Peripheral Artery Disease and Exercise in Patients with Diabetes

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Introduction

Peripheral artery disease (PAD) is a chronic condition characterized by atherosclerotic stenoses and/or occlusions in the arteries of the lower extremities. PAD has a significant negative influence on mobility and quality of life and is associated with increased morbidity and mortality [1, 2]. When PAD is present in addition to diabetes, outcomes are often far worse for patients. Thus, there is great importance for treating PAD and diabetes using currently established therapies as well as an impetus for developing novel treatment options to improve health outcomes. In this chapter, we will review (1) the scope of the problem of PAD among adults with diabetes, (2) the pathophysiology of PAD, (3) relevant diagnostic testing, (4) exercise program options and optimal prescription among adults with both conditions, (5) current findings related to the outcomes of exercise programs, and (6) recommendations for future trials to treat patients with both PAD and diabetes.

Prevalence, Risk Factors, Health Impact, and Economic Burden

PAD affects an estimated 200 million adults worldwide, with a prevalence that dramatically increases with age [3, 4]. PAD has also been estimated to occur in approximately 10% of Americans over age 60 and 21% over age 80 [5]. There is a significant racial disparity; the rate of PAD among African Americans is approximately twice as high as among non-Hispanic whites, at any given age [5]. Using 2010 US census data, it appeared women age 40 and older had slightly higher prevalence of the disease than men [6].

Smoking, hypertension, and hyperlipidemia are highly related to the development of PAD. In particular, tobacco use via smoking is a key risk factor for developing PAD (odds ratio = 4.46; 95% confidence interval [CI] 2.25–8.84) [7].

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Diabetes is also a major risk factor for PAD as an estimated 20–30% of adults with diabetes are affected by PAD [8–11]. Approximately 30–40% of people with PAD experience claudication [3, 10], which is marked by ischemic pain and discomfort in the lower limbs with walking that subsides with cessation of walking. However, patients with PAD who also have diabetes are less likely to report classical symptoms of claudication, possibly due to altered pain perception related to the presence of peripheral neuropathy [12, 13]. Thus, the estimated rates of PAD in patients with diabetes are likely underestimated. Other concurrent health problems, such as heart failure and pulmonary disease, may prevent sufficient physical activity to produce limb symptoms; thus PAD may be underdiagnosed in these patient populations as well [4]. More severe or long-standing diabetes appears to increase the risk of developing PAD [14]. The combination of PAD and diabetes puts individuals at a greater risk of poor health outcomes, compared to either condition alone [15], and is particularly true in regard to cardiovascular complications. In fact, adults with PAD and diabetes have a 2–3.5-fold greater rate of mortality than those with PAD alone [16]. The survival curves depicted in Fig. 22.1 [17] show a greater risk of death within 10 years for patients with PAD and comorbid diabetes compared to those who have PAD without diabetes (risk ratio = 2.51; 95% CI, 1.72–3.66; $p < 0.001$). Patients with PAD and diabetes when compared to adults with PAD alone also have poorer lower extremity function [12] and self-reported quality of life [18]. In addition to affecting quality of life, increased severity of claudication is associated with impaired balance and physical function [19], and diabetes is believed to exacerbate the deterioration in these surrogate outcomes [20].

The milieu of factors present in concomitant disease in patients with PAD and diabetes results in not only a significant burden on the patient, but also leads to high economic costs for treatment. A seminal PAD-specific study examining Medicare enrollment and treatment utilization estimated an annual total cost of over $4 billion resulting from the disease [21]. When coupled with the staggering national costs of diabetes (estimated at ~$245 billion), this data clearly underscores the critical need for cost-effective treatment plans for patients with both diseases [22].

Pathophysiology

The pathophysiological and metabolic changes associated with diabetes are described elsewhere in Chap. 3. Much less is known about the disordered physiological processes brought on by the interaction of PAD and diabetes together. The proatherogenic changes linked to diabetes, including inflammation, endothelial cell dysfunction, and hypercoagulability, are also thought to be significant contributors to the development of PAD [13]. The principal cause of PAD is atherosclerosis, which causes progressive narrowing or occlusion of the arteries that supply blood and oxygen to the legs. Atherosclerosis results from a complex series of processes that include endothelial dysfunction and systemic inflammation. The vascular endothelium regulates blood flow by various mechanisms. Endothelial dysfunction is associated with a decrease in the ability of the blood vessel to dilate in response to changes in flow. The endothelium also produces several factors that can prevent thrombosis and promote thrombolysis. Disruption of these factors is the first step in the development of atherosclerosis. Increased low-density lipoprotein (LDL) cholesterol and increased plasma glucose contribute to activation of endothelial cells and recruitment of inflammatory cells into the intima. Hypertension and cigarette smoking also promote endothelial dysfunction and atherosclerosis. As this process continues, foam cells develop, which can be visualized as a "fatty streak" on the surface of the arterial wall. The next stage is the development of an atheroma, initiated by interactions between lymphocytes and macrophages. This can result in neovascularization, which is associated with interplaque hemorrhage and vascular remodeling to accommodate the growing atherosclerotic plaque. Advanced lesions contain a lipid pool within the plaque covered by a fibrous cap. Plaques that have a thick fibrous cap and smaller
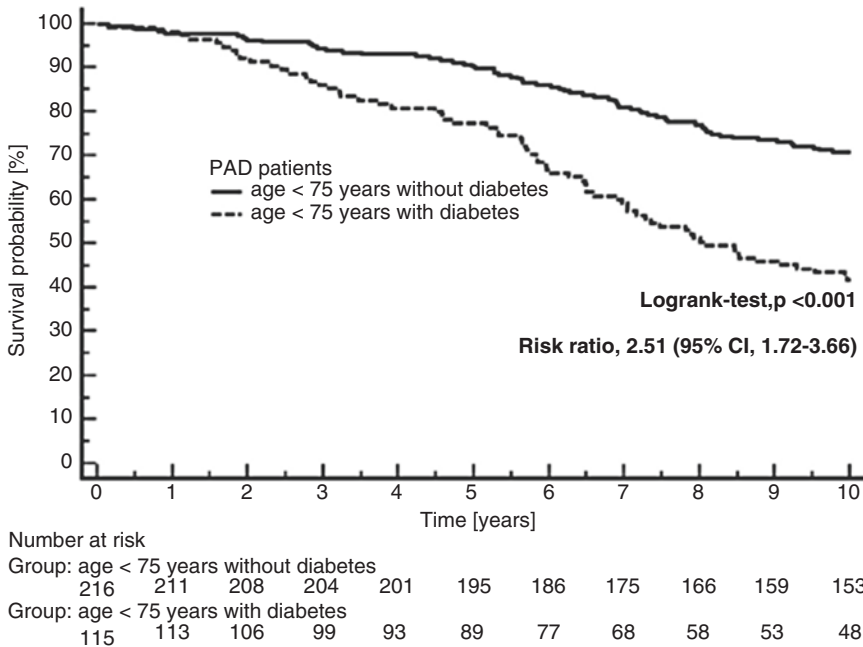
Fig. 22.1 Survival analysis in patients with peripheral artery disease only vs. those with both peripheral artery disease and diabetes. (Reprinted from Mueller et al. Mortality rates at 10 years are higher in diabetic than in non-diabetic patients with chronic lower extremity peripheral arterial disease. *Vascular Medicine* 2016; Oct 21 (5):445–452, with permission from Sage Publications. *PAD* peripheral artery disease)

lipid pool within the plaque are often more stable and less prone to rupture. These plaques cause narrowing of the arterial lumen and may result in chronic exertional ischemic symptoms such as those seen in patients with PAD. In contrast, plaques with a thin fibrous cap and larger lipid pool are more prone to rupture, exposing the thrombogenic material inside the plaque to blood, resulting in platelet activation and thrombus formation, often causing an acute event [23].

The narrowing of the vessel creates a turbulence of flow across the stenosis, further increasing the risk of platelet activation and thrombogenesis. Figure 22.2 [24] demonstrates the blood flow in a normal artery versus an artery narrowed by an arterial stenosis. In the normal artery, there is laminar flow of blood. Normally functioning endothelial cells regulate the vasodilation necessary to maintain optimal flow of blood and sufficient oxygenation of the skeletal muscle, even during lower extremity exertion. In the diseased artery, the stenosis creates high resistance, which may result in development of a collateral vessel, turbulent flow, decreased pressure across the stenosis, impaired endothelial function, and the inability to increase flow during exertion. This results in a mismatch of oxygen supply and demand, insufficient oxygenation to the skeletal muscles, and high oxidative stress.

Clinical Signs, Symptoms, and Diagnostic Testing for PAD

Clinical Presentation of PAD

Patients with PAD present across a spectrum of symptoms from asymptomatic to critical limb ischemia (CLI). It is estimated that up to 40% of patients with PAD report having no obvious exertional symptoms. However, there is evidence that PAD patients who report being asymptomatic actually have a slower gait speed and are more functionally impaired than people of similar age
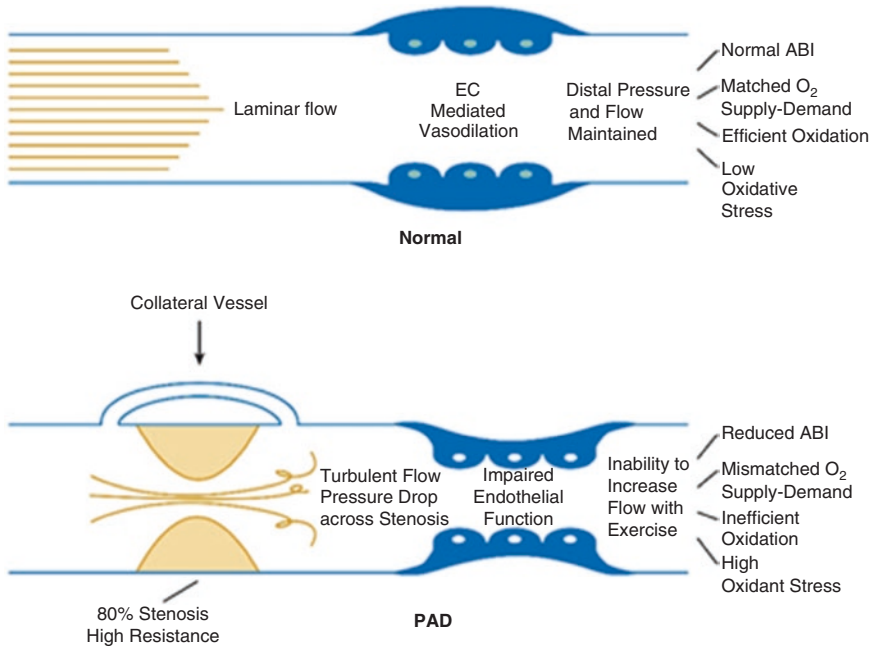
Fig. 22.2 Comparison of blood flow in normal vs. stenotic peripheral arteries. (Reprinted from *Vascular Medicine: A Companion to Braunwald's Heart Disease*, 2nd edition, Hiatt WR and Brass EP [24]. Pathophysiology of Peripheral Artery Disease, Intermittent Claudication, and Critical Limb Ischemia. Pp 223–230, 2013, with permission from Elsevier Inc. *ABI* ankle-brachial index, *EC* endothelial cell, *PAD* peripheral artery disease)

who don't have PAD [25]. Additionally, many asymptomatic patients will become symptomatic if they complete a peak walking test. This indicates their asymptomatic state is a result of not exerting themselves sufficiently during normal daily routine to reach the threshold where symptoms would occur.

The hallmark symptom claudication has several characteristics. It generally occurs in the lower extremities, although the term "claudication" has also been applied to upper limb pain as a result of subclavian stenoses/occlusions. Depending on the site of the partial or full blockage, claudication typically occurs in the calves, thighs, or buttocks. It is consistent and reproducible, it steadily increases as the exertion increases, and patients report not being able to walk through claudication if they try to continue at the same pace. In a majority of PAD patients who experience claudication, there is relief within 10 min of rest [26]. Patients will describe that they will go for a walk, and after a certain distance, they begin to get a cramping or aching feeling in their calf. If they keep walking, it gets continually worse, until finally they are forced to stop. Approximately 40–50% of patients who are symptomatic have an atypical presentation such that their lower extremity discomfort does not meet all the classic criteria of claudication [27, 28]. So, for example, the pain may be exertional, but doesn't consistently resolve with rest, or it may not consistently limit exercise at a reproducible distance and vary from day to day.

CLI is the most severe manifestation of PAD and is caused by severe progressive atherosclerosis. Blood flow to the lower extremity is insufficient to adequately supply tissue even at rest. As a result, progression to ulcers, gangrene, and amputation can occur [29, 30]. The pain at rest which can occur is characterized as an ache or a discomfort in the arch of the foot or toes, and it is usually exacerbated with leg elevation. Patients are most uncomfortable when lying flat with their legs elevated. The small loss of gravitational force when a patient lies down can cause a shift from the

tissue having sufficient blood flow to be comfortable, to progression to the ischemic rest pain. Often the pain is relieved when the foot is in a dependent position. This can interfere with sleep, and patients with rest pain will often describe waking up at night having pain in the ball or the arch of their foot and having to dangle the foot off the side of the bed to obtain relief. This poor circulation condition results from inadequate perfusion and triggers adverse responses in the microcirculation [31]. Circulating tissue factors associated with endothelial injury and activation of the clotting system further decrease blood flow and promote thrombosis in the arterial circulation [32]. This contributes to disease progression and perfusion that is insufficient to supply the distal tissue. CLI develops in 1% of patients with claudication per year, and approximately one million Americans present with CLI annually. The risk of progressing from claudication to CLI increases dramatically in those who have cardiovascular ischemic risk factors. Individuals with diabetes have a fourfold risk, and individuals who continue to smoke have a threefold risk of progressing from claudication to CLI [4]. Ulcerations as a result of CLI are typically found distally in the toe region and/or on the heels. They cause intense pain and may become dry, devitalized, or black at the end stage. Gangrene may also be an unfortunate consequence for those with CLI. Patients with ulcers and gangrene are more likely to progress to amputation than those with rest pain, and 1–3.3% of patients with claudication will progress to amputation. Patients with both diabetes and CLI carry a grave prognosis, as 5-year amputation rates have recently been defined to be as high as 34.1%, compared to patients with only CLI at 20.4% ($p = 0.015$) [33].

Diagnostic Testing for PAD

Ankle-Brachial Index The ankle-brachial index (ABI) is the most cost-effective tool that can confirm the diagnosis of PAD. It should be the first diagnostic test used when PAD is suspected. The concept of the ABI is that the systolic blood pressure in the leg should be approximately the same or slightly higher compared to the systolic blood pressure in the arm. The ABI should be a routine test for individuals who have a history or physical exam consistent with PAD, including an abnormal pulse exam, non-healing lower extremity ulcers, claudication or other exertional leg symptoms, or ischemic rest pain. An abnormal ABI is a very powerful predictor of future atherosclerotic cardiovascular events [34]. The lower the ABI, the worse the prognosis. The ABI can be performed in a clinician office with a manual blood pressure cuff and a handheld Doppler device. Sensitivity for ABI has ranged from 68 to 84% and specificities from 84 to 99% [35]. The interpretation of the ABI is as follows: 1.00–1.40 = normal; 0.91–0.99 = equivocal; and ≤0.90 diagnostic of PAD [36]. There are some limitations to the ABI. It can be falsely elevated when the pedal arteries are non-compressible because of the calcium deposits in the walls of the artery, therefore the blood pressure cuff cannot compress that artery and an accurate systolic pressure reading is not possible. This is most likely to occur in patients with diabetes, chronic kidney disease, or advanced age. Values >1.40 are considered abnormally elevated and in those individuals the ABI is nondiagnostic, and other tests need to be completed to confirm the diagnosis of PAD. Additionally, the ABI is insensitive to very mild occlusive disease and iliac occlusive disease. When the ABI is normal at rest, but there is a high suspicion of PAD because of symptoms or risk factors, additional tests can be performed to confirm the disease (e.g., exercise ABIs).

Toe-Brachial Index The toe-brachial index (TBI) is performed in the same manner as the ABI with the use of a special toe cuff. Measurements are made with a photoplethysmograph. This test is performed when the ABI is abnormally elevated and therefore nondiagnostic. A normal TBI value is ≥0.70.

Segmental Pressure Examination The segmental pressure examination is a physiologic test similar to the ABI with the addition of pressure measurements at multiple levels of the leg,

including the high thigh, low thigh, calf, and ankle. Measurement at multiple locations allows more precise understanding of the location of the lesion. A segmental pressure test is considered abnormal if there is more than a 20 mmHg decrease between a segment within the same leg, or between the original segment and the corresponding segment on the contralateral leg.

Pulse Volume Recording The pulse volume recording (PVR) reflects the change in volume of a leg segment with each pulse [37]. The waveform evaluation allows assessment of arterial flow in areas where arteries are calcified because it does not rely on compression of the artery to obtain a measurement [38]. Figure 22.3 shows images for PVR obtained during a segmental pressure test.

Exercise Testing Exercise testing in patients with PAD can aid in diagnosis and will provide valuable information about functional ability. In patients with symptoms consistent with claudication but a normal resting ABI, a treadmill test can be performed. The ABI is measured at rest prior to beginning exercise. During the exercise test, patients walk on a treadmill to a point of significant claudication symptoms. Immediately following the cessation of exercise, the ABI is repeated. Patients whose symptoms are a result of arterial insufficiency will have at least a 20 mmHg drop in ankle pressure following exercise. When that drop is compared with the elevated arm pressure usually seen with exercise, the ratio of ankle to arm pressure will be lower, which is diagnostic of PAD. A peak treadmill test will also measure how far a patient can walk before their symptoms force them to stop. This can be helpful in determining whether claudication is the limiting symptom versus other symptoms such as shortness of breath, angina, or musculoskeletal pain that does not arise from arterial insufficiency.
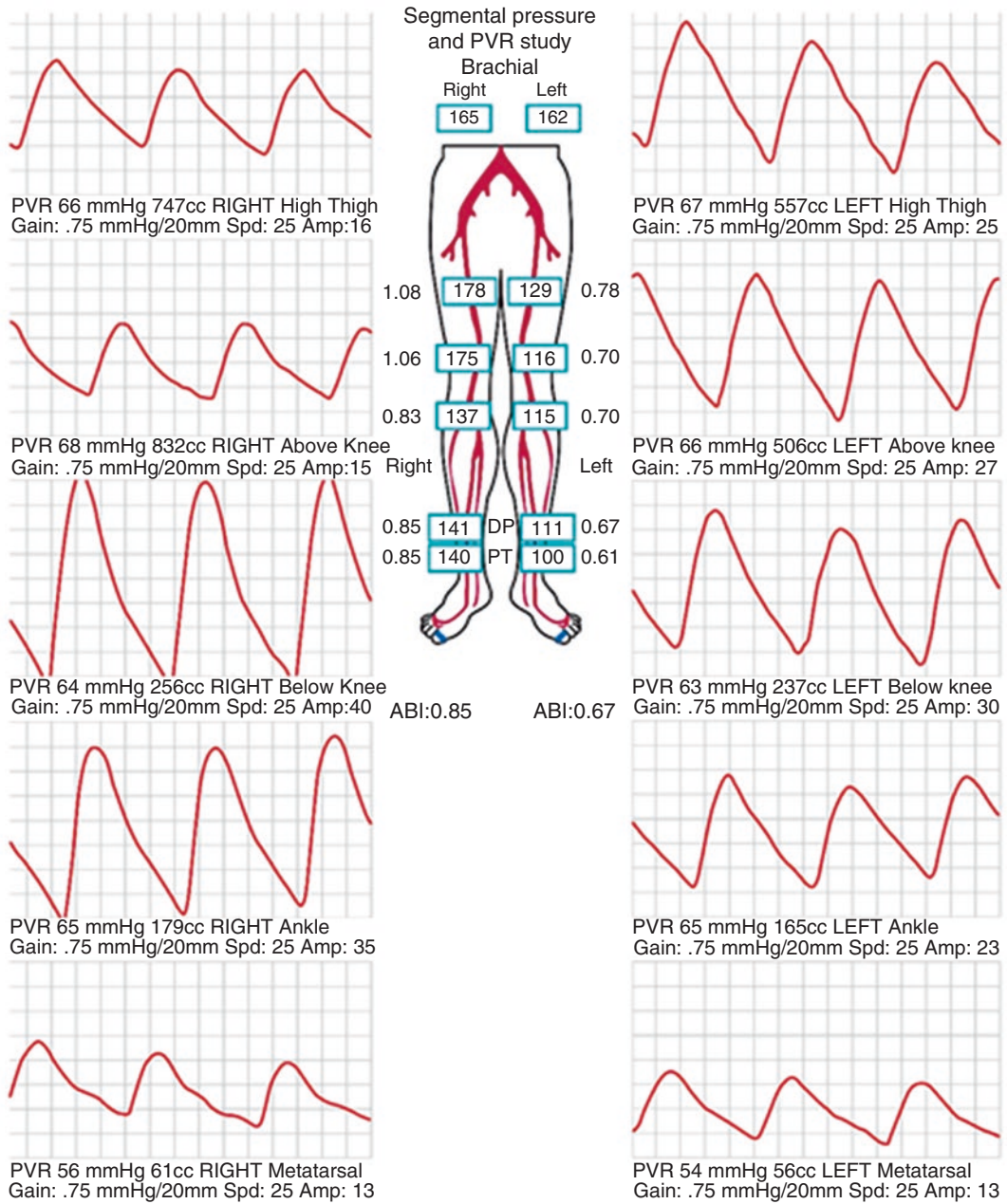
Diagnostic Imaging Procedures Duplex ultrasound is a noninvasive, relatively inexpensive imaging procedure that allows visualization of the lumen of the arteries of the lower extremity, and is indicated to determine diameter and location of stenoses. Computed tomography angiogram (CTA) and magnetic resonance angiogram (MRA) are noninvasive imaging procedures that allow visualization of the lower extremity arteries and are indicated to identify the location of atherosclerotic plaque. CTA requires the use of a contrast agent to maximize the quality of the images, and can be contraindicated in individuals with diabetes who are taking metformin or in those who have chronic kidney disease. MRA uses a contrast agent called gadolinium to enhance the images, which is less toxic than CTA contrast. MRA may not be an option for patients with implanted metal in addition to taking longer and being more expensive than a CTA. Because of the cost and exposure to contrast agents, both of these procedures are generally recommended to aid in planning a revascularization procedure. Digital subtraction angiogram (DSA) is an invasive imaging procedure that takes x-ray images of the lower extremity arteries, while injecting iodizing contrast material through a catheter threaded through the artery. Individuals with diabetes or chronic kidney disease are more at risk during this procedure because of the use of the contrast dye. Similar to CTA and MRA, DSA is indicated when a revascularization procedure is planned. Table 22.1 provides a summary of the diagnostic tests available for PAD.

Treatment Options for PAD and Diabetes

A full discussion of the various treatment options available for patients with both PAD and diabetes is beyond the intent of this chapter. Therapies are generally divided into noninvasive optimal medical treatment, revascularization, and in advanced stages, lower limb amputation. Optimal medical therapy targets several areas of health comprehensively, and further treatment is often dependent on the severity of the disease and subsequent symptom presentation. With all disease populations including those with PAD and diabetes, control of modifiable risk factors (e.g., smoking) is paramount to the treatment regimen. Reducing premature adverse cerebrovascular and cardiovascular events through pharmacological therapy (e.g., antiplatelet agents, statins,

Segmental pressure and PVR study

Brachial
Right 165   Left 162

PVR 66 mmHg 747cc RIGHT High Thigh
Gain: .75 mmHg/20mm Spd: 25 Amp:16

PVR 67 mmHg 557cc LEFT High Thigh
Gain: .75 mmHg/20mm Spd: 25 Amp: 25

1.08 | 178   129 | 0.78
1.06 | 175   116 | 0.70
0.83 | 137   115 | 0.70

PVR 68 mmHg 832cc RIGHT Above Knee
Gain: .75 mmHg/20mm Spd: 25 Amp:15

Right   Left

PVR 66 mmHg 506cc LEFT Above knee
Gain: .75 mmHg/20mm Spd: 25 Amp: 27

0.85 | 141 DP 111 | 0.67
0.85 | 140 PT 100 | 0.61

PVR 64 mmHg 256cc RIGHT Below Knee
Gain: .75 mmHg/20mm Spd: 25 Amp:40   ABI:0.85   ABI:0.67

PVR 63 mmHg 237cc LEFT Below knee
Gain: .75 mmHg/20mm Spd: 25 Amp: 30

PVR 65 mmHg 179cc RIGHT Ankle
Gain: .75 mmHg/20mm Spd: 25 Amp: 35

PVR 65 mmHg 165cc LEFT Ankle
Gain: .75 mmHg/20mm Spd: 25 Amp: 23

PVR 56 mmHg 61cc RIGHT Metatarsal
Gain: .75 mmHg/20mm Spd: 25 Amp: 13

PVR 54 mmHg 56cc LEFT Metatarsal
Gain: .75 mmHg/20mm Spd: 25 Amp: 13

Fig. 22.3 Segmental pressure measurements and pulse volume recording. Right leg has a pressure drop between low thigh and calf consistent with superficial femoral/popliteal artery stenosis. Left leg has a pressure drop at level of high thigh consistent with iliofemoral artery ste-nosis. (Reprinted from *Vascular Medicine: A Companion to Braunwald's Heart Disease*, 2nd edition, Gerhard-Herman et al. [37]. Vascular Laboratory Testing. Pp 148–165, 2013, with permission from Elsevier. *ABI* ankle-brachial index, *PVR* pulse volume recording)

hypertension medications) is a mainstay in current medical therapy paradigms. Table 22.2 provides a brief summary of risk factors and treatment options for those factors in PAD patients with diabetes. A

goal of any treatment method for PAD should focus on symptomology associated with the disease. For patients with claudication, medications have largely proven unsuccessful or demonstrated minimal

Table 22.1 Diagnostic testing for peripheral artery disease

Test	Description	Indication
Ankle-brachial index	Noninvasive procedure that assesses the ankle versus brachial systolic arterial pressure. Measured with a Doppler ultrasound device with a 4–8 MHz transducer.	To confirm diagnosis in patients with clinical suspicion of PAD. The ABI is somewhat less useful in patients with diabetes due to increased prevalence of medial artery calcification than can raise the ABI [114].
Toe-brachial index	Ratio of the systolic blood pressure measured at the great toe to that of the brachial artery. Measured with a Doppