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A walking intervention to reduce inflammation in patients with diabetes and peripheral arterial/artery disease: A pilot study

Tracie C Collins and Philip Twumasi-Ankrah

Abstract

Objectives: In this pilot study, we sought to determine whether walking reduces inflammation in patients with diabetes mellitus and peripheral arterial/artery disease.

Methods: We obtained blood samples from patients with diabetes mellitus and peripheral arterial/artery disease. Intervention participants were advised to walk for 50 min 3 days per week for 6 months. Participants completed assessments of comorbidities and walking ability. Difference-in-difference analyses were used to assess the relationship between group assignment and each biomarker over time.

Results: We randomized 55 participants (control = 25 and intervention = 30). At 6 months and based on *p* values of <0.20, vascular cellular adhesion molecule, beta-2 microglobulin, total cholesterol, and triglycerides demonstrated a greater decrease among participants randomized to the intervention compared to the control.

Conclusions: Walking may reduce inflammation in persons with diabetes mellitus and peripheral arterial/artery disease. Further research is needed to determine the impact of walking on inflammation in persons with vascular disease.

Keywords

Peripheral arterial/artery disease, walking, inflammation

Introduction

Peripheral arterial/artery disease (PAD) results from atherosclerosis of the abdominal aorta and arteries of the lower extremities. The disease affects 8–12 million US adults. One of the most common risk factors for this disease is diabetes mellitus (DM). Among primary care clinic diabetic patients aged 50–69 years, the prevalence of PAD is as high as 29%.[1]

As an atherosclerotic illness, PAD is associated with systemic inflammation. Markers of inflammation that have been linked to PAD include C-reactive protein (CRP), fibrinogen, soluble intercellular adhesion molecule (sICAM), soluble vascular cell adhesion molecule (sVCAM), and interleukin 6 (IL-6).[2–6] Convincing evidence exists for the role of CRP in the development and progression of PAD. In both the Physician's Health Study and the Women's Health Study,[7,8] participants with the highest CRP levels at baseline showed up to a sevenfold higher risk of severe PAD compared to participants with lower CRP levels. Ridker et al.[9] identified that CRP levels were elevated in individuals with claudication and were highest in patients with PAD who required limb revascularization. In addition, patients with PAD tend to have lower levels of physical activity as compared to persons without PAD.[10,11] This lower level of activity has been linked, albeit cross-sectionally, to increased inflammation.[5] Elevated levels of IL-6, sVCAM, and fibrinogen are associated with smaller calf sizes in persons with PAD.[6] Furthermore, higher sVCAM is associated with lower calf strength. These associations suggest an inverse relationship between levels of inflammation and favorable calf muscle characteristics, which may contribute to walking impairment in patients with PAD.[6] Additional biomarkers of interest in persons with PAD include lipids, beta-2 microglobulin, monocyte chemoattractant protein (MCP), and albumin. In a pilot work completed by the principal investigator, high-density lipoprotein (HDL) levels increased while triglycer-

Department of Preventive Medicine and Public Health, School of Medicine, The University of Kansas, Wichita, KS, USA

Corresponding author:
Tracie C Collins, Department of Preventive Medicine and Public Health, School of Medicine, The University of Kansas, 1010 N. Kansas St., Ste 1406, Wichita, KS 67214-3199, USA.
Email: tcollins2@kumc.edu

ide levels decreased in veterans with PAD who were randomized to an unsupervised walking intervention.[12]

Very few studies have assessed the role of walking therapy to improve biomarker levels in persons with PAD. The objective of this pilot study was to identify the potential effects of a home-based walking intervention on markers of inflammation (biomarkers) in patients with DM and PAD.

Methods

The study was conducted during the primary author's (T.C.C.) role as a faculty member at the University of Minnesota. As such, the Institutional Review Board approved all aspects of the study. All participants provided informed consent.

Recruitment, eligibility, and screening

For this pilot study and with limited funding, we obtained a consecutive subsample from participants randomized to the parent study. For the parent study, we recruited participants between January 2007 and March 2009. For this pilot study, participants were recruited from 2008 to 2009. Participants were recruited from clinics and communities in the Twin Cities metro area of Minnesota based on self- or physician-referral. We distributed recruitment flyers at health fairs, community centers, and churches. Additional methods of recruitment included radio advertisements, word of mouth, and postcards.

The study included men and women aged 40 years and older with a diagnosis of PAD (resting or post-exercise ankle brachial index (ABI) of <0.90 or a toe brachial index < 0.7[13]), a diagnosis of DM type I or II (medical history of medication use or diet control for hyperglycemia), and leg symptoms at the time of enrollment (as captured by the San Diego Claudication Questionnaire (SDCQ)).[14] Additional details about eligibility have been published.[15]

Potential participants were screened through telephone interviews. Research staff assessed medical history and administered the SDCQ. The SDCQ was used to ascertain leg symptoms.[14] Additionally, staff administered the Physical Activity Readiness Questionnaire (PAR-Q), a 7-item questionnaire that detects signs and symptoms that would contraindicate exercise.[16] Eligibility was confirmed with treadmill testing and ABI measurements.[17] For persons with an ABI > 1.3, indicating arterial calcification, we obtained toe brachial indices.[13]

Randomization

Eligible individuals were randomized to intervention or control using permuted blocks with randomized block sizes 2, 4, 6, or 8 to ensure equal numbers in both groups. Outcomes were analyzed according to the randomized allocation (intention to treat).

Standard care

All participants viewed a 7-min educational video about PAD and its clinical leg symptoms, life-threatening consequences of PAD (heart attack and stroke), other adverse outcomes (walking disability), and strategies for disease and risk-factor management (smoking cessation, weight control, and aerobic activity). After the video, each participant met face-to-face with the research coordinator. The coordinator queried participants regarding their use of self-management behaviors (i.e. glucose monitoring and blood pressure monitoring) and provided them with a calendar in which to document their daily glucose results, weekly blood pressures, and any routine lipid results provided by their primary care physician.

Intervention group procedures

Intervention group subjects participated in a home-based walking program with three components: (1) a one-on-one interaction with the research coordinator at baseline and following the above described assessment of self-management behaviors, (2) walking training and weekly group walking classes with an instructor, and (3) biweekly telephone calls for 6 months. Full details of the intervention have been published.[15]

For the baseline interaction, which occurred on the same day and following the treadmill exam, discussion focused on the participant's current stage of change,[18] as determined from his or her responses to Part 1 of the Patient-centered Assessment and Counseling for Exercise (PACE) protocol (e.g. "I have been thinking of starting to exercise in the next 6 months" = 2 or "I've been doing vigorous exercise 3 or more days per week for the last 6 months or more" = 8).

Within 1 week of the baseline visit, participants were scheduled to complete two 1-h walking training sessions, led by an experienced exercise instructor. These sessions served as reinforcement and facilitated treatment adherence.[23] Sessions were held at the University of Minnesota or another location suitable for walking (e.g. a park). Session one was designed to facilitate interaction among participants. The exercise instructor asked participants to describe what they hoped to gain from walking for exercise. The group then discussed strategies for staying in the walking program. Session two was a practice walking session with the exercise instructor and one or more participants.

Participants were then encouraged to walk 1 day per week with the study exercise instructor along with other participants, as available, and to continue walking on their own at least 3 days per week for a minimum of 4 days of walking each week; participants were advised to walk totally for 50 min for each session and, using their pedometers, to increase the number of steps by 50 each session.

Attention control group procedures

Individuals randomized to the attention control group participated in bimonthly phone calls with the research

coordinator. During these calls, lasting 10–15 min, control group participants shared and discussed the information documented in their calendars on blood glucose, blood pressure, and cholesterol levels (if available) and their smoking habits, if applicable. The Exercise Behaviors Questionnaire was also administered.

Measures

At baseline only, the Lifestyle and Clinical Survey (LCS) was administered to ascertain sociodemographics and comorbidities. This instrument has a summary kappa statistic for reliability of 0.81 (95% confidence interval (CI) = 0.78–0.84) and a summary kappa statistic for validity of 0.58 (95% CI = 0.52–0.64).[20]

For the parent study, the primary outcome was change from baseline to 6 months in mean maximal treadmill walking distance, determined from using the Gardner–Skinner graded exercise treadmill test with electrocardiographic monitoring.[21]

We captured the participant's ability to walk in the community (i.e. lower limb function) using the validated interviewer-administered Walking Impairment Questionnaire (WIQ).[22] Health-related quality of life was measured using the Medical Outcomes Study 36-item Short-Form Health Survey (MOS SF-36®).[23] We administered the Stanford Patient Education Research Center Exercise Behavior Survey during each of the follow-up phone calls. The exercise behavior survey is a 6-item instrument that includes questions regarding the type of activity and the length of time during which the patient engaged in that activity during the past week.[24]

