Chapter 3
The Role of Exercise in Treating Symptomatic Claudication in Patients with Peripheral Arterial Disease

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Exercise has been recognized as an important first step in treating patients with peripheral arterial disease (PAD) and claudication. Exercise does improve walking performance as a sole therapy or in combination with revascularization. There is a greater benefit when revascularization and exercise are combined [1]. In this chapter, we review data on exercise in symptomatic PAD patients with claudication.

Peripheral arterial disease (PAD) affects more than 200 million people worldwide and is associated with a poor quality of life, higher cardiovascular mortality, and higher major adverse limb events. A large percentage of patients with PAD are asymptomatic, and a smaller percentage has advanced limb ischemia. The remaining patients fall in the category of claudication or atypical limb pain. Claudication is defined as pain in the affected leg with exertion that resolves within 10 min of rest. The first-line treatment of claudicants, advanced limb ischemia patients, and asymptomatic patients is different. There is a consensus that patients with rest pain or ulcerations (chronic limb-threatening ischemia or CLTI) need to undergo revascularization to save their limbs as a first-line therapy. CLTI patients have a very high rate of amputation and cardiovascular death [2]. On the other hand, first-line treatment of asymptomatic patients is preventative with a focus on smoking cessation, exercise, high-dose statins, and antiplatelets. Revascularization for asymptomatic patients is not warranted in the majority of patients. Finally, exercise is now considered a first-line treatment for patients with claudication [1], with or without the addition of cilostazol. High-dose cilostazol 100 mg twice daily had a variable response in individual PAD patients, but there is an overall improvement in walking distance with this drug [3]. Failure of this initial conservative approach generally implies proceeding with revascularization. In patients, however, with very limiting

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symptoms and a significant compromise of their quality of life, a combined approach of preventative therapy, cilostazol, exercise, and revascularization may provide an optimal combined initial treatment strategy.

Definitions

Supervised exercise (SE): structured aerobic exercise under direct supervision in a facility.

Home-based exercise (HE): structured aerobic exercise performed at home.

Peak walking distance (PWD): maximum distance that can be walked before stopping because of limiting claudication on a treadmill test.

Peak walking time (PWT): maximum time that can be walked before stopping because of limiting claudication on a treadmill test.

6-min walk test (6 MW): maximum walking distance on a 6-min walking test.

Endurance shuttle walk test (ESWT): constant-load walk at submaximal capacity with endpoint is how long the subject can walk.

Medical Outcomes Short Form-36 (SF-36): questionnaire that assesses functional status and quality of life (QOL) and is non-disease-specific.

Walking Impairment Questionnaire (WIQ): self-reported measure of walking capacity and limitations. It incorporates speed and distance as well as stair climbing.

Vascular Quality of Life Assessment (VascuQOL): PAD-specific questionnaire. It assesses social and emotional well-being, activities, symptoms, and pain.

Peak walking performance: "the maximum distance or time walked, measured by an exercise treadmill, 6 MW, or shuttle walk within an individual study" [1].

Absolute claudication distance (ACD) is defined as the number of meters a patient walks before intolerable severe claudication occurs.

Vascular Effects of Exercise

Benefits of exercise in PAD patients include suppression of inflammatory processes, improving endothelial function and increasing nitric oxide synthase, remodeling of skeletal muscle by increasing capillary density, changing in microRNA expression, and increasing in arteriogenesis and angiogenesis. Angiogenesis is the budding of newly formed capillaries induced by hypoxia, whereas arteriogenesis is triggered by exercise and is the formation of functional collaterals from pre-existing arterio-arteriolar connections [4].

Exercise and/or Revascularization Versus Control

A meta-analysis of 27 randomized trials by Biswas et al. [1] showed that peak walking performance is better with exercise than control at 18-month follow-up. Depending on the measurement method, there was a net improvement of 8% (using 6MWD) to 54% (as measured by exercise treadmill testing). Furthermore, exercise improved claudication onset and QOL. Similarly, lower extremity revascularization (endovascular or surgical) resulted in superior peak waking distance and claudication onset on follow-up between 6 and 18 months. Using exercise treadmill, improvement in peak walking distance was about 54% based on strong evidence (level B) with additional strong evidence that this was sustained beyond 18 months. When exercise was compared to revascularization, a net benefit of peak walking performance using treadmill testing was 94% with exercise when compared to revascularization between 6 and 18 months. Weaker evidence suggested that in the first 6 months, revascularization performed better than exercise. Using the PAD-specific VascuQOL questionnaire, exercise and revascularization performed similarly. Finally, the combination of exercise and revascularization had the best improvement in peaking walking performance as measured by treadmill testing through 18 months of follow-up when compared to either exercise alone (156% net benefit) or revascularization alone (73% net benefit). Based on this most recent comprehensive meta-analysis, it appears that a revascularization-first approach to treat patients with limiting claudication will likely yield a quicker improvement in symptoms and along with exercise, a superior and sustained benefit will likely be seen on long follow-up [5]. Although the evidence is not strong, the combination therapy also led to less repeat revascularization at 12–18 months, whereas revascularization alone increased the need for repeat revascularization. Exercise combined with revascularization seems to yield the opposite outcome of less need for revascularization and therefore is a critical component of a comprehensive treatment of the patient [1, 5].

Exercise Programs for PAD Patients

The benefits of exercise are not immediate as normally seen with revascularization. A long-term commitment to exercise is critical to achieve the desired positive and durable results. Exercise can be performed in a supervised facility or at home [6, 7]:

(a) Supervised exercise training (SE).
(b) Home-based exercise training (HE).

Supervised exercise (SE) consists of at least 30–60 min of therapeutic exercise in patients with established symptomatic PAD and conducted in a hospital outpatient setting or physician's office supervised by qualified and trained individuals and under the direct supervision of a physician or an advanced practice provider trained in both basic and advanced life support. The trainer needs to determine the appropriate training modality and its intensity and educate the patient about what to expect from the exercise program. The program is a 12-week program with the option of extending this to 36 sessions. Transitioning the patient to a long-term program is important to continue to benefit from exercise.

Home-based exercise training (HE) is not as well defined as SE. The typical length is three to five sessions per week for 8–12 weeks. Long-term data beyond 36 weeks is not available. HE is flexible and generally better adhered to than SE and is more affordable. However, long-term data on HE and its impact is not clear although short-term improvements in functional capacity, QOL, and cardiovascular risk profile seem to be similar to SE despite the superiority of SE in improving maximal walking and claudication distances. HE however may carry some risks as in-person supervision is not available. Therefore, this is best suited for those who are stable and are mild- to moderate-risk patients.

There are several methods of exercise that have been evaluated. Data however comparing these methods remain of poor quality in general. These include supervised walking exercises, exercises to strengthen leg muscles, exercises that strengthen both arms and legs (Nordic), cycling, and arm ergometry. In a review of the types of exercise training on intermittent claudication, Janssen et al. [7] concluded that the various modalities of exercise were all beneficial in improving mean walking distance (MWD) and pain-free walking distance (PFWD). These different modes of exercise when compared to walking showed no clear differences for MWD or PFWD at 12 weeks or at the end of training. Also the walking impairment questionnaire (WIQ) distance score was not different between the two groups. The certainty of this evidence was judged by the authors to be low because of bias concerns and small sample size.

A sex-related difference in response to supervised exercise has been reported. Gommans et al. [8] reported on data from the prospective 2010 Exercise Therapy in Peripheral Arterial Disease (EXITPAD) study that randomized patients to SE or a walking advice. Analysis included 113 men and 56 women. ACD improved in both males and females but was significantly better in males during the first 3 months (Δ 280 m for men vs Δ 220 m for women; $p = 0.04$). Also the absolute walking distance was shorter for women after 1 year (565 m vs 660 m; $p = 0.032$). QOL and WIQ were similar however.

Cost-Effectiveness of Exercise for PAD

Bermingham et al. [9] reviewed data on cost-effectiveness of SE vs unsupervised exercise (USE). SE was cost-effective in 75% of model stimulations with an incremental cost-effectiveness ratio of £711 to £1608 per QALY gained. The authors concluded that SE should be made widely available and be a first-line treatment for

PAD patients with claudication. When compared to revascularization, SE was a more cost-effective primary treatment and was associated with more cost savings at a 5-year time (−€6412, 95% credibility interval (CrI) −€11,874 to −€1939) [10]. In order to reduce cost, a stepped-care model (SCM) that needs to be implemented with SE is the first strategy to treat claudicants. When this strategy was implemented among DUTCH patients, average cost of claudication treatment was 6% lower than a revascularization-first strategy [11]. Cost-effectiveness for revascularization needs to be looked at on the long term. The benefit of revascularization is lost on long-term follow-up (5 years). No improvement in QOL or walking capacity is seen following revascularization when compared to a non-invasive treatment approach at 5 years. The revascularization cost was also twice than that of the non-invasive conservative approach ($13,098 vs $6965, $p = 0.02$) [12].

Summary

Exercise is a very effective treatment for patients with intermittent claudication. Structured exercise is an ideal first approach to treatment but may not be affordable or convenient for some patients. HE is a good alternative. Both SE and HE require adherence to the program by the patient to optimize benefit, and the program should be at least for 3 months. The exercise program should be tailored to the patient, and several modalities of exercise are effective when compared to a supervised walking exercise. Although revascularization is effective in improving peak walking performance early after revascularization and likely more so in the very symptomatic patients, QOL and walking capacity are not superior to a non-invasive approach at 5 years and are costlier. A combination approach of SE and revascularization is promising as an initial first treatment, but the data is not strong, and more evidence is needed.

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