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Effects of a Low-Intensity Walking Intervention on Walking Performance Measures in Patients with Peripheral Artery Disease

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The purpose of this study was to examine the effects of a low-intensity (pain-free) walking intervention on walking performance and self-report measures in patients with peripheral arterial disease (PAD). Thirty-three participants who experienced intermittent claudication were assigned to either a walking group (n = 18) or a comparison group (n = 15). The walking group performed a structured walking program (pain-free walking, 5 days per week for 12 weeks). The comparison group maintained their usual daily activities. Tests of walking performance included a treadmill test (pain-free, functional and maximal walking distances were measured) and the 6-minute walk test. Self-perception of walking ability was determined using the walking impairment questionnaire. Circulatory measures were obtained from the ankle-brachial index, (ABI). Participants were assessed at the beginning (Week 1) and end of the study (Week 12). Members of the walking group significantly increased their walking performance and self-perception of walking ability, whereas the ABI remained the same. These results show that participation in a 12-week, low-intensity (pain-free) exercise program can enhance physical performance, perception of walking ability and maintain the ABI suggesting that a home-based exercise program is a viable alternative to traditional exercise programs prescribed for patients with symptomatic PAD.

Keywords: *peripheral artery disease, exercise, walking performance, ankle-brachial index, walking impairment questionnaire*

Introduction

Peripheral artery disease (PAD) is a common manifestation of atherosclerosis whereby blood flow to the lower extremities is reduced (Selby 2008). As a result, patients with lower extremity PAD are often limited in their walking ability. Although a relatively unrecognized and under-treated disease, between 10 to 20% of the population over age 55 may have PAD (Regensteiner and Hiatt 1998) and its prevalence increases with increasing age with reports of over 30% of adults over the age of 70 affected by the disease (Aronow 2009, Oka 2006). Approximately 15% of patients with PAD seek medical care for classic symptoms of intermittent claudication (IC), defined as cramping, aching, pain, weakness or fatigue in the legs that occurs with exertion and is relieved after 5 to 10 minutes of rest (Treat-

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Jacobson et al. 2019). The goal of treating patients with PAD is to reduce cardiovascular events as well as improve walking performance and quality of life (Hiatt et al. 2014). Lifestyle interventions, including dietary modifications, smoking cessation, physical exercise, pharmacologic interventions and surgery are used in the treatment of PAD (Dobesh et al. 2009, Hiatt 2001). Regular participation in light-intensity physical activity has been shown to reduce the risk of cardiovascular disease and all-cause mortality in patients with PAD and intermittent claudication by 50% (Gardner et al. 2020).

Supervised-treadmill exercise training programs are recommended by the American Heart Association/American College of Cardiology (AHA/ACC) as a Class I intervention (i.e., general agreement on treatment effectiveness) for patients with PAD (Gerhard-Herman et al. 2017). Such exercise programs have been successful in enhancing walking ability as measured by improvements in maximum walking distance. However, a recent systematic review conducted on the availability of supervised exercise programs for patients with PAD indicated that only 30.4% of patients have access to supervised exercise programs worldwide (Makris et al. 2012). This finding, in addition to the costs and travel time involved have led clinicians to consider home-based exercise programs (recommended as a Class IIa intervention) as a viable alternative to supervised treadmill exercise.

This study was performed with 33 patients with intermittent claudication. Participants were recruited from a larger on-going cohort study designed to examine factors that are associated with functional performance in patients with PAD. The walking program used for this study was based upon an intervention designed by Brown et al. (1994) that has been used with success in patients with cardiovascular disease (Brown et al. 1994, Goldie et al. 2013, Hua et al. 2009). Eighteen participants participated in our intervention. The specific research question was:

> Can a low-intensity, pain free walking intervention in patients with PAD improve walking performance measures, self-assessment of walking ability and ABI?

A literature review was performed to determine the extent other researchers had investigated the effects of a home-based, over-ground, pain-free walking intervention on performance measures, self-assessment of walking ability and ABI. This is followed by a presentation of the methods and results of this study. The final section of this paper discusses the results and limitations of this study as well as implications for future clinical practice.

Literature Review

A review of the literature was performed to examine the effects of walking exercise in patients with PAD. Electronic databases including Ovid Medline (1950 to date), Cumulative Index for Nursing and Allied Health Literature (CINAHL [EBSCO]); PubMed, Web of Science, Google Scholar and the Cochrane Library were searched for relevant publications written in English and available on-line. The reference lists associated with published manuscripts were also searched. The

following keywords were used in the search: "peripheral artery (arterial) disease", "peripheral vascular disease", "peripheral arterial occlusive disease", "intermittent claudication", "physical activity", "exercise" and "walking". Review papers and controlled trials (randomized and non-randomized) that focused on walking interventions and published since 1960 were examined for this review.

Several different outcome measures are used to determine the effects of an exercise intervention on walking ability in patients with PAD. These include performance times (or distances) on treadmill tests, the distance walked in 6-minutes (the six-minute walk test), self-report measures (focusing on walking impairment and quality of life) as well as the ankle-brachial index (the ABI). The ABI, a measure of the blood pressure in the foot relative to that in the arm, can be used to assess the extent of occlusion of the arterial lumen in the lower leg. A ratio of 1.00 is normal, whereas ratios of 0.7 to 0.9, 0.5 to 0.69 and < 0.5 are representative of mild, moderate and severe disease classifications (Shammas 2007).

Many supervised as well as home-based exercise programs for patients with PAD encourage participants to exercise to severe leg discomfort. Exercise to maximum pain tolerance has been shown to consistently improve walking performance (pain-free and maximal walking distance), six-minute walk distance and self-report measures (such as improved scores on the walking impairment and quality of life questionnaires) (McDermott et al. 2013, Nicolai et al. 2010). However, a recent meta-analysis of studies that examined the effects of exercise to maximum pain tolerance for intermittent claudication reported little change in the ankle-brachial index (mean difference 0.04, 95% CI 0.00 to 0.08) following training (Lane et al. 2017).

Despite the benefits associated with regular exercise to severe leg discomfort, one drawback is that patients with PAD can exhibit an elevated blood pressure response to this type of exercise (Bakke et al. 2007). In addition, higher intensity exercise (above 50% of the maximum aerobic capacity) requires activation of the sympathetic nervous system (accompanied by withdrawal of the parasympathetic nervous system) leading to increases in HR to meet metabolic demands (Goldsmith et al. 2000). This could further accentuate any underlying cardiovascular complications that the patient might have.

Pain-free exercise training has several advantages over exercise programs that encourage participants to walk to severe pain. These include greater participant engagement (due to minimal pain) (Rejeski et al. 2008), decreased ischemic-induced inflammatory responses (Martinez et al. 2009), minimal activation of the sympathetic nervous system (Goldsmith et al. 2000) and improvement in aerobic capacity (Martinez et al. 2009). Several studies have examined the effects of low-intensity, pain-free walking interventions in patients with peripheral artery disease (see Table 1). The majority of these studies are treadmill-based, with only one study having participants perform over-ground walking exercise (Mannarino et al. 1989).

Boyd et al. (1984) examined 8 patients (6 men and 2 women) with intermittent claudication. Participants performed pain-free exercise (3 times per week; starting at 25 min and progressing to 40 min; for 12 weeks) which could be completed using a treadmill, bike or a track. Pain-free exercise training performed over 12

weeks significantly increased pain-free walking distance (PFWD) by 138% and 44% in maximum walking time (MWT) however, ABI did not change.

Mannarino et al. (1989) then examined the effects of a daily 1-hr, pain free walking session performed over 6 months on pain-free walking time (PFWT) and maximum walking time (MWT) in 8 patients with PAD compared to 8 control patients receiving placebo medication. PFWT increased 87% and MWT increased 67% in the exercise group. However, there were no changes in the ABI, calf blood flow or transcutaneous oxygen pressure. Thus, it was thought that the improvements in walking performance measures may be due to a change in skeletal muscle metabolism, a redistribution in blood flow or an increase in the pain threshold.

In a study involving 80 participants, Mika et al. (2005) demonstrated that treadmill training, up to 85% of the distance to the onset of claudication pain, performed three times per week over 12 weeks leads to a significant 119.2% improvement in the PFWD (or time to onset of claudication pain) without triggering an inflammatory response. There were no changes in leukocyte count, neutrophil count or microalbuminuria following training, indicating that no ischemic-reperfusion injury occurred with this type of exercise program. This provides support that pain-free exercise therapy is low-risk in patients with PAD.

Similar results have been shown to occur following twelve weeks of treadmill exercise training up to mild/moderate pain level in elderly patients with PAD and IC (Tsai et al. 2002). Patients in the exercise group (n = 27) were encouraged to walk on a treadmill up to 30 min, 3 times per week at pain level scores between 2 and 3; whereas participants in the control group (n = 26) maintained their usual lifestyle. Improvements in walking function (PFWD, MWD and 6MWT) as well as health-related quality of life (QoL) measures were observed. The authors reported that an improvement of perceived physical health, enabled the patients to become more functionally independent.

The efficacy of various protocols has been examined by Gardner et al. (2005) and Martinez et al. (2009). Gardner et al. (2005) examined the effects of exercise intensity on walking performance measures following a low-intensity (40% of maximal exercise capacity) or high intensity (80% of maximal exercise capacity) walking program in 64 patients with PAD. Although this 6-month exercise program had participants walk to maximum pain tolerance on a treadmill, 3 times per week for 15-40 min, the improvements in PFWD (109%) and MWD (61-63%, respectively) were similar between the two training intensities. Thus, low intensity exercise training can induce similar changes in performance measures as high intensity exercise training can, provided that the total volume of exercise is the same.

Martinez et al. (2009) examined the effects of three different pain-free exercise training program durations on walking outcome measures. Participants walked on a treadmill twice a week for 30 to 50 minutes at an intensity below their individualized pain threshold. Eighty-four participants were allocated to three different training duration groups: 1) 2–9 weeks (n = 28), 2) 10–14 weeks (n = 30), and 3) 15–94 weeks (n = 26). 10–14 weeks of training was optimal for achieving the most (122%) improvement in maximum walking distance.

Barak et al. (2009) attempted to identify various mechanisms that could contribute to the improvement in walking performance that is observed with low intensity, pain-free exercise training. They estimated oxygen consumption (EVO_2), determined the metabolic equivalent (MET) and estimated the total and rate of energy expenditure (ETEE and EREE, respectively) during exercise, before and after 6 weeks of training, on a treadmill (twice per week for 45 min). EVO2, MET, ETEE and EREE all improved with training (20%, 20%, 80% and 20%, respectively). In addition, they found a 104% increase in maximum walking distance (i.e., 1.0 km), a 55% increase in duration (i.e., 13.3 minutes more) and a 41% increase in walking rate (i.e., 0.9 km/hr faster). The results of pain-free studies for patients with PAD are summarized in Table 1.

Table 1. *Studies on the Effect of Pain-Free Exercise (Walking) Training on PAD Outcome Measures*

			Training			**Outcome measures**		
Author (year)	Sample Size (n)	Study Length (wks)	Freq. (times/wk)	Duration (min)	Mode	Walking Performance	Self-Report	ABI
Barak et al. (2009)	10	6	2	45	TM	↑ MWD		
Boyd et al. (1984)	8	12	3	25-40	TM, Bike, Ground	↑ PFWD ↑ MWT		↔
Gardner et al. (2005)	31	24	3	15-40	TM	↑ PFWD ↑ MWD	↑ WIQ-D ↑SF36-PF	↔
Mannarino et al. (1989)	16	24	7	20-60	Ground	↑ PFWD ↑ MWD		↔
Martinez et al. (2009)	84	94	2	30-50	TM	↑ MWD		
Mika et al. (2005)	80	12	3	___	TM	↑ PFWD		

Legend: ABI = Ankle-Brachial Index; MWD = Maximum walking distance; MWT = maximum walking time, PFWD = pain-free walking distance; TM = treadmill; WIQ-D = walking impairment questionnaire distance score; wk = week; ↑ = increase; ↔ = no change.

Brown and colleagues (Brown et al. 1994) have used over-ground low-intensity exercise conditioning program lasting three months in their research. A recent publication examined the effects of this low intensity, pain-free walking intervention on heart rate variability (HRV) in patients with PAD (Brenner et al. 2020). HRV was analyzed via spectral analysis. It was reported that HRV increased following 12-weeks of training, this demonstrated a change in autonomic balance (i.e., an increase in PNS activity and a decrease in sympathetic modulation). Over time, these changes may improve sympathetic regulation and increase peripheral blood flow leading to an improved ability to walk.

The purpose of this element of the study was designed to examine the effects of a 12 week, progressive, home-based, low-intensity (pain-free) walking exercise program on performance, self-report measures and ABI in participants with PAD. It was hypothesized that patients diagnosed with PAD and IC who participated in this intervention would increase their MWD, 6MWT distance and self-report measures with no change in ABI.

Methodology

This experimental, 12-week study, used a pre-test, post-test comparison group design (Neutens and Rubinson 2010) to examine the effects of a walking intervention in patients with PAD. The study was conducted between July 2011 and December 2013 inclusive, was approved by Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board (Study Code: NURS-268-11) and was conducted in accordance with the Declaration of Helsinki. Written, informed consent was obtained from all participants prior to enrollment in the study.

