Pain-free treadmill exercise for patients with intermittent claudication: Are there gender differences?

Krishna Dipnarine¹, Sharon Barak²,³,⁴, Coleen A Martinez¹, Eliezer Carmeli⁵ and Christine B Stopka¹

Abstract
Intermittent claudication, a common symptom of peripheral arterial disease, results in insufficient blood flow and oxygen supply to lower extremity muscles. Compared to men, women with peripheral arterial disease have a higher rate of mobility loss with peripheral arterial disease due to poorer lower extremity functioning. This study evaluates the effect of supervised pain-free treadmill exercise on improving performance in women with intermittent claudication due to peripheral arterial disease in comparison to men. A total of 26 participants (women, n = 9, 34.62%; mean age = 67.58 ± 5.59 years; averaging 23.46 ± 3.91 visits and 10.46 ± 0.99 weeks in the program) diagnosed with peripheral arterial disease, with symptoms of intermittent claudication, partook in a 45 min treadmill walk, twice per week, below the participant’s minimal pain threshold. Female participants’ change scores showed 752%, 278% and 115% improvement in mean walking distance, duration and rate, respectively. Men improved 334%, 149% and 80%, respectively. Significant differences (p < 0.05) in pre and post measurements within each group support positive outcomes. No significant differences between groups were observed (Cohen’s d effect size > 0.80). Our results suggest that women reap similar benefits from this low-intensity treadmill program in comparison to men.

Keywords
Peripheral arterial disease, intermittent claudication, low-intensity exercise therapy, treadmill exercise therapy

Introduction
Peripheral arterial disease (PAD) is a condition in which the flow of blood through peripheral arteries is decreased, resulting in peripheral limb ischemia and muscle pain in the calves, thighs or buttocks termed ‘intermittent claudication’ (IC).¹,² IC is a common symptom of PAD, due to a decrease in blood flow to the lower extremities, resulting in insufficient oxygen supply to meet muscle metabolic demands.³ Most recent estimates as of 2007 indicate that approximately 8.5 million Americans are affected by PAD,⁴,⁵ including more than 5 million adults in the U.S. ages 60 and older, with two-thirds being asymptomatic.⁶

Through individual participant data from meta-analyses, the pooled prevalence of PAD in men and women increased as age increased.⁷ However, for patients > 80 years, PAD was more prevalent in men.⁷ According to the US 2010 census data, more women than men had PAD between ages 40–49 years and >70 years.⁷ In another study (n = 6880 patients), PAD prevalence in men was higher in the younger age group (<85 years old) compared to women, with a reversal in this trend after the age of 85 years.⁸,⁹ Only one-half of women with PAD are symptomatic,¹⁰ which produces an issue in detection of PAD through routine clinical histories.⁷ Furthermore, in addition to the classic symptoms of cramping and muscle pain in the leg muscles upon exertion, women have the atypical symptoms of leg and heel discomfort present during rest or exercise, which are not localized to the muscle.⁷

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Women experience the effects of PAD at least as much as, if not more, than men. More specifically, women with PAD have a higher rate of mobility loss due to poorer lower extremity functioning compared to men. Moreover, from hospital discharge data from New York, New Jersey, and Florida, Vouyouka et al. found that, for women receiving surgical interventions for PAD, mortality rates were substantially higher compared to men after adjusting for co-existing conditions. This lends support for more non-invasive approaches for PAD treatment to reduce pain and increase function.

Accordingly, Brenner et al. and Hirsch et al. call for more research to detect any differences between men and women regarding their response to exercise interventions such as that used in the present study. Due to previous low inclusion rates of women in supervised exercise studies, Hirsch et al. suggest a pooled analysis of data related to female participation to compare gender differences. Consequently, the rationale of this study is a need to detect any gender differences in response to the current methods of treatment for symptomatic PAD to reduce the onset of functional limitations and ultimately improve the quality of life of women with PAD.