Biomarkers

Blood draws were completed following the baseline treadmill visit and again at the 6-month treadmill visit. A 9-mL serum separator tube was used to collect the original blood sample. The samples were allowed to clot for 30 min and then centrifuged at 3200 r/min for 10 min. The serum was aliquoted, using 2.0-mL vials, as follows:

1. 1.5 mL into one red cap vial, for sICAM, IL-6, sVCAM, and MCP;
2. 1.5 mL into one red cap vial, for beta-2 microglobulin, lipid panel, CRP, and albumin.

Serum in excess of 3.0 mL was discarded. Samples were stored at −80°C and analyzed in batch by the Collaborative Studies Clinical Laboratory at the University of Minnesota Medical School.

Adverse events

During each biweekly phone call, study staff asked whether the patient had developed chest pain, shortness of breath, or any symptoms requiring hospitalization in the past 2 weeks. If the participant responded yes, he/she was asked about diagnostic testing, final diagnosis, and whether the hospital physician stated that the participant could continue in the study. In addition, study staff ascertained leg symptoms, testing for PAD (e.g. angiography), or invasive therapy for PAD.

Statistical analysis

In this analysis, continuous variables were summarized by mean and standard deviation (mean ± SD). Summary of categorical variables included number and percentage of subjects by level of category of the variable. For the calculation of proportions, denominators were based on nonmissing data unless otherwise stated. To test differences between intervention and control groups, Fisher's exact chi-square test was used to determine the association between categorical variable and treatment groups. For categorical variables with more than two levels, the Mantel–Haenszel chi-square test was preferred. For mean differences between groups at baseline, the analysis of variance (ANOVA) was utilized to determine whether there was any significant difference between groups. The p values for statistical tests are provided.

For the analyses of changes in biomarker values between treatment and sessions, we utilize the difference-in-difference (DiD) method. This is a generalization of the usual paired t-test. The DiD analysis proceeds in two stages. First, the obtained differences in the observed values for the biomarkers at different time points (pre and post). Then, a regular two-sample t-test is run on the two sample differences between the two groups (treatment vs controls). DiD methods like analysis that involve the time × group interaction term allow for time-invariant unobserved differences between treatment groups, in particular it removes differences in unobserved characteristics that are constant over time and that affect individual biomarker outcomes in a constant way. The observed DiD analysis corresponds to the difference in least square means analysis using general linear modeling (GLM) and also to the time × group interaction in ANOVA/GLM.

Since the distribution of the differences in biomarker values between the pretreatment and posttreatment sessions was heavily influenced by outliers, we derived the winsorized means for the test of the difference between mean changes in biomarker values from baseline to 6 months. Winsorization is a method for reducing the effects of extreme values in the sample, and it is more robust when data findings can be heavily influenced by outliers.[25–28] Winsorized means are an attractive alternative to the sample mean for skewed populations. According to Rivest,[27] even in the presence of heavy skewness, the winsorized mean provides, for all practical purposes, the largest efficiency. Student's t-test was used in determining the differences between the winsorized means of differences in biomarkers values. Clinically significant

differences were assessed at a p value < 0.2. All analyses were conducted using Statistical Analysis System (SAS) (version 9.3; SAS Institute Inc., Cary, NC).

Results

Baseline characteristics

In the larger study, we enrolled 145 participants. For this pilot study, we obtained blood samples from 55 consecutive participants (control = 25 and intervention = 30). Table 1 gives baseline characteristics of participants within the pilot study. Of the 55 participants, there were 42 men and 13 women; the mean age was 66.7 ± 0.7 years. Study participants were predominantly Caucasian (89.1%), had at least a high school education (89.1%), and were obese (mean body mass index (BMI) of 34.1 ± 8.6).

Atherosclerotic risk factors were common; 41 (74.5%) participants were former or current smokers and 42 (76.4%) had hypertension.

At baseline, distance to onset of claudication pain was 144.8 ± 144.8 m for all participants. Control subjects could walk a distance of 128.7 ± 112.6 m till onset of claudication pain, whereas participants in the intervention group could walk 160.9 ± 160.9 m (p value = 0.5491). The maximal walking distance, that is, the total distance a participant could walk from the start of the treadmill until maximal leg pain was 414.4 ± 241.4 m (control = 386.2 ± 257.5; intervention = 434.5 ± 241.4; p value = 0.4983). Participants' mean score on the Stanford Patient Education Research Center Exercise Behavior Questionnaire for all participants was 16.6 ± 14.7, which is equivalent to fewer than 30 min of exercise per week. Control subjects had a score of 16.2 ± 15.1, while intervention subjects had 16.9 ± 14.5 (p value = 0.8179).

Participants' normed profile scores on the general purpose SF-36 questionnaire are also detailed in Table 1. The social functioning summary score was 50.8 ± 8.5. Four subscales were within one SD of the norm: role—physical = 40.2 ± 14.9, bodily pain = 46.2 ± 9.4, general health = 43.6 ± 9.4, and vitality 45.0 ± 13.2.

Table 1 also describes the study groups using baseline values of outcome measures. At baseline, winsorized mean values for the biomarkers were as follows: intercellular adhesion molecule (ICAM) = 255.9 ± 87.4, IL-6 = 4.1 ± 3.5, vascular cell adhesion molecule (VCAM) = 902.8 ± 306.6, MCP-1 = 418.6 ± 132.4, beta-2 microglobulin = 3.3 ± 1.8, total cholesterol = 171.7 ± 39.9, triglycerides = 232.9 ± 178.1, HDL = 3.8 ± 15.1, low-density lipoprotein (LDL) = 86.2 ± 30.9, and CRP = 5.0 ± 5.4.

There were no significant differences between the control and intervention groups in baseline characteristics with the exception in use of cilostazol, which was more commonly used by participants in the control group (20%) as compared to the intervention group (3.3%).

Efficacy of intervention

Considering changes from baseline to 6 months, the effect of the intervention of the biomarkers under discussion in this presentation is detailed in Table 2. At 6 months and based on p values of <0.20, changes in the winsorized means for VCAM (control, 37.1 ± 124.1; intervention, 5.1 ± 88.2; p value = 0.20), beta-2 microglobulin (control, 0.3 ± 0.9; intervention, 0.2 ± 0.5; p value = 0.04), total cholesterol (control, 1.3 ± 19.7; intervention, −10.1 ± 26.3; p value = 0.12), and triglycerides (control, −0.3 ± 62.2; intervention, −32.1 ± 106.9; p value = 0.12) demonstrated a trend toward a greater decrease among participants in the intervention group as compared to the control group. In addition, there were decreases in LDL (control, −0.7 ± 19.2; intervention, −1.5 ± 13.1; p value = 0.62) and CRP levels (control, −0.8 ± 3.0; intervention, −0.4 ± 4.9; p value = 0.39). Even though the changes in biomarker values after 6 months from the baseline for the intervention compared to the control group are not at levels that would constitute statistical significance, they are important clinical indicators of the trend in the effect of the intervention on these markers of inflammation.

Adverse events

No unanticipated adverse events were reported among randomized participants.

Discussion

Our home-based walking intervention involving minimal supervision reduced total cholesterol, triglycerides, and surprisingly, HDL in persons with DM and PAD. There were no notable trends for changes in additional biomarkers (i.e. sICAM, IL-6, sVCAM, CRP, and LDL) comparing the intervention and control groups. This is one of the first studies, albeit a pilot, to assess the effect of home-based walking therapy on levels of inflammatory markers in persons with DM and PAD; the findings here are of profound clinical importance.

Prior work has demonstrated an association between vascular inflammation, PAD severity, and maximal treadmill walking distance. In the work by Nylaende et al.,[29] fasting blood samples were drawn from 127 participants with PAD (mean age = 66 years, 36% females); PAD severity was captured by the angiographic score. Tumor necrosis factor-alpha, IL-6, MCP-1, and CD-40 ligand were all significantly correlated with PAD severity. After adjustment for age, smoking, DM, hypertension, homocysteine, and hypercholesterolemia, MCP-1 and CD40L remained statistically significantly associated with PAD severity. However, IL-6 was found to be inversely correlated with maximal treadmill walking distance. In our work, we did not find an association between IL-6 and home-based walking. Similarly, in the work by Schlager et al.,[30] supervised exercise training for 6 months was not

Table 1. Baseline characteristics by randomized group.