Participants

Study participants were recruited from a cohort study, designed to examine factors associated with physical function in patients with PAD, held in a vascular clinic in an acute care hospital located in southeastern Ontario, Canada. Participants of the cohort study who had checked a box on their consent form allowing them to be contacted to participate in other studies were contacted by phone, or in-person, and were invited to participate in the study. Patients 18 years of age or older, diagnosed with stable PAD (Zwierska et al. 2005) including symptoms of intermittent claudication and an ankle brachial index (ABI < 0.9) were included in the study. Exclusion criterion included the inability to read and/or write English; current involvement in a structured exercise program; comorbid conditions that limited exercise participation (i.e., congestive heart failure, COPD, severe arthritis, limb amputation); living in a nursing home; wheelchair dependency; presence of non-compressible arteries (ABI > 1.2; (Amini et al. 2013) or cognitive impairment (i.e., dementia or Alzheimer's disease).

Forty-eight patients (28 men and 20 women), who met the eligibility criteria, volunteered to participate in the study. Participants ranged in age between 49 and 88 years (mean ± SD, 67.8 ± 8.1 years) with an ABI averaging at 0.54 ± 0.18. Thirty-three participants (aged 66.3 ± 7.9 years) completed the study. Reasons for drop-out from the study included a lack of interest (n = 3), injury unrelated to the study (fall, n = 2), fibromyalgia (n=2), anxiety (n=1) and renal failure (n = 1) or inability to complete all parts of the testing protocol (n=6).

Procedure

Pretesting

Participants were asked to refrain from strenuous physical activity for 24 hours and from consuming alcohol or caffeine at least 12 hours prior to their arrival at the exercise testing laboratory. Upon arrival at the laboratory, eligible participants were given an explanation of the study, provided an opportunity to have their questions answered (if any) and gave their written, informed consent to testing. Relevant demographic and medical information (including age, gender, education, marital status, occupation, co-morbidity and medication use) was obtained from the participants. Anthropometric measures (height, weight) were obtained, using a

health-o-meter scale (Healthometer Corporation, Bedford Heights, Ohio Body), from which body mass index (BMI, weight/height $[m]^2$) was determined. Body composition (percent body fat) was determined from skinfolds taken at 4 locations (triceps, biceps, subscapular and suprailiac crest) using a Harpenden skin fold caliper and body assessment software package (Batty international, West Sussex, UK). A soft, plastic measuring tape was used to measure waist and hip circumferences which allowed for the calculation of the waist to hip ratio.

Ankle-Brachial Index

Following a 10-minute rest period in the supine position, the right and left brachial and crural pulses (dorsal pedis artery and posterior tibial artery) were measured using a bi-directional Doppler device (ES-100 VX mini-dop, Kovin Technologies Canada, Winnipeg, Manitoba) the ABI for each leg was calculated using the mean of the ankle systolic pressures on each foot divided by the average pressure in both arms except when there was a 10 millimeter or more difference, in which case, the higher pressure was used (Klein and Hage 2006). The ABI was assessed at the beginning (Week 1) and end of the study (Week 12), with the lower of the ABI readings (i.e., the ABI of the more deceased extremity) obtained at each test time being reported.

Treadmill Test

A symptom-limited exercise test was performed using a TRUE performance treadmill (PS 300, ST. Louis, MO). This test was conducted at the beginning (Week 1) and end of the study (Week 12). Following the Gardner-Skinner protocol (Gardner et al. 1991) participants began walking on the treadmill at 1.1 miles per hour (mph), 0% grade. Walking speed was gradually increased by 0.1 mph every 10 seconds until 2 mph (3.22 km/hour) was reached. The speed was then held constant at 2 mph (3.22 km/hr) and the gradient was increased every two minutes thereafter by 2% until maximal claudication pain, exhaustion or 30 minutes had elapsed. Participants were asked to indicate when they initially experienced pain or discomfort (pain-free walking distance, PFWD), when they would normally stop walking (functional claudication distance, FCD) as well as when pain was so severe that they were required to stop walking (maximal walking distance, MWD). Functional claudication distance (FCD) was defined as the distance covered when a patient would prefer to stop walking as a result of the claudication pain as most people do not stop initially when they first experience pain (Kruidenier et al. 2009).

Six-Minute Walk Test

Following the treadmill test, participants rested until their leg pain resolved and then performed the six-minute walk test (6MWT) which measures an individual's ability to walk a pre-defined track or course (commonly set up in a corridor) for 6-minutes. For this study, participants walked up and down a hospital corridor

around a marker set at a specific distance (27.4 m [90.0 ft], limited by the length of the hallway). They were instructed to walk as far as possible in 6-minutes and were allowed to stop walking during the test to rest when they experienced pain or discomfort in their lower extremities. The distance covered in 6-minutes was measured and recorded.

Walking Impairment Questionnaire

Participants completed the Walking Impairment Questionnaire (WIQ) while they recovered from the treadmill test and before they participated in the six-minute walk test. This is a self-administered, disease-specific questionnaire consisting of 14-items with three subscales (distance, speed and stairs) that assesses the presence of peripheral arterial disease as well as the effect of the disease on perceived walking ability (Nicolai et al. 2010). This questionnaire also contains questions to rule out other factors besides PAD as the cause of impairment (i.e., pain, stiffness or aching in the joint; chest pain, shortness of breath, or heart palpitations). Responses were scored on a Likert scale from 0 to 3 (with 0 for "unable to do", 1 for "much difficulty", 2 for "some difficulty" and 3 for "no difficulty"). WIQ subscales scores were obtained by multiplying the number representing distance (feet), speed (mph) or stairs climbed (steps) by degree of difficulty. A total score was determined from each of these measures. A score of 100 represented no difficulty in walking long distances, walking fast or being able to climb three flights of stairs and a score of 0 represented extreme limitation in a measure.

Exercise Training Protocol

Following pretesting (Week 1), participants were randomly assigned to either a 12-week walking intervention program (walking group) or to a sedentary comparison group. Participants selected their group assignment from sex-specific envelops, which had slips of paper labeled as either "walking group" or "comparison group". For the walking group, participants were provided with a structured exercise program which began with walking 0.4 kilometers per day (until the onset of claudication pain, Borg CR-10 score $\leq$ 2), 5 days per week at an intensity $\leq$ 40% of the heart rate reserve (this corresponded to a rating of perceived exertion [RPE] between 11 and 13) at the onset of the study. This was followed with a gradual increase in walking distance every two weeks to reach 3.2 kilometers per day by the end of the study (Brown et al. 1994). Participants were given verbal as well as written instructions on the walking intervention and were provided with an activity diary. They were instructed on how to measure their own heart rate (HR), on how to use Borg's RPE and CR-10 pain scales as well as what to record in their activity diary. Members of the comparison group were asked to maintain their usual lifestyle for the duration of the study and were also provided with an activity diary to record any physical activity (including type, duration and HR) they performed during the week. These individuals were also instructed on how to take their own HR.

Every two weeks, follow-up phone calls were made to all participants to address any concerns/questions the participants may have had and to monitor participants'

compliance to the study protocol. At Week 12, all participants returned to the lab for follow-up testing (which included the treadmill test, 6MWT, assessment of ABI and completion of the WIQ).

Statistical Analysis

The IBM Statistical Package for Social Sciences, Version 27 (IBM SPSS, Chicago, IL) was used for all data analyses. Baseline anthropometric, demographic characteristics and data from the activity diaries were compared using either an independent T-test for continuous data or Chi-square analysis for categorical data. Data that was not normally distributed was log transformed prior to analysis. Walking performance measures, self-report scores and ABI measures were analyzed using repeated-measures ANOVA with one between-group factor (Group: Walking, Comparison) and one within-group factor (Time: Week1, Week 12). Pearson correlation coefficients were calculated based upon delta values (Week 12 - Week 1) obtained for performance measures, WIQ scores and ABI measures. The level of significance was set at $p \leq 0.05$ (2 tailed). Results are presented as means (SD).

Results

Baseline anthropometric and demographic characteristics of the participants are presented in Table 2. There were no significant differences in any of these measures between members of the comparison group and the walking group. The majority (85%) of participants in the study had a disease severity of either moderate or severe. Most patients (75%) experienced claudication symptoms in their calves with the remaining experienced claudication symptoms in the thigh, buttocks or other location (most commonly the foot).

Table 2. *Baseline Characteristics of Participants (n=33) who Completed the Study*

Variable	Comparison Group (n = 15)	Walking Group (n = 18)	p-value
Age (years) (M ± SD)	63.7 (8.5)	68.6 (6.9)	0.077
Sex (men) (n, %)	9 (60)	12 (67)	0.692
ABI (M ± SD)	0.48 (0.17)	0.56 (0.20)	0.237
PAD (years) (M ± SD)	7.1 (4.7)	8.0 (9.2)	0.741
BMI (kg/m^2)	26.4 (5.2)	27.6 (5.2)	0.516
Percent fat (%)	31.5 (10.7)	33.7 (9.0)	0.523
Waist:Hip Ratio (M ± SD)	0.93 (.08)	0.93 (.08)	0.983
Maximal walking distance (m) (M ± SD)	252.1 (198.9)	364.0 (172.6)	0.097
Overall WIQ score	38.5 (18.4)	52.4 (21.5)	0.058

Legend: ABI = ankle-brachial index; PAD = peripheral artery disease; BMI = Body Mass Index); WIQ = Walking Impairment Questionnaire.

Members of the walking group were compliant with the prescribed exercise protocol. Analysis of the participant's written activity diaries indicated that participants in the walking group exercised significantly (p=0.039) more frequently than participants in the comparison group averaging at 5.2 ± 1.6 days/ week (97 ±

37% compliance) *vs* 3.3 ± 2.4 days/week. By the end of the study, participants in the walking group exercised for a significantly longer duration than the participants in the comparison group (38.5 ± 19.1 *vs* 25.1 ± 16.2 min per session). Members of the walking group covered 2.65 ± 2.10 km/session (74 ± 9%) by the end of the study, whereas members of the comparison group did not record the distance covered.

The original data for the ABI obtained at entry into the study (Week 1) and at the end of the study (Week 12) are presented in Table 3. The ankle-brachial index (ABI) measures were not normally distributed and, as a result, these values were transformed into the logarithm to the base 10 values before doing parametric analysis. Comparison of resting log ABI measures at entry (Week 1) with those obtained at the end of the study (Week 12) indicated a time by group interaction, $F(1, 31) = 4.354$, $p = 0.045$, whereby the ABI decreased on the comparison group and increased in the walking group after 12 weeks. There were no other main effects for the ABI measures.

Table 3. *ABI Measures, Walking Performance Measures and WIQ Scores for the Comparison and Walking Groups. Values are presented as Means (SD)*

	Comparison Group (n = 15)		**Walking Group (n = 18)**	
Variable	Week 1	Week 12	Week 1	Week 12
ABI	0.48 (0.17)	0.44 (0.12)	0.56 (0.20)	0.62 (0.21)
Treadmill test				
PFWD (m)	118.6 (116.0)	144.6 (104.7)	168.3 (90.8)	233.1 (115.3)
FCD (m)	203.3 (163.3)	226.8 (144.1)	284.7 (137.8)	418.8 (196.5)*
MWD (m)	252.1 (198.9)	278.1 (176.7)	364.5 (172.6)	488.5 (209.5)*
6MWT (m)	332.9 (98.2)	338.5 (66.7)	335.5 (87.3)	347.6 (92.0)
Self-report WIQ				
Distance score (%)†	36.3 (23.8)	58.6 (31.1)	52.0 (30.5)	62.6 (29.8)
Speed score (%)†	40.0 (25.6)	43.9 (21.1)	48.4 (24.2)	57.6 (22.8)
Stair climb score (%)†	39.2 (21.9)	45.3 (19.2)	56.7 (25.7)	66.4 (26.5)
Overall (%)†	38.5 (18.4)	49.3 (17.5)	52.4 (21.5)	62.2 (22.5)

Legend: PFWD=pain-free walking distance; FCD=functional claudication distance; MWD=maximal walking distance; 6MWT=six-minute walk test; WIQ=walking impairment questionnaire; * =$p<0.05$ significant between-group effect based upon delta values; † = Significant main effect of time (Week 1 *vs* Week 12).

Outcome measures obtained on the treadmill test (PFWD, FCD and MWD) are reported in Table 3. The treadmill data were not normally distributed, thus, logarithmic values to the base 10 were calculated for PFWD, FCD, and MWD at week 1 and at week 12. Repeated measures ANOVA was then performed on these data. Main effects of time were observed for the PFWD, $F(1, 30) = 10.134$, $p = 0.000$; FCD, $F(1,30) = 10.556$, $p = 0.003$, and MWD, $F(1,30) = 86.971$, $p = 0.000$. Furthermore, participants in the comparison group tended to have lower performance measures at entry into the study compared to the exercise (walking) group. As a result, delta values (i.e., change over time) were calculated for PFWD, FCD and MWD before undergoing a univariate analysis of variance. A significant "group" effect for FCD $F(1, 30) = 7.038$, $p = 0.013$ and MWD measures $F(1,30) = 6.778$, $p = 0.014$ was observed, with members in the walking group walking

further than members in the comparison group by the end of week 12. There were no significant main effects or interactions for performance (distance walked) on the 6MWT.