A reduction in the ability to ambulate due to IC, fatigue and numbness is a mechanism by which PAD may promote cardiac and cerebrovascular disease. Farah et al. also found that the reverse effect exists. Cerebrovascular disease was shown to be associated with lower total walking distance. Furthermore, the cluster of hypertension, diabetes, cerebrovascular disease, coronary artery disease and chronic obstructive pulmonary disease was associated with lower claudication distance using the graded maximal treadmill test.

Women have a higher rate of mobility loss with PAD due to poorer lower extremity functioning compared to men. Patients with PAD completing supervised exercise training were found to have a higher level of event-free survival compared to patients who did not. Golomb et al. support the use of exercise for protecting against coronary artery disease and cerebrovascular disease due to its beneficial effects on the risk factors of insulin resistance, hypertension and dyslipidemia. When comparing the performance of women vs. men’s level of community-based physical activity based on daily ambulatory cadence, women with IC were found to ambulate slower and for shorter durations, experiencing claudication pain onset and maximal claudication pain sooner than men.

For patients with IC, a minimum of 30–45 min of supervised exercise training should be performed at least three times per week. There are various beneficial exercise therapy protocols for patients with IC. Exercise therapy interventions vary from maximal pain to pain-free treadmill exercise, unsupervised vs. supervised, home-based and interval training. Villemur et al. showed a statistically significant benefit for supervised training vs. unsupervised training. Vouyouka et al. found that interval treadmill training (with 3 min of active work-out followed by 3 min of active recovery, increasing intensity by increasing speed and treadmill slope) resulted in improved walking distance, although it was not specified how the program tailored to patients’ onset of claudication pain.

In their review, Lane et al. found that, compared to a placebo or usual care (e.g. antiplatelet therapy, pneumatic foot and calf compression, vitamin E), exercise therapy (i.e. variations of walking, skipping or running regardless of duration, frequency or intensity across studies) showed improvements in maximal (and pain free) walking distance, even at the three- and six-month follow-up, sustainable for over two years. Furthermore, Hirsch et al. found that patients with PAD showed consistent and clinically significant improvements with exercise training, regardless of gender. However, the intensity of the exercise programs was not specified.

Several studies call for patients to walk on a treadmill to maximal pain intensity. Having a motivated patient is important in adhering to an exercise plan and post-training on a continuous basis. Gardner et al. reported an 84% adherence rate, while using the maximal claudication pain method. However, the authors in the present study posit that having patients walk to their maximal-pain threshold may deter them from adhering to exercise programs (a reduction in motivation due to discomfort associated with exercise), and this method may place patients as an increased risk for further medical complications.

Given that women reportedly have a greater loss of mobility due to IC compared to men, this study focuses on investigating the effect of supervised pain-free treadmill exercise therapy on improving performance and reducing functional decline in women, in comparison to men, with IC due to PAD.

Methods
Participants

All participants were counseled on their rights and gave informed consent to participate after being made aware of the risks and benefits of the program, knowing that the program was free of charge and they can stop participating in the study at any time. Participants were referred from vascular surgeons from the Gainesville, FL and Charlottesville, VA areas. Inclusion criteria consisted of participants who were clinically diagnosed
with PAD, with symptoms of IC while ambulating. Therefore, these patients were more limited peripherally rather than centrally. Patients had to be able to commute to the exercise sessions twice a week, residing within a 90 min travel radius. Individuals who did not receive permission from their physician to participate in the exercise program were excluded.

Martinez et al.\textsuperscript{29} reported that a program lasting from 10 to 14 weeks produced the most improvement in exercise performance, compared to a 2–9 week program, which produced the second best, and 15 or more weeks, in which participants could be considered to be in the maintenance stage. Therefore, the analysis was further restricted to only the participants that participated for 10–14 weeks, comparing performance based on gender using pooled data reported from previous studies.\textsuperscript{3,26–30}

**Treatment protocol**

The study was approved by the Institutional Review Board at the University of Florida. The treatment protocol was as reported in previous studies.\textsuperscript{3,26–30} The protocol (see Figure 1) consists of having participants walk on a treadmill (Model 2000, Star Trac Treadmill, Unisen Inc, Tustin, CA) for 30 to 50 min