	Total (n = 55)	Control (n = 25)	Intervention (n = 30)	p value*
Age, mean (SD)	66.7 (10.7)	66.9 (11.2)	66.6 (10.4)	0.9163
Female, *n* (%)	13 (23.6)	5 (20.0)	8 (26.7)	0.5623
Race, *n* (%)				
Caucasian	49 (89.1)	22 (88.0)	27 (90.0)	0.3793
African American	4 (7.3)	1 (4.0)	3 (10.0)	
American Indian[a]	1 (1.8)	1 (4.0)	0 (0)	
Unknown	1 (1.8)	1 (4.0)	0 (0)	
Education ≥ high school, *n* (%)	49 (89.1)	20 (80.0)	29 (96.7)	0.0484
BMI, mean (SD)	34.1 (8.6)	33.9 (7.5)	34.3 (9.6)	0.7705
HbA1c, mean (SD)	7.2 (1.5)	7.2 (1.2)	7.3 (1.7)	0.8367
Prior MI, *n* (%)	10 (18.2)	5 (20.0)	5 (16.7)	0.3936
Current smoker, *n* (%) (n = 41)	5 (12.2)	1 (5.26)	4 (18.2)	0.8212
Smoked at least 100 cigarettes during lifetime, *n* (%)	41 (74.5)	19 (76.0)	22 (73.3)	0.8212
Number of cigarettes smoked per day, *n* (%)				
0–4	1 (2.6)	0 (0)	1 (5.0)	0.4996
5–15	12 (30.8)	7 (36.8)	5 (25.0)	
One pack per day	9 (23.1)	3 (15.8)	6 (30.0)	
More than one pack per day	17 (43.5)	9 (47.4)	8 (40.0)	
Resting ABI, mean (SD)	–	0.72 (1.2)	0.73 (1.7)	0.8861
Renal insufficiency, *n* (%)	2 (3.6)	1 (4.0)	1 (3.3)	0.8954
Hypertension, *n* (%)	42 (76.4)	19 (76.0)	23 (76.67)	0.9538
High blood cholesterol, *n* (%)	37 (67.3)	14 (56.0)	23 (76.7)	0.1039
Prior cerebrovascular event or transient ischemic event, *n* (%)	4 (7.3)	1 (4.0)	3 (10.0)	0.3936
Medication use for claudication, *n* (%)	6 (10.9)	5 (20.0)	1 (3.3)	0.0484
Treadmill walk, maximum pain distance, m	414.4 (241.4)	386.2 (257.5)	434.5 (241.4)	0.4983
Treadmill walk, onset of pain distance, m	144.8 (144.8)	128.7 (112.6)	160.9 (160.9)	0.5491
Exercise behavior score	16.6 (14.7)	16.2 (15.1)	16.9 (14.5)	0.8179
WIQ[b]				
Walking distance	43.6 (31.7)	39.7 (30.5)	46.8 (32.8)	0.7147
Walking speed	43.9 (26.6)	46.6 (28.9)	41.6 (24.7)	0.3374
Stair climbing	47.4 (30.8)	50.7 (29.4)	44.7 (32.2)	0.4729
MOS SF-36, mean (SD)				
Physical functioning	38.3 (9.5)	39.5 (9.04)	37.2 (9.9)	0.3776
Role—physical	40.2 (14.9)	41.6 (14.2)	38.9 (15.7)	0.8091
Bodily pain	46.2 (9.4)	47.0 (9.0)	45.6 (9.8)	0.5130
General health	43.6 (9.4)	42.9 (8.9)	44.3 (9.9)	0.4375
Vitality	45.0 (13.2)	43.1 (12.4)	46.6 (13.9)	0.4660
Social functioning	50.8 (8.5)	51.6 (8.5)	50.1 (8.7)	0.7280
Role—emotional	19.3 (3.0)	19.3 (2.7)	19.3 (3.2)	0.8034
Mental health	29.5 (12.7)	28.5 (13.1)	30.3 (12.6)	0.5409
Biomarker levels				
Soluble intercellular adhesion molecule	255.9 (87.4)	239.9 (58.678)	263.9 (96.7)	0.2652
Interleukin-6	4.1 (3.5)	4.5 (3.2)	3.7 (3.5)	0.3286
Soluble vascular cell adhesion molecule	902.8 (306.6)	928.6 (301.9)	877.5 (304.3)	0.5362
Monocyte chemoattractant protein	418.6 (132.4)	438.9 (139.9)	402.6 (124.9)	0.3193
Beta-2 microglobulin	3.3 (1.8)	3.6 (2.1)	2.9 (1.6)	0.1586
Total cholesterol	171.7 (39.9)	161.6 (41.4)	181.9 (40.1)	0.0729
Triglycerides	232.9 (178.1)	175.1 (120.4)	272.2 (193.6)	0.0273
High-density lipoprotein	43.8 (15.1)	44.7 (15.9)	42.6 (14.1)	0.6014
Low-density lipoprotein	86.2 (30.9)	80.4 (29.6)	91.6 (32.7)	0.2193
C-reactive protein	5.0 (5.4)	5.3 (6.0)	4.8 (4.9)	0.6989

ABI: ankle brachial index; WIQ: Walking Impairment Questionnaire; BMI: body mass index; MOS SF-36: Medical Outcomes Study 36-item Short-Form Health Survey; SD: standard deviation; MI: myocardial infarction.

For the baseline outcome measures, we present means and SDs.

*Fisher's exact test for categorical variables and *t*-tests for continuous variables.

[a]Two answered more than one category; *t*-tests comparing means of the two randomized groups.

[b]Each domain is scored on a 0–100 scale, 0 representing a complete inability to perform the task and 100 representing no limitations in walking short and long distances, walking at a fast pace, and climbing three flights of stairs.

Table 2. Comparison of intervention and control groups, change from baseline to 6 months.

	Total, mean (SD)	Control, mean (SD)	Intervention, mean (SD)	*p* value*
Soluble intercellular adhesion molecule	6.72 (38.5)	8.4 (36.0)	4.6 (40.6)	0.2097
Interleukin-6	0.29 (4.6)	0.1 (5.1)	0.5 (4.5)	0.6558
Soluble vascular cell adhesion molecule	19.72 (109.8)	37.1 (124.1)	5.1 (88.2)	0.1972
Monocyte chemoattractant protein	7.55 (99.4)	−13.1 (106.3)	37.6 (114.6)	0.5827
Beta-2 microglobulin	0.24 (0.8)	0.3 (0.9)	0.2 (0.5)	0.0329
Total cholesterol	−5.29 (24.5)	1.3 (19.7)	−10.1 (26.3)	0.1231
Triglycerides	−20.93 (96.4)	−0.3 (62.2)	−32.1 (106.9)	0.1205
High-density lipoprotein	−1.0 (6.8)	1 (7.1)	−2.7 (5.9)	0.2747
Low-density lipoprotein	−1.24 (17.9)	−0.7 (19.2)	−1.5 (13.1)	0.6182
C-reactive protein	−0.54 (4.5)	−0.8 (3.0)	−0.4 (4.9)	0.3853

SD: standard deviation.
*p value from a t-test.

associated with changes in markers of inflammation including CRP, IL-6, and soluble P-selectin. In contrast, in the work by Saetre et al.,[31] supervised exercise training delivered for only 2 months significantly reduced plasma levels of endothelial inflammatory markers E-selectin and intercellular adhesion molecule-1. Such findings may reflect the role of exercise to reduce endothelial-specific markers but not more general markers of atherosclerosis and inflammation.

Persons randomized to our home-based walking program demonstrated a reduction in triglyceride levels as compared to participants randomized to our attention control group. This trend has been demonstrated in prior work denoting the benefits of exercise on lipid profiles.[32–35] However, surprisingly, HDL did not increase in response to exercise. Furthermore, although this pilot study was underpowered to observe statistical significance, there was a greater decrease in HDL among persons in our home-based walking group as compared to those in our attention control group, which should have clinical significance in the consideration of low-cost low-intensity treatment options for diabetics with PAD. Reasons for this decrease in HDL are not clear, but may be a reflection of the higher use of cilostazol in the control as compared to intervention group. Cilostazol is an oral agent that is used to improve walking distance in patients with symptomatic PAD.[36,37] In addition to its positive impact on lower limb function, cilostazol is known to increase HDL.[37] Further work is needed to determine whether these effects are enhanced when combined with walking therapy.

Limitations of the study include the small sample size. As this was a pilot study, our findings reflect trends, and further work is needed to definitively address our hypothesis in a larger trial. Our pilot study is the first to determine the effect of a home-based walking program on inflammatory markers in persons with DM and PAD.

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T.C.C. interpreted data and was the lead writer of the manuscript; P.T.-A. led data analysis and assisted with writing.

Declaration of conflicting interests

There are no disclosures.

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