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Effects of Alpha-Lipoic Acid Supplementation in Peripheral Arterial Disease: A Pilot Study

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ABSTRACT

Objective: To examine whether 3 months of lipoic acid (LA) supplementation improved walking tolerance and delayed claudication pain onset in peripheral arterial disease (PAD).

Design: Randomized, double-blind, controlled study.

Setting: General Clinical Research Center.

Subjects: Twenty-eight (28) participants (15 men, 13 women) with PAD (ankle brachial index range 0.9–0.4, mean age 73.2 ± 1.6 years).

Intervention: LA (600 mg/day) or placebo for 3 months.

Outcome measures: Walking tolerance was assessed by 6-minute walk test distance, 4-meter walk time, initial claudication pain time (ICT) and distance (ICD), and peak claudication pain. Serum was assessed for inflammation (C-reactive protein [CRP]) and oxidative stress (lipid hydroperoxides) as potential mechanisms for changes in walking tolerance.

Results: ICT increased 34.4% and 15%, ICD was reduced by 40.5% and 18%, and peak claudication pain ratings were reduced by 93% and 7% in LA and placebo groups, respectively. Although the improvements in peak pain and ICT achieved significance within the LA group (both $p < 0.05$), the interactions of group by time were not found to be significant ($p > 0.05$). Oxidative stress and CRP measures were not different between groups by month 3 ($p > 0.05$). There were no serious side-effects associated with the LA.

Conclusions: LA may confer pain relief during exercise. However, longer and larger trials are warranted to determine long-term effects of LA alone or combined with other interventions on PAD symptoms.

INTRODUCTION

Peripheral arterial disease (PAD) is a debilitating,[1] potentially lethal, burgeoning systemic atherosclerotic condition that causes blood flow obstruction and claudication,[2] and it is associated with poor walking tolerance.[3] During exercise, PAD induces repeated ischemic reperfusion insults within active muscle,[4] thereby activating inflammation and free radical formation.[4,5] Free radicals impair vasodilation,[6,7] and may contribute to claudication pain. One potential intervention to restore vasodilation is dietary antioxidants. Although some studies show improvements in walking tolerance with single or combined supplements ([n-3] polyunsaturated fatty acids, oleic acid, folic acid, and vitamins B_6 and E);[8] other studies do not.[9] There is insufficient evidence to determine whether antioxidants are effective against intermittent claudication, despite the low cost and lack of serious side effects.[10] Long-term use of combined antioxidants such as vitamins E, C, and β-carotene does not affect coagulation factors in PAD.[11] Positive effects with LA on walking tolerance and pain in PAD have been found with intravenous preparations of antioxidants,[12] methods that are not feasible or inexpensive for daily use. Hence, the available data regarding antioxidants on PAD dysfunction are conflicting.

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Alpha lipoic acid (LA), naturally found in red/organ meats, spinach, broccoli, potatoes, yams, carrots, beets, and yeast, is a potent thiol-containing antioxidant, and may have several effects relevant to PAD pathology and leg symptoms. LA scavenges free radicals and recycles other antioxidants,[13] suppresses vascular inflammation[14,15] and free radicals in the endothelium,[16] restores vasorelaxation in damaged endothelia,[17] and increases vasodilatory capacity.[18] Importantly, LA reduces symptoms in painful diabetic neuropathy, a condition characterized by microvascular insufficiency and lower leg pain;[19] 2 months of LA (600 mg/day) causes a 57%–65% reduction in leg pain and improvement of peripheral nerve function.[20,21] Also, microcirculation is reestablished with LA in this population within 6 weeks.[22] LA might confer similar reductions in leg pain and improve lower limb function in PAD. Therefore, this study investigated the effects of LA supplementation on walking tolerance in PAD.

MATERIALS AND METHODS

Participants

Participants were recruited from the Central Virginia region through newspaper ads, flyers, and clinic advertisements from February 2004 to November 2005. The inclusion criteria were: ≥50 years of age, no current smokers, no liver or kidney disease, and no ambulatory barriers, an ankle–brachial index (ABI) measure ranging between 0.3 and 0.9 (nonsurgical PAD) and claudication pain with walking. Sixty potential candidates responded to the advertisements, and 28 persons screened negative for the ABI criteria despite persistent leg pain. Thirty-two (32) persons with leg pain and ABI between 0.3 and 0.9 were enrolled into the study.

All participants read and signed a written informed consent statement. The protocol of the study was approved by the Institutional Review Board for Studies Involving Human Subjects at the University of Virginia (UVA). All testing was completed at the UVA General Clinical Research Center (GCRC). During the study, four persons dropped out because of (1) a fall and injury, (2) a move away, (3) recommendation of the physician because of cardiac risk related to the walking tolerance assessment, and (4) discovery of a kidney disease that was unrevealed at study entry.

Study design

This was a double-blind, randomized, controlled clinical pilot study. Participants were randomized to receive either LA (600 mg/day) or placebo during the study. The study duration of 3 months was chosen for this study based on previous animal and human studies that showed improvements in both leg pain symptoms[21] and alterations in oxidative stress[23] with LA supplementation during a 2–3-month supplementation period.

Lipoic acid and placebos

LA was supplied by Integrative Therapeutics, Inc. (ITI) (Green Bay, WI). Quality assurance, U.S. Food and Drug Administration Certificates of Analyses, stability testing results, and chemical formulations were provided to the investigators for the LA and placebo by ITI. Each LA capsule contained alpha-LA (10%, 100 mg) and microcrystalline cellulose (90%) contained within a natural polysaccharide capsule (capsule derived from water, gelatin, and titanium dioxide). Placebo capsules of identical appearance, smell, color, and texture were derived from microcrystalline cellulose within the same polysaccharide capsule. The actual LA content of the LA capsules exceeded 85%.

Participants were randomly assigned to the active LA or placebo by the UVA Investigational Pharmacist (using a computer-generated list); the investigators were blinded as to who was receiving the treatment (capsules were matched and provided in opaque bottles, and the investigators and biostatistician had no knowledge of group assignment until the completion of the study). Participants consumed 300 mg LA in the morning and evening on an empty stomach to improve absorption.[24] Participants recorded consumption of supplements in pill logs, and pill counts were performed every 4 weeks by the GCRC staff to ensure compliance. All study measures were completed at baseline, and months 1, 2, and 3. Only the health questionnaire was completed once at baseline.

Participant safety

Safety parameters were regularly collected from all participants during the study period. The UVA Human Investigations Committee worked with the investigators to monitor subject self-reported side-effects during the experimental period. Assessments were collected weekly by the investigators by phone and monthly at the UVA-GCRC. Participants reported any unusual symptom or side-effect to the study coordinator. Hepatic enzyme and protein panels were performed at 1 month for each subject to monitor potential systemic physiologic risks to the subject. Electrocardiograms, blood pressures, and subjective assessments of cardiac discomfort were performed during each exercise testing session.

Study measures

Health questionnaire. A medical history form was provided to each participant regarding comorbidities, weight loss within the last 6 months (≥10 pounds), joint–low back pain, fatigue and anxiety, and PAD history if applicable. Each participant provided a description of current leg pain and discomfort symptoms at rest and during activity using the following terms: cramping, burning, aching, sharp stabbing, numbness, and tingling. The level of physical activity (frequency and duration of regular walking exercise) was recorded.

ABI measurement. The ABI technique described by McDermott et al.[25] was used. Investigators performed the blood pressure measures for each limb in the same order for all participants. For quality control, two technicians performed the blood pressure measures on each participant. The ABI was calculated by dividing the higher of the two lower extremity arterial pressures, and for each leg by the highest arm brachial artery pressure. If brachial artery pressures differed by ≥10 mm Hg, subclavian stenosis in the arm with lower pressure was suspected, and the highest brachial artery pressure was used in the calculation.[26]

Walking tolerance and ability. Walking tolerance and ability were measured using the 6-minute walk test[27] and the 4-m walking velocity test[28] as previously described, both performed at the fastest paces.

Blood analyses. Venous blood samples were collected into heparinized vacutainer tubes. Plasma samples were immediately frozen and stored at −70°C until analysis. Blood samples were analyzed for lipid hydroperoxides (PEROX, a biomarker of oxidative stress),[29] and high sensitivity C-reactive protein (hs-CRP, a measure of inflammation)[7] Blood samples were also analyzed for cholesterol and lipid subfractions and hepatic enzyme and protein panels.

PEROX measurements. PEROX were quantified using the colorimetric ferrous oxidation/xylenol orange technique previously reported, using cumene hydroperoxide as the standard for this assay.[29] Hydroperoxide formation was reflected by the accumulation of a purple chromatophore within the sample that was read at 580 nm. All samples were performed in triplicate. The coefficient of variation for this assay was 4%.

hsCRP. hs-CRP was analyzed in the GCRC Core Laboratory using a commercial enzyme-linked immunosorbent assay kit (Immulite 2000, Diagnostic Products Corporation, Los Angles, CA). Samples were performed in duplicate.

Cholesterol. All samples were analyzed by the UVA Health System Clinical Core and Toxicology Laboratories using standard laboratory procedures. Plasma cholesterol subfractions (total cholesterol, high-density lipoproteins [HDL-C], triglycerides) were assessed spectrophotometrically using an Olympus AU640 Chemistry Analyzer at 600 nm (Olympus cholesterol calibrator, Cat#DR0040, Olympus, Center Valley, PA). HDL-C was isolated by removal of low-density lipoproteins (LDL) and chylomicrons from the plasma samples by a mixture of polymers and polyanions. LDL-C concentrations were estimated from the formula: LDL-C = total cholesterol − HDL-C − (triglycerides/5). All samples were performed in duplicate.

Statistics. Data were analyzed using SPSS software (v. 14) (Chicago, IL). Baseline group differences were analyzed using chi square (χ^2) tests for categorical variables and independent *t* tests for continuous variables. In this pilot study, repeated-measures analysis of variance (ANOVA) models covaried for baseline measures were performed to evaluate the effects of LA versus placebo over time on the individual dependent variables of walking tolerance, hs-CRP, and PEROX. The between-group factor was group assignment (LA, placebo) and the within-group factor was time (1, 2, 3 months). When significant group differences occurred over time, simple main effects were analyzed using one-way repeated measures ANOVAs. Change scores (Δ; difference in value from baseline to 3 months for each participant) and percent change scores were calculated for all dependent variables above. A secondary analysis was performed to determine whether the presence of five regular walkers in the LA group influenced the results. Repeated-measures analysis of covariance models were used to determine differences over time between the LA + walking, LA, or placebo groups on the dependent variables as described above. Because of the different sample sizes in the three-group analysis, Kruskal-Wallis tests were used to determine whether Δ values of walking tolerance variables or blood measures were different among groups. The level of significance was set at 0.05 for all statistical tests. *Post hoc* analyses were performed on the main outcome variables to show the power levels achieved in each analysis.

RESULTS

Subject characteristics and risk factors

Subject characteristics are shown in Table 1. There were similar PAD histories in the LA and placebo groups (2.8 ±

Table 1. Participant Characteristics (N = 28), Means ± SD Are Shown

	Placebo (N = 12)	*LA (N = 16)*
Men (% of group)	50	56
Age (years)	70.7 ± 18.9	75.1 ± 8.2
Height (cm)	165.0 ± 8.6	165.4 ± 8.9
Weight (kg)	82.9 ± 13.2	78.3 ± 18.3
BMI (kg/m^2)	30.7 ± 5.5	28.7 ± 5.6
Blood pressures (mm Hg)		
Systolic	141.8 ± 12.7	144.6 ± 23.2
Diastolic	71.5 ± 5.0	73.0 ± 11.4
MAP	95.5 ± 8.0	97.4 ± 15.6
ABI right	0.75 ± 0.2	0.73 ± 0.1
ABI left	0.70 ± 0.2	0.80 ± 0.2
PAD history (years since diagnosis)	2.4 ± 2.3	2.8 ± 4.0
Years using PAD medications	1.4 ± 1.8	0.3 ± 0.7[a]
Medication type use (%)		
Pletal	41.7	6.3[a]
β-blockers	16.7	6.3
Diuretics	58.3	62.5
ACE inhibitors	16.7	50.0[a]
Statins, lipid lowering	58.3	68.8
Aspirin	66.7	62.5

[a]Different from placebo group at $p < 0.05$.

BMI, body–mass index; MAP, mean arterial pressure; ABI, ankle–brachial index; LA, lipoic acid; PAD, peripheral arterial disease; ACE, angiotensin-converting enzyme; SD, standard deviation.

4.0 and 2.4 ± 2.9, years with PAD). The placebo group used PAD medications longer than the LA group ($p < 0.05$). Within the LA group, 5 participants were identified as regular walk exercisers (walked ≥20–30 minutes a day, ≥4 times per week). The LA group had higher total cholesterol and triglyceride levels than the placebo group ($p < 0.05$; Table 2). The LA group also had more specific comorbidities (coronary disease, high blood lipids, and hypertension), and more comorbidities associated with low walking tolerance than the placebo group.

Safety and side effects

Leg pain symptoms experienced by the participants are presented in Table 3. Side-effects reported from the LA group included self-perceived weight gain (1), increased tingling in the legs and feet (3), mild stomach queasiness (1), leg muscle strain (1), and angina (1; both unrelated to study treatment). No side-effects were reported by the placebo group.

Walking test performance

Peak pain ratings and initial claudication time (ICT) values achieved significance over time only within the LA group (Table 4, $p < 0.05$). However, the baseline to month 3 6-minute walk test distances were not different between the LA and placebo groups over time, nor was the percent change in walk distance from baseline to 3 months (8.4% versus 7.0%; $p > 0.05$; Table 4). The changes in ICT, initial claudication distance (ICD), claudication distance, peak pain, and 4-m walk test time were not statistically different between the LA or placebo groups over time ($p > 0.05$).

The subset of regular exercisers was separated from the LA group and analyzed as a third group (LA + regular walking). ICT and peak pain ratings were found to be significantly lower in the LA + regular walking group over time ($p < 0.05$). Claudication distance decreased over time in the LA + walk group compared with the LA or placebo group ($p > 0.05$). Also, the peak pain rating at minute 6 of the walk test was less in the LA + walking group compared to the LA or placebo groups by month 3 ($p < 0.05$).

Oxidative stress and inflammation

Oxidative stress and inflammatory markers are presented in Table 5. There were no differences between the LA and placebo groups in PEROX or hs-CRP over time ($p > 0.05$). There were no significant differences between LA + walking, LA, or placebo groups in the hs-CRP or lipid hydroperoxides over time ($p > 0.05$).

Table 2. Risk Factors for Peripheral Arterial Disease and Major Comorbidities in Lipoic Acid (LA) and Placebo-Treated Groups

	Placebo (N = *12*)	*LA* (N = *16*)
Total cholesterol (mmol/L)	3.79 ± 0.36	4.57 ± 0.71[a]
Triglycerides (mmol/L)	2.66 ± 1.06	4.67 ± 1.73[a]
HDL-C (mmol/L)	2.44 ± 2.02	1.22 ± 0.34
LDL-C (mmol/L)	1.89 ± 0.14	2.56 ± 0.85
Former smoker	2	0
Major comorbidities		
Coronary conditions (%)	25.0	56.3[a]
Hypertension (%)	66.7	81.3[a]
Arthritis (%)	50.0	50.1
Diabetes mellitus (%)	25.0	25.0
High blood lipids (%)	33.3	62.5[a]
Anemia (%)	16.7	25.0
Digestive disorders (%)	16.7	31.3
Depression (%)	16.7	6.3
Comorbidities related to poor walking tolerance (no.)	3.5 ± 1.7	4.8 ± 2.2[a]
Number of walk exercisers	0/12	5/16

Self-report medical conditions are presented as percent of total answers as "yes." Values are means ± standard deviation.

[a]Different from placebo group at $p < 0.05$.

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Table 3. Self-Reported Lower Leg Pain/Discomfort Symptoms at Rest and Postexercise in all Participants

	Placebo		*LA*	
	Baseline	*3 month*	*Baseline*	*3 month*
Resting leg pain/ discomfort type				
None	4	8	4	3
Distressing	5	2	1	1
Sharp	0	1	0	0
Aching	6	2	3	5
Burning	0	1	1	4
Cramping	0	1	2	1
	Placebo		*LA*	
	Baseline	*3 month*	*Baseline*	*3 month*
Postexercise pain/ discomfort type				
None	5	8	5	3
Distressing	1	1	0	0
Sharp	0	0	0	0
Aching	6	3	3	4
Burning	1	1	1	4
Cramping	1	1	1	1

Values are presented as numbers of persons within the respective groups with that symptom.

LA, lipoic acid.

DISCUSSION

This pilot study examined whether LA improved walking tolerance and claudication pain in PAD. Although im-

Table 4. Six-minute Walk Test and 4-m Walk Test Performances in Placebo or Lipoic Acid (LA) Supplemented Groups

	Placebo			*LA*				
	Baseline	*Month 3*	Δ	*Baseline*	*Month 3*	Δ	*INTXN group*time (sig value)*	*Power*
Distance (m)	375.9 ± 91.2 (312–426)	395.8 ± 83.8 (336–441)	(21.3)	365.1 ± 124.0 (282–416)	380.7 ± 126.6 (309–443)	(18.9)	.992	0.41
ICT (seconds)	129.8 ± 113.1 (58–201)	157.6 ± 145.1 (65–249)	(19.4)	123.2 ± 106.1 (55–174)	211.5 ± 132.2 (142–284)	(34.4)	.373	0.43
ICD (m)	150.2 ± 150.5 (54–242)	201.9 ± 162.1 (97–300)	(27.0)	169.6 ± 145.9 (74–234)	233.4 ± 159.1 (149–317)[a]	(22.1)	.232	0.41
CD (m)	231.2 ± 150.4 (53–242)	180.0 ± 162.4 (64–228)	(−3.5)	238.6 ± 129.3 (73–234)	151.0 ± 156.1 (64–229)	(−40.5)	.505	0.22
Peak pain rating at 6 minutes (points)	2.3 ± 1.2 (1.5–3.0)	2.0 ± 1.2 (1.2–2.8)	(−0.18)	2.1 ± 1.2 (1.4–2.9)	1.3 ± 1.2 (0.8–2.1)[b]	(−0.93)	.482	0.53
4–m time (seconds)	3.1 ± 1.1 (2.4–3.8)	3.0 ± 1.2 (2.2–3.6)	(−0.08)	3.3 ± 0.1 (2.7–3.7)	3.1 ± 0.6 (2.8–3.5)	(−0.10)	.703	0.31

Values are means ± standard deviation (95% confidence intervals). For each participant, the Δ score of each variable was determined as the difference from month 3 to baseline values. The average of these differences is presented as the mean Δ score in the table above.

[a]$p = 0.09$ different from baseline within the respective group.

[b]Significantly different from baseline within the respective treatment group at $p < 0.05$.

INTXN, interaction; ICT, initial claudication time; ICD, initial claudication distance; CD, distance walked with claudication pain.

Peak pain ratings are presented as values from a 0–4 scale (0 = no pain, 4 = maximal leg pain).

Table 5. Blood Measures of Oxidative Stress and Inflammation Before and After 3 Months of Treatment in Lipoic Acid and Placebo Groups

	Placebo			*LA*				
	(baseline)	*3 months*	Δ	*(baseline)*	*3 months)*	Δ	*INTXN group*time (sig value)*	*Power*
PEROX	2.1 ± 0.8 (1.3–2.9)	2.1 ± 0.7 (1.4–2.7)	−0.03 ± 0.95	2.4 ± 0.5 (1.9–2.7)	2.6 ± 0.9 (1.5–3.8)	0.12 ± 0.57	0.226	0.30
hs-CRP	1.0 ± 0.9 (0.4–1.6)	0.9 ± 1.0 (0.3–1.6)	−0.11 ± 1.29	0.6 ± 0.5 (0.3–0.9)	0.6 ± 0.7 (0.2–1.1)	0.07 ± 0.32	0.585	0.14

Values are means ± standard deviation (95% confidence intervals). For each participant, the Δ score of each variable was determined as the difference from month 3 to baseline values. The average of these differences is presented as the mean Δ score in the table.

PEROX, lipid hydroperoxides (nmol/mL); hs-CRP, high sensitivity C-reactive protein (pg/mL).

provements in peak exercise pain ratings and ICT were found within the LA group, there were no statistical differences in walking tolerance, oxidative stress, or inflammation between the LA and placebo over time. Despite the lack of significant interactions, these improvements in walking tolerance with LA are clinically important. Moreover, LA was well tolerated and was not associated with any serious side-effects in PAD.

These findings are in partial agreement to previous literature relating LA use to comparable debilitating leg symptoms. For example, LA was shown to be effective against diabetic neuropathic symptoms.[30] LA (600 mg/day) reduced leg/foot pain and symptoms up to 63.5% within 3 weeks in neuropathy sufferers.[31] LA might correct microcirculation impairment,[22] and reduce oxidative stress, and vascular dysfunction.[30] LA is taken up by vascular endothelial cells[16] and may counteract inflammation, oxidative stress, and endothelial dysfunction in PAD.

In this study, improvements in ICT (increase of 34.4%), claudication distance (reduction 40.5%), and peak claudication pain ratings (reduction 93%) occurred with LA. These changes are similar to those reported for other interventions for PAD such as exercise[32] or pharmacologic agents such as cilostazol (changes range from 36% to 65%).[33] The magnitude of peak pain reduction with LA achieved here (71%) is considered clinically meaningful.[34] The lack of significant interactions (group*treatment over time) is likely caused by low power in these analyses and/or masked by the large placebo effect. Participants consistently expressed at study enrollment the desire to alleviate the debilitating leg pain because they were unable to undergo surgery, and were likely anticipating that the study would abolish or reduce leg pain, regardless of randomization group.

Group differences between the LA and placebo groups may help explain the lack of significant interactions in this small study. The LA group contained persons who had more complicating disease risk factors, higher cholesterol, and more comorbidities associated with poor walking tolerance (4.9 versus 3.5), and a shorter duration of vasoactive drug use compared to the placebo group (0.3 versus 1.4 years). Walking improvements may have been delayed in the LA group during the study. Statistical differences might have been observed with a longer treatment duration or a higher dosage of LA.

Inflammation and oxidative stress

This study also examined whether inflammation (hs-CRP) and oxidative stress (PEROX) were modifiable with LA. We did not observe any statistical changes in either measure with LA at month 3 compared to placebo. To our knowledge, there are no data available regarding the effect of LA on CRP concentrations. Our findings are in contrast, however, to a previous study that showed attenuation of lipid peroxidation in diabetic neuropathy with 600 mg LA/day for 70 days.[35] LA reduces levels of other related inflammatory proteins such as interleukin-6 in proinflammatory conditions such as the metabolic syndrome.[36] Alternatively, some participants may have responded better than others to the LA. For example, 25% and 42% of LA-treated participants did not show reductions in CRP and PEROX, respectively. The dose of LA may have been inadequate to counter the prevalence and/or severity of inflammatory and oxidative stress-inducing comorbidities. Coronary conditions, hypertension, and hyperlipidemia may excessively tax tissue antioxidants[37–39] and overwhelm the ability of LA to protect against inflammation and oxidative stress. A final interpretation is that LA was ineffective in reducing hs-CRP and PEROX at this dose.

Regular walking effects and LA

The unanticipated randomization of five regular walkers to the LA group generated an interesting and clinically important finding. The LA + regular walking subset of participants demonstrated significant improvement in ICT, claudication distance, and peak claudication pain during walking compared to the LA or placebo groups. LA and walking exercise may be more effective than LA alone in improving walking tolerance. Walking exercise has been shown in several studies to improve ICT and ICD[40–43] and in one study, walking improved ICT, ICD, and 6-minute walking distance.[40] LA and regular walking may interact to improve blood flow via several collective endothelial cellular pathways. The magnitude of improvements in the LA + walking group is clinically important, because similar improvements in previous studies are also associated with improved quality of life in PAD.[40,44] A final possibility is that exercise alone, not the LA, induced these improvements by 3 months.

Safety of LA in PAD

This pilot study indicated that LA (600 mg/day) was well tolerated by the participants and was easy to administer. Thirty-one percent (31%) of participants using LA experienced mild side-effects including nausea/queasiness (6%), tingling of the foot (18%), and weight gain (6%). No participants discontinued the study because of these symptoms. The prevalence of gastrointestinal discomfort was lower in the present study compared to a previous report using an LA intervention;[34] we interpret these findings to show that the risk-to-benefit ratio of the intervention is low.

Study limitations and future directions

Future studies require larger cohorts for a longer duration to determine when optimal adaptations occur, and whether these adaptations alter PAD prognosis. The degree of clinical improvement in leg pain and discomfort[19] and walking ability[32] with the addition of LA to standard, nonsurgical

treatment is predicted to be approximately 25%. With a power calculation of 0.80, and a confidence interval of 0.95, a sample size (in addition to the 14% expected dropout) was calculated to be 46 participants. This small population in this study may not represent the general population; a larger sample size would distribute the effect of comorbidities. Also, there were no regular walkers in the placebo group who could have been separated out for analysis. Finally, the dosage or formulation of LA (600 mg/day) may not have been optimal for this population. Doses of LA between 200 and 1800 mg/day have been considered "safe" in humans with minimal side effects.[45] Future studies should use LA doses greater than 600 mg/day to determine whether walking tolerance can be improved in PAD.

CONCLUSIONS

Three months of LA supplementation did not significantly improve walking tolerance, oxidative stress, or inflammation. However, regular walkers who took LA responded favorably to the intervention and demonstrated significant improvements in walking tolerance. The combination of LA and walking exercise may be potentially useful in the treatment of PAD symptoms.

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