![Figure 1. Pain-free exercise treadmill protocol.](https://example.com/figure1.png)

*Note: Adapted from Barak S, Stopka CB, Martinez CA, Carmeli E. Benefits of low-intensity pain-free treadmill exercise on functional capacity of individuals presenting with intermittent claudication due to peripheral arterial disease. *Angiology* 2009; 60: 477–486, with permission.*
two days per week, below the participant’s minimal pain threshold (defined as a score of 0.5 to 1 on the IC Pain Scale, see Table 1).3,26–30 When participants felt IC pain, the speed of the treadmill was reduced by approximately 0.80 km with participants continuing to walk until the pain subsided. The patients would not stop unless they were at the minimum speed on the treadmill and a lower speed was not possible. In that situation, the participant would step off the treadmill and participate in proprioceptive neuromuscular facilitation stretching of the leg muscles. Once the pain diminished, the treadmill speed was increased until participants were walking >0.1 mph than the speed that elicited IC pain. In comparison to the maximal-pain method, participants in this study continued to walk at a decreased speed when they felt minimal pain, rather than walking until maximal pain was elicited and then stopping to recover.

**Outcome measures**

Outcome measurements included walking distance (km [min], duration [min], and speed [miles per hour, mph; kilometers per hour, kmh]) as recorded directly from the treadmill’s screen.

**Statistical analysis**

To answer the main question, as to the effect of supervised low-intensity pain-free treadmill exercise therapy program on functional capacity in women vs. men with IC due to PAD, four different types of analyses were conducted. First, mean differences between men and women in age, number of training sessions and in the three walking performance measures (i.e. walking distance, duration, and rate) were compared using independent t-tests. Second, differences from pretest to posttest in walking performance were analyzed independently for men and women using paired t-test.

Third, effect sizes (ES) in each group (men and women) were calculated using Cohen’s d (mean Δ/standard deviation average from two means)41 to determine whether women and men react similarly/differently to the intervention. For within-subjects studies, a correction for the dependence among means was conducted using the correlations between the two means following the Morris and DeShon’s42 equation. In general, values smaller and equal to 0.20 are considered trivial ES, values between 0.21 and 0.50 as small ES, values 0.51–0.80 as moderate ES, and values greater than 0.80 as large ES.41

Fourth, the percentage change from pretest to posttest in the three walking performance parameters was calculated to determine whether the improvements of men and women were similar. Men and women’s mean differences in percentage change were evaluated using independent t-tests. In addition, mean percentage changes were ranked. The similarity of the ranks’ ordering was then evaluated by using the Kruskal–Wallis test (H test).43 If the Kruskal–Wallis test was positive (p < 0.05), then a test for pairwise comparison of subgroups was conducted according to Conover.44

In between group differences in age and number of training sessions’ level of significance were set at 0.05. In the within and between-group analyses of the three walking performance indexes, the level of significance was set at 0.05 and adjusted to 0.017 (0.05/3 = 0.0166) using the Bonferroni procedure.

**Results**

A total of 26 individuals participated in this study (women, n = 9, 34.62%). Participants’ mean age was 67.58 ± 5.59 years. Program participation averaged 23.46 ± 3.91 visits and 10.46 ± 0.99 weeks (Table 2). No significant differences were observed in men and women mean age (66.76 ± 5.29 and 69.11 ± 6.13 years, respectively). No significant differences were observed in the number of training sessions for men and women (23.58 ± 3.96 and 23.22 ± 4.02, respectively).

**Table 1.** Intermittent claudication pain scale.

<table>
<thead>
<tr>
<th>Score</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No pain, no tightness or no tiredness</td>
</tr>
<tr>
<td>0.5</td>
<td>No pain, but some tightness or tiredness</td>
</tr>
<tr>
<td>1</td>
<td>Slight pain, but very minimal, very tolerable</td>
</tr>
<tr>
<td>2</td>
<td>Moderate pain, more than slight, but still tolerable</td>
</tr>
<tr>
<td>3</td>
<td>Severe pain, it really hurts, it is barely tolerable</td>
</tr>
<tr>
<td>4</td>
<td>Intolerable pain, exercise must cease immediately</td>
</tr>
</tbody>
</table>


**Table 2.** Cohen’s d for the mean difference (repeated measures) in walking performance.

<table>
<thead>
<tr>
<th></th>
<th>Men (n = 17)</th>
<th>Women (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walking distance</td>
<td>3.56</td>
<td>3.60</td>
</tr>
<tr>
<td>Walking duration</td>
<td>3.81</td>
<td>4.34</td>
</tr>
<tr>
<td>Walking rate</td>
<td>1.11</td>
<td>2.52</td>
</tr>
</tbody>
</table>

Note: Cohen’s d calculation: mean Δ/standard deviation average from two means; large differences: Cohen’s d > 0.80; Cohen’s d is based on a single-pooled standard deviation; Cohen’s d was corrected for dependence between means, using Morris and DeShon’s (2002) equation.
Walking performance

Figures 2 to 4 display the training effect on walking distance, duration and rate, respectively, for men and women. Paired t-test analysis shows that for female participants there was a significant difference from pre to posttest in: mean walking distance (pretest = 0.35 mi (0.56 km), posttest = 1.73 mi (2.78 km), p < 0.001); mean walking duration (pretest = 17.72 min, posttest = 47.17 min, p < 0.001); and mean walking rate (pretest = 1.06 mph (1.71 kmh), posttest = 2.20 mph (3.54 kmh), p < 0.001). Comparatively, for male participants, there was also a significant difference from pre to posttest in: mean walking distance (pretest = 0.53 mi (0.85 km), posttest = 2.04 mi (3.28 km), p < 0.001); mean walking duration (pretest = 21.18 min, posttest = 49.71 min, p < 0.001); and mean walking rate (pretest = 1.43 mph (2.30 kmh), posttest = 2.17 mph (3.49 kmh), p = 0.003).

Table 3 shows the percent change in walking performance parameters. For female participants, change scores showed approximately 752% improvement in mean walking distance, 278% in walking duration and 115% in walking rate. For men, change scores were 334%, 149%, and 80%, respectively.

Comparisons between men and women

Both men and women presented large ES (Cohen’s d > 0.80) in all walking performance parameters (Table 2). Independent t-tests revealed no significant differences were observed between men and women in the three walking performance measures in both pre and posttests. Comparing men and women percent change scores, no significant between-group differences were observed in both pretest and posttest for each of the above performance measures (Table 3).

Discussion

Walking performance – Gender differences

The female participants in this study, on average, improved walking performance mean distance by...
752%, mean duration by 278% and mean rate by 115%. Male participants improved 334%, 149%, and 80%, respectively. Similarly, Stopka et al.45 found that male and female participants following the same protocol utilized in the present study, walking twice a week for an average of nine weeks, resulted in an overall combined improvement in mean walking distance (408%), duration (163%) and speed (94%) (p < 0.01).

Independent t-tests revealed no significant differences between men and women in the three walking performance measures in both pre and posttests in the present study. These results are congruent with previous studies, which show that women with PAD experience similar outcomes from participating in a low-intensity pain-free treadmill exercise therapy program when compared to men.30 The analysis conducted by Hirsch et al.7 also found that there were clinically meaningful responses to maximal-pain exercise training programs for patients with PAD, regardless of gender. The present study provides support that a similar benefit can be obtained from low-intensity pain-free therapy for women with PAD.

Given that Gardner et al.21 found that the female participants’ preferred speed may be lower than their potential speed (which may be due to perceived fear of the impending pain, especially from activities such as climbing stairs due to greater calf muscle ischemia), perhaps the use of low-intensity pain-free therapy can help them achieve the goal of walking at a faster speed than their preferred speed by reducing the potential fear barrier and restoring confidence as function is regained.

**Comparison of maximal-pain vs. pain-free approach**

The results in the present study show a clear improvement in performance outcomes compared to baseline measures. These walking capacity improvements can contribute to the increase in participant’s range of daily activities and decrease their degree of disability. Bulmer and Coombes1 mentioned that most studies regarding patients with PAD and exercise training had the participants walk until moderate to maximal claudication pain was felt, and then the patients would stop to rest before continuing to walk. Using the
low-intensity pain-free method, as was used in the present study, allows the patient to continue to walk at a reduced pace, while there is a slight sensation of pain or discomfort, or to do proprioceptive neuromuscular facilitation stretches if the speed was at the lowest possible setting on the treadmill.\textsuperscript{3,26–30}

Historically, the near maximal-pain approach has been recommended to enhance walking performance. In their meta-analysis, Gardner and Poehlman\textsuperscript{24} found that the near maximal-pain method, applied during sessions of at least 30 min in length and at least three times per week for more than 6 months, yielded an increase in mean distance to onset of claudication (179\%, \(p < 0.001\)) and to maximal-pain (122\%, \(p < 0.001\)). Similarly, Gardner et al.\textsuperscript{23} observed an increase in treadmill distance walked to onset of claudication (134\%, \(p < 0.001\)) and to maximal-pain (77\%, \(p < 0.001\)). However, there was no change in
Claudication pain relief time. There was also an increase in the distance walked to the onset of pain during the 6-minute walk test (44%, p < 0.001). Crowther et al. reported no improvement in walking speed after a 12-month graded maximal-intensity treadmill program for 3 days/week, 25 min per session. This is in comparison to the low-intensity pain-free method, applied only twice per week, for 10–14 weeks, as in this current study, yielding a 752% and 334% improvement in walking distance for women and men, respectively. While not evaluated in the present study, future studies can monitor the claudication pain relief time over the course of the low-intensity pain-free program to see if there is a gradual reduction in the time required for women with PAD to regain function.

Mika et al. found that both pain-free and moderate-pain treadmill training produced significant improvement in walking performance in patients with IC. However, slightly better results were seen with the moderate vs. pain-free group (post-training walking duration was prolonged by 10% (p < 0.001) vs. 9% (p < 0.001), and time walking without pain improved by 120% (p < 0.001) vs. 93% (p < 0.001), respectively.

Adherence

Adherence was not measured in the present study. However, a previous study using the same method reported a 100% attendance rate with no attrition. The authors of the present study posit that the maximal-pain method, although capable of producing favorable results, may also deter patients from participating in exercise therapy due to the nature of discomfort, especially since women potentially have the atypical symptoms of leg and heel discomfort present during rest or exercise. Gardner et al. reported a high adherence rate (84%) using the maximal-pain method. Müller-Bühl et al. in their evaluation of adherence to a community-based supervised walking program for patients with PAD, reported that only 16% (36 out of 462) had regular attendance over the three-month program, although the intensity of the program was not specified.

A short two-month program, walking to maximal claudication pain three times per week, was found to be advantageous for high adherence, positive outcomes and lower costs compared to longer versions (e.g. six months). Martinez et al. reported that the best improvements in walking performance were seen with a 10–14 week low-intensity pain-free program with patients participating just three times per week, compared to a 2–9 week program or greater than 15 weeks. Methods that increase and maintain adherence can benefit from further study to assist in program planning for best patient outcomes.

Delivery of exercise therapy

Bendorrmacher et al. reported that supervised exercise therapy to increase walking distance in patients with PAD is feasible in a community-based setting, yielding effective results similar to clinic-based programs. Similarly, Barak et al. have shown that conducting a low-intensity pain-free treadmill exercise therapy program is efficacious at a community fitness center (“Fit for Life,” Gainesville, FL). This lends support to implement the low-intensity pain-free method in other fitness centers, thereby providing convenient access to this type of program for patients with PAD. Gardner et al. found that a home-based exercise program, using the maximal-pain method, was efficacious and showed improvements in performance similar to a supervised-exercise program. Similar studies with home-based low-intensity pain-free therapy have not been conducted.

Future directions

Limitations of this study include that there were no control group. However, given the nature of PAD with the symptoms of IC, the women in a control group could experience further morbidity and/or mortality due to lack of physical activity and functional impairment. Also, the sample size was small, which could have an effect on the statistical significance observed in this study.

Gardner et al. found that only 37% of women with diabetes and PAD in their study reported an increase in the claudication onset time using the maximal claudication pain method, compared to 100% of men with diabetes and PAD. Farah et al. found clustered co-morbid conditions to be associated with lower walking capacity using the maximal-pain method. Barak et al. have shown positive results in improved walking performance in patients with PAD and co-morbid conditions. The effect of using the low-intensity pain-free method to improve walking capacity can be further investigated in patients with PAD and clustered concurrent conditions.

Evaluating the self-perceived ability of patients undergoing pain-free treadmill therapy to walk and engage in activities, such as climbing stairs can identify areas in which motivation techniques or program modifications can be implemented to increase adherence both during and after participating in exercise therapy. Even though some of the participants in the present study had to drive approximately 90 min each direction to come to the therapy sessions, they were willing to, perhaps due to the mode of delivery (pain-free). This willingness to participate can be further studied, as it was not evaluated in the present study. The walking impairment questionnaire can be used to evaluate...
patient perceptions. Furthermore, adherence to a program using the maximal-pain method in comparison to the pain-free method can be evaluated to see what aspects of an exercise program are most beneficial for positive patient outcomes, and what factors would increase participation and adherence.

The techniques utilized by Gardner et al.\textsuperscript{49} could be implemented using the low-intensity pain-free method to observe performance improvements from a home-based exercise program, which may further increase convenience and accessibility for women with PAD compared to a supervised training program at a facility. The effects of unsupervised exercise for maintenance after completing a treadmill program remain speculative and can benefit from further study. Perhaps, a hybrid therapy session can be developed (i.e. using the low-intensity pain-free therapy in a facility, followed by a home-based version to ensure maintenance of function). The method used by Gardner\textsuperscript{23} to determine if there is an increase in daily physical activity (using an accelerometer) due to rehabilitation can be utilized in future studies using low-intensity pain-free therapy.

Based on Medicare data from 2001 regarding PAD healthcare costs, the cost burden was approximately $4.37 billion, with inpatient care accounting for 88% of that figure.\textsuperscript{50} Given that the medical complications from PAD result in a high economic burden, a randomized control trial evaluating the different approaches to treadmill therapy (maximal-pain vs. moderate-pain vs. pain-free), and the various delivery mechanisms (unsupervised vs. supervised, home-based vs. fitness-center-based and program length) would allow for an understanding of the best use of resources to facilitate positive outcomes for patients with PAD.

Conclusions

The results of this study show support for the use of low-intensity pain-free exercise therapy for women with IC due to PAD. A majority of the literature regarding exercise therapy for patients with PAD prescribe the maximal-pain method to increase time to claudication onset and improve performance measures. However, the low-intensity pain-free method has consistently shown improvements in performance outcomes. This presents an opportunity to implement programs that are inviting to patients with PAD so that they can be proactive in their treatment for PAD. This approach may improve quality of life through improving their ability to walk farther, for a longer time, and at an improved rate. In addition to utilizing this method of therapy, lifestyle changes to reduce the impact of comorbid conditions often seen in patients with PAD would allow for a reduction in the impact of PAD on the health and well being of patients. Furthermore, determining which aspects of an exercise program appeal to participants, both male and female, may improve adherence and maintenance. Most importantly, it will be invaluable to determine the aspects of a therapy program, which would result in the most positive patient outcomes. These components can then be utilized to structure the most effective and efficient program delivery. Future studies can compare the benefits of various therapy programs for patients with PAD, such as the low-intensity pain-free method, to reduce the negative effects of PAD and IC, enhance quality of life and lower the cost of care. This study provides support that low-intensity pain-free treadmill therapy can be used to improve walking performance outcomes for women with PAD, especially given their higher rates of functional decline and historically low inclusion in such studies.

Conflicts of interest

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