ANOVA performed on the results of the Walking Impairment Questionnaire revealed a main effect of time (Week 12 *vs* Week 1) for the distance score $F(1, 31) = 7.740$, $p = 0.009$, the speed score, the stair-climbing ability score $F(1, 29) = 5.042$, $p = 0.033$ and overall WIQ score, $F(1, 29) = 8.305$, $p = 0.007$, with each of these scores increasing over time (i.e., by Week 12).

All of the correlation coefficients between the change in performance scores and the change in ABI measures over time were significant (Table 4). In addition, the stair-climbing score and the overall walking impairment score were significantly correlated with the change in distance covered on the six-minute walk test.

Table 4. *Correlation Coefficients between Change in Scores in Objective Measures of PAD Disease Severity and those Obtained on the Walking Impairment Questionnaire over Time*

Variable	Ankle-Brachial Index (ABI)	Maximal claudication distance (MCD)	Six-minute walk test (6MWT)
Performance measures			
ICD	0.384*	0.592	-0.233
FCD	0.374*	0.716	-0.051
MWD	0.485**	------	-0.049
6MWT	0.425*	-0.049	------
WIQ – Score			
Distance walked	-0.003	0.263	0.208
Speed walking score	0.015	0.232	-0.047
Stair climbing score	0.027	0.059	0.580**
Overall score	0.015	0.288	0.363*

Legend: ICD = Initial claudication distance (ICD); FCD = functional claudication distance; WIQ = walking impairment questionnaire, * = $p < 0.05$ (2-tailed), ** = $p < 0.01$ (2-tailed).

Discussion

Sixty-nine percent of participants completed our study. Other studies examining the effects of a walking intervention on patients with PAD have reported that between 34 to 77% of participants completed their study (Mouser et al. 2009, Wullink et al. 2001). Differences in study length (12 weeks *vs* 24 weeks or more), type of walking intervention (i.e., pain-free walking vs maximum pain tolerance), the amount of feedback or support provided by the investigators are contributing factors to the variation in the attrition rate. Our limited number of dropouts indicate that our pain-free walking intervention was well-received by the participants.

The major finding of this study is that participants in the walking group demonstrated a significant increase in walking ability and maintained their ABI measures following the walking intervention. In addition, self-perception of walking ability as determined by the WIQ improved by the end of the study in both groups. These results support our hypothesis that patients diagnosed with

PAD and IC who participated in this intervention would increase their MWD, 6MWT distance and self-report measures and is supported by the literature.

Martinez et al. (2009) examined changes in pain-free walking distance, duration and speed in relation to various exercise program durations and concluded that a walking program continuing for 10 to 14 weeks led to the greatest changes in walking performance (122% in distance, 56% in duration, and 43% in speed). In this study, participation in the 12-week low-intensity, high frequency, walking intervention, led to a significant 47% increase in functional claudication distance and a significant 34% improvement in maximal walking distance. The results of this study are comparable to other reports indicating an improvement in walking performance measures following pain-free or low intensity exercise training in patients with PAD (Barak et al. 2009, Boyd et al. 1984, Gardner et al. 2005, Mannarino et al. 1989, Martinez et al. 2009, Mika et al. 2005).

However, members in the comparison group also increased their PFWD by 22%, FCD increased by an average of 12% and the MWD by 10%. The increase in walking distances observed in our comparison group may be attributed to an unwarranted increase in physical activity levels by members of the comparison group during the study as they were aware that they were taking part in an exercise study.

The 6MWT is an alternative measure of walking endurance that is a more useful measure to assess the effects of over-ground training (McDermott et al. 2020). Only one study examined the effects of an exercise program (3 times per week; 30 min/session; 12 weeks in duration; performed at mild to moderate pain intensity) on the six-minute walk test (6MWT) and reported a 21% increase in distance covered by the exercise group as well as improvements in perceived walking ability (Tsai et al. 2002). Although not statistically significant, the exercise intervention used in this study improved the 6-minute walk performance by 12.1 meters. This is noteworthy in that a 12-meter improvement in the 6-minute walk test has been considered a small, clinically meaningful change (or the smallest change that patients consider beneficial) (Gardner et al. 2018). Also interesting is the finding that participants in the comparison group performed better on the 6MWT compared to the treadmill test, since they had relatively little training on the treadmill. Members of the comparison group increased their walking distance by 5.6 meters at the end of the study. Extending our study further for an additional 3 months might have seen greater improvements in the 6MWT results.

The majority of studies reported that the ABI does not change with pain-free exercise training, especially over the short term (Boyd et al. 1984, Gardner et al. 2005, Mannarino et al. 1989) suggesting that there was no further progression of the disease over the duration of the study. However, one study which involved supervised treadmill-exercise to maximum pain tolerance, performed 3 days per week over 6 months reported a significant ($p < 0.01$) 3.3% increase in ABI in the exercise group (Izquierdo-Porrera et al. 2000). Our study found a significant correlation between ABI measures and all of the performance measures, indicating that changes in the ABI may contribute to the improvement observed in walking performance. The consequence of a reduction in ABI (as occurred in the

comparison group) is a subsequent decline in performance (McDermott et al. 2004).

Members of both groups attained higher scores on the walking impairment questionnaire at week 12. There were no significant differences between the groups on the distance, speed, stairs and overall scores. The lack of change in speed score indicated that patients with PAD did not walk faster following this type of walking intervention and this is supported by the data obtained on the 6MWT which indicated a small, albeit non-significant change in walking distance. Correlation analysis of changes in walking performance measures and changes in scores on the walking impairment questionnaire indicate that the results of the WIQ may be more closely related to changes in overground walking ability (as detected by the 6MWT). We found that the change in stair climbing ability and overall walking impairment scores were significantly correlated to the changes that occurred on the 6MWT, over time. This indicates that the WIQ may be a more sensitive tool in detecting changes that occur following an overground training program. This supports the finding that treadmill testing results are not always interchangeable with the 6MWT results in the assessment of walking endurance and self-perceived walking ability in patients with PAD (McDermott et al. 2020).

Researchers have proposed several different mechanisms to explain the improvement in performance measures that occur after exercise training. Regular (walking) exercise can lead to an improvement in walking economy (Womack et al. 1997), an increase in muscle blood flow (Boyd et al. 1984) and/or a change in skeletal muscle enzymatic activity (Dahllöf et al. 1974). An improvement in walking economy would lead to a reduction in oxygen demands. Boyd et al. (1984) reported an increase in muscle blood flow following pain-free exercise training in patients with PAD. Although Dahllöf et al. (1974) could not find a significant increase in calf blood flow following training, they did find greater storage of fuels (lipids and glucose) within the muscle as well an increase in succinic oxidase activity indicating increased capacity of the mitochondria respiratory chains. In addition, we have found that a low-intensity, high frequency exercise training program in patients with PAD can alter the sympatho-vagal balance (as reflected through heart rate variability measures) in favor of increased parasympathetic tone (Brenner et al. 2020). A reduction in sympathetic vasoconstriction can lead to an improvement in tissue perfusion resulting in an increased blood flow to calf muscles and an increased ability to walk. It is most likely that the factors contributing to the enhanced walking performance that is observed following exercise training is multifactorial and that future research is needed in this area.

Limitations

A major limitation of this study was that participants of the comparison group did not maintain their usual lifestyle during the study. Many members of the comparison group increased their level of physical activity during the study by walking more or participating in exercise classes (e.g., aqua-fit or resistance training). The increase in walking distances observed in our comparison group

may be attributed to an unwarranted increase in physical activity levels by members of the comparison group during the study as they were aware that they were taking part in an exercise study This may have reduced our ability to detect any significant between-group differences. However, it should be pointed out that this finding is not unusual and has been reported by others (Mika et al. 2005).

Secondly, this study was three months in duration. Therefore, the results of this study may not be generalizable to studies that are shorter or longer duration. Also, overground walking was used as opposed to treadmill exercise. A third comparison group who used a treadmill for their exercise protocol would have been desirable.

Conclusion

The results of this study provide support for the efficacy of a structured, progressive pain-free home exercise (walking) program for patients with PAD. Following 12-weeks of training, this study found a significant increase in functional claudication distance and maximal claudication distance in addition to maintaining the ABI in members of the walking group. Moreover, members of the walking group reached a minimal clinically important difference in the 6MWT (12 meters) following training. These changes can lead to an increased in self-perceived walking ability and this was found with the WIQ. Based upon the results of this study, clinicians who work with patients who have PAD with intermittent claudication should encourage regular pain-free walking at home. An increase in walking performance may lead to an improvement in functional independence and subsequently allow the patient to carry out their activities of daily living to a greater extent.

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