Current and Emerging Treatments for People Living with Lower Limb Ulcers

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Background

Lower limb ulcers (LLUs) are common, with a prevalence of 0.8 to 2.2 patients per 1000 population, doubling in incidence in people aged over 65. Only 20% of ulcers heal within three months, and 50% take longer than one year to heal. Venous ulcers are the most common LLUs and have been shown to cost 2% of the national health budget in the UK.[1] Diabetes-related foot ulcers (DFU) occur in up to 25% of individuals affected with diabetes during their lifetime and were recently found to be implicated in 79% of all minor amputations and 61% of major amputations in Australia and New Zealand.[2] Arterial ulcers become increasingly common with age and will be discussed below.

Management of Venous Leg Ulcers (VLU)

The basic tenets of VLU management are:

- Confirming the diagnosis: Ulcer location (generally lower third of calf) and associated features (swelling, venous skin changes, venous dermatitis)
- Excluding arterial disease (see below) and other causes of ulceration (e.g., vasculitis, malignancy)
- Utilizing compression therapy (graduated compression bandaging or compression stockings)
- Ordering early venous incompetence ultrasound (also known as a venous Duplex scan)

Early Ablation of Superficial Venous Incompetence

The Early Venous Reflex Ablation (EVRA) trial studied 450 patients who had venous ulceration for six weeks to six months, and an ankle-brachial pressure index (ABPI) less than or equal to 0.8 (i.e., no or minimal arterial disease as assessed by the clinician). Venous incompetence scanning demonstrated primary or recurrent superficial venous incompetence (great or short saphenous vein), either with or without deep vein incompetence. These patients were randomized to one of two study groups: 1) standard compression therapy or 2) compression therapy and early endovenous saphenous vein ablation with laser, radiofrequency, sclerotherapy or glue.[3]

The study found that ulcer healing time was quicker in the early ablation group (HR 1.38, 95% CI 1.13–1.68, p = 0.001). Median healing time was 56 days for the early ablation group ver-

sus 82 in the compression only group. Recurrence rate was also lower after one year, at 11.4% versus 16.5%. The two treatment arms were cost neutral, but there was a significant gain in quality adjusted life years.[4] It is important to note that appropriate compression therapy resulted in excellent healing times in the control as well as treatment group.

Approaches to the Non-healing Venous Ulcer

If a venous ulcer is not responding to compression with or without ablation in about two months (i.e., ulcer halved in area), clinicians should consider a punch biopsy to exclude other causes. If arterial disease cannot be excluded clinically, clinicians can use toe pressure measurements to guide the level of compression the patient should receive. The presence of calf swelling and ulceration above the ankle often makes taking an ABPI reading challenging or unreliable. Doppler waveforms can be used to exclude significant arterial disease (see below). It is important to note that recurrence rates are high when there is residual venous incompetence or if there is unrepaired deep venous incompetence. Therefore, in the setting of deep vein or residual superficial vein incompetence, long-term compression (usually with class 2 or 3 knee-high compression stockings) should be worn.

Assessment of Arterial Disease in Lower Limb Ulcers

Assessing for ischemia is important for determining etiology and the likelihood of healing of lower limb ulcers. Unfortunately, clinical examination is often unreliable, particularly in patients with diabetes, renal failure and leg swelling.

Chronic Limb-threatening Ischemia (CLTI)

CLTI is a spectrum of disease that includes patients with objectively documented peripheral arterial disease (PAD) *and* any of the following:[5]

- Ischemic rest pain (ankle pressure < 50 mmHg, toe pressure < 30 mmHg)
- Diabetes-related foot ulcer
- Non-healing lower limb or foot ulceration (> 2 weeks)
- Gangrene involving any portion of the lower limb or foot

Patients with CLTI have a high risk of poor outcomes in terms of amputation-free survival. There is a three-step approach for revascularization of these patients, which can be remembered using the acronym **PLAN:**

1. Estimated **P**atient risk (procedural as well as long-term survival)
2. Severity of **L**imb threat (wound, ischemia and foot infection [WIfI][6])
3. **AN**atomical pattern and severity of disease (using the Global Limb Anatomic Staging System [GLASS]). For revascularization, clinicians need to assess arterial disease from the aorta to the foot, including aorto-iliac, femoro-popliteal and tibial-foot occlusive disease. When tissue loss is present, clinicians plan revascularization to ensure in-line flow with a target artery path from aorta to foot to support wound healing.[5]

Revascularization Treatment Options for CLTI/Arterial Ulcers

The optimal approach to revascularization is determined by patient fitness, anatomical distribution of disease and availability of a suitable vein for bypass. Endovascular (e.g., angioplasty, stent), open surgery (e.g., bypass, endarterectomy) or combined (hybrid) procedures are equally valid. Medical management, including statin therapy, antiplatelet therapy, control of hypertension and diabetes as well as smoking cessation, are all critical components of therapy in patients with CLTI.

Adjunctive Therapies for Lower Limb Ulcers

The Role and Impact of Exercise on Lower Limb Ulcer Healing and Pain Management

In 2019, Kesterton and colleagues conducted a feasibility trial of supervised exercise training in adults with venous leg ulcers.[7] Sixteen participants (56% male, mean age 65 years, 81% retired and 19% employed in sedentary occupation) complet-

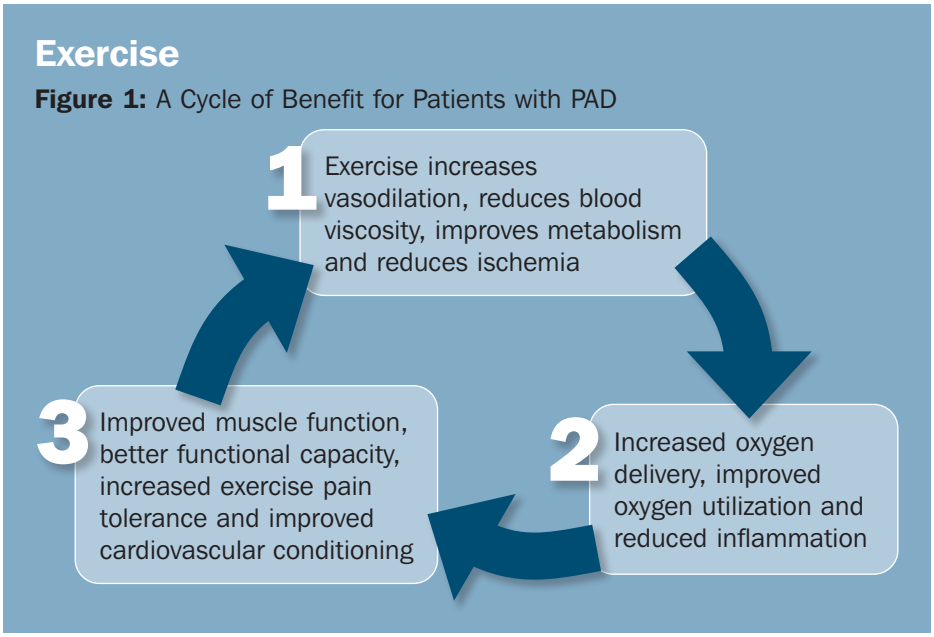
ed face-to-face interviews about what led them to the trial and what they found beneficial in the trial.

Many patients reported living a sedentary, cautious lifestyle due to fear of injury, pain, reduced mobility, lack of education, and advice to rest and be careful. On the other hand, patients reported that support from others, individualized intervention and supervision by a specialized exercise professional were a key benefit of the trial. All participants found some benefit from the intervention, such as improved wound healing, physical benefits, improved psychological well-being, positive impact on comorbidities or improved self-management strategies for long-term health conditions.[7]

Exercise Intervention

Within the body we see arterial obstruction, endothelial dysfunction, increased blood viscosity, mitochondrial dysfunction, and ischemia and free radical creation. Overall these result in decreased oxygen delivery, decreased oxygen utilization and increased inflammation in the tissues. The outcome for the person with PAD is progressive atherosclerosis, loss of muscle mass, claudication, functional limitations and cardiovascular deconditioning. This in turn feeds back into the impairments we see in the body, creating a downward spiralling effect.[8] When exploring the mechanisms of functional impairment in PAD, the protective and potentially reversing effect of exercise can be seen (see Figure 1).

There are four main types of exercise that have been shown to be beneficial in patients with PAD.[9]



SUPERVISED EXERCISE TREADMILL TRAINING

Supervised exercise treadmill training is well established in the literature to benefit patients with PAD.[7] There are very specific guidelines for prescribing this training:

- **Intensity:** 40–60% maximal workload based on baseline that brings on claudication within 3–5 minutes
- **Duration:** 30–50 minutes of intermittent exercise
- **Claudication intensity:** Moderate to moderate/severe
- **Work-to-rest ratio:** 5–10 minutes to reach claudication followed by rest until pain is dissipated (usually within 2–5 minutes)
- **Frequency:** Three times per week, supervised
- **Program duration:** At least 12 weeks
- **Progression:** Every 1–2 weeks to achieve a full 50 minutes. As individuals can walk beyond 10 minutes without claudication, increase the treadmill incline or speed to keep walking bouts to 5–10 minutes
- **Maintenance:** Lifelong maintenance at least two times per week

STRUCTURED HOME-BASED TREADMILL EXERCISE

This form of exercise intervention can have a positive effect on claudication and function.[10] While home-based programs are generally more access-

ible and remove the stress of constant monitoring, supervised program outcomes have been found to be superior to home-based programs. However, results are similar to those achieved in supervised programs when home-based programs include specific prescription; contact with an exercise professional or coach; specific, recorded goals; and the use of a pedometer or activity monitor.

PAIN-FREE WALKING EXERCISE TRAINING

Pain-free walking exercise training is low intensity, only bringing patients to minimal claudication. Patients should start a 0.4 km per day and increase the distance every two weeks until they reach 3.2 km. Patients should walk five days per week at ≤ 40% heart rate reserve (HRR) and rating or perceived exertion (RPE) 11–13 until they feel minimal claudication. Patients should use a logbook or activity monitor to record progress.[11]

LEG AND ARM ERGOMETRY

Both leg and arm ergometry have shown positive effects on claudication and function; however, they are not as profound as with treadmill training programs. Studies that found positive effects with this intervention were structured and involved an exercise professional.[12]

The Role of an Audible Handheld Doppler

As discussed earlier, identifying and treating the cause of a wound and its underlying physiological processes are the first steps in achieving wound healing. When looking at lower leg wounds, it is important to determine arterial blood supply using the ABPI to rule out PAD and determine that blood supply is sufficient to heal the wound.[13] While these tests are helpful, ABPIs have several disadvantages:

- They are time-consuming
- They can cause patient discomfort and pain
- Results can be affected by calcified vessels (leading to elevated ABPI value)[14]
- They are not always easily accessible
- They are costly
- There is a significant chance of user error

An audible handheld Doppler (AHHD) can be used in place of a traditional ABPI to rule out arterial disease.[14] An AHHD transmits a waveform that is interpreted to determine ABPI level (see Figure 2).

A triphasic (three distinct phases/sounds) or biphasic (two distinct phases/sounds) waveform means the patient's ABPI is 0.9 or greater and there is enough blood flow to close a wound. It also means compression can be safely initiated. If

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Deirdre O'Sullivan-Drombolis has been a physical therapist for over 20 years. In 2010 she graduated from the inaugural class of the Wound Healing program at the University of Western Ontario. Since that time she has used these skills to work with clients with chronic wounds, conduct research, participate in publications such as the Wounds Canada Best Practice Recommendations, and share knowledge by teaching numerous courses in the area of wound care for organizations like Wounds Canada and the Ontario Physiotherapy Association. As a physical therapist her passion is the promotion of safe physical activity for all and empowering patients to be able to participate in their life and maximize their independence.

Suzanne Stewart is a Registered Nurse and NSWOC currently working in Calgary, Alberta, at the Sheldon M. Chumir Wound Clinic. She completed her BScN at the University of Alberta in 2009 after which she quickly developed an interest in wounds while working on a medical teaching unit at the Foothills Medical Hospital. She briefly took a break from nursing in 2012 to pursue a lifelong dream of going to pastry school; however her love for wound care eventually brought her back to nursing. In 2018 she enrolled in the NSWOCC WOC Education Program to further her ongoing passion for wound care. She has experience in providing wound education in long-term care and supportive living settings, participating in skin and wound research and providing wound care in the acute and community settings.

Figure 2: Waveforms

Type		Waveform
Triphasic	• ABPI is 0.9 or greater	
Biphasic	• ABPI is 0.9 or greater	
Monophasic Absent	• arterial disease cannot be ruled out • refer to vascular lab	

there is a monophasic (only one distinct phase/sound) waveform, or the waveform is absent, further assessment is required and referral to a vascular lab for a full Duplex is needed.[13]

USING AN AHHD

This test requires an 8 MHz handheld Doppler and conductive gel. The patient does not have to lie down and can remain in a comfortable position. The clinician locates the dorsalis pedis (DP) and posterior tibial (PT) pulses, uses a generous amount of conductive gel and gently applies the Doppler at a 45-degree angle.[13]

ADVANTAGES OF AHHD

AHHD is fast (about one minute of listening), cost-effective (about half the price of an ABPI) and pain-free.[12] AHHD requires less equipment and training than an ABPI, results are not affected by calcification and it can be done at the bedside. It is important to note that while an AHHD can *rule out* vascular disease, it does not diagnose the presence and severity of vascular disease.[16]

Conclusion

Lower limb ulcers are common, significantly impact an affected individual's quality of life, and are costly to treat. Diagnosing the cause of the ulcer is critical to successful management. Many affected individuals have ulcers with mixed etiology, which makes diagnosis and therapy challenging. ■

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