 2.3 to 86.9 [+ or -] 2.4[degree]F (P < 0.0001), and the temperature of the big toe had risen from the initial visit value of 74.4 [+ or -] 4.2 to 82.4 [+ or -] 4.8[degree]F (P < 0.0001). And at the last visit the flow at the metatarsal area had risen

Table 1—Effect of transdermal L-arginine cream on temperature

	Metatarsal ([degrees]F)	P vs. visit 1
Visit 1	82.0 [+ or -] 2.3	
Visit 2	84.1 [+ or -] 3.4	0.004
Visit 3	87.0 [+ or -] 2.4	<0.0001
Visit 4	86.1 [+ or -] 2.4	<0.0001
Visit 5	86.9 [+ or -] 2.4	<0.0001
	Big toe ([degrees]F)	P vs. visit 1
Visit 1	74.4 [+ or -] 4.2	
Visit 2	77.7 [+ or -] 5.3	0.01
Visit 3	83.6 [+ or -] 4.9	<0.0001
Visit 4	80.6 [+ or -] 5.4	<0.0001
Visit 5	82.4 [+ or -] 4.8	<0.0001

Data are means [+ or -] SD.

Table 2—Effect of transdermal L-arginine cream on flow

	Metatarsal (AU)	P vs. visit 1
Visit 1	8.7 [+ or -] 4.3	
Visit 2	10.8 [+ or -] 5.9	NS
Visit 3	10.8 [+ or -] 4.8	0.05
Visit 4	11.6 [+ or -] 8.3	NS
Visit 5	11.6 [+ or -] 5.5	<0.0001
	Achilles (AU)	P vs. visit 1
Visit 1	8.4 [+ or -] 2.5	
Visit 2	8.5 [+ or -] 3.9	NS
Visit 3	9.2 [+ or -] 3.9	NS
Visit 4	10.0 [+ or -] 4.2	0.06
Visit 5	11.4 [+ or -] 5.5	0.02

Data are means [+ or -] SD.

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from 8.7 [+ or -] 4.3 to 11.6 [+ or -] 5.5 AU ($P < 0.0001$), and flow at the Achilles area had risen from 8.4 [+ or -] 2.5 to 11.4 [+ or -] 5.5 AU ($P = 0.02$). While the failure of the L-arginine effect to wash out removed the opportunity for placebo control, the improvement in temperature and flow were substantial and highly statistically significant.

Though puzzling, one explanation of the persistence of the L-arginine effect is that the local tissue concentration of L-arginine becomes high enough to cause inactive monomers of eNOS to form active dimers.

We conclude that in the patients we studied with diabetes, treatment of their feet with a transdermal preparation of L-arginine improved both flow and temperature, and this effect was surprisingly long lasting. Such improvement of compromised local blood flow should be beneficial and could reduce the complications of the disease. ●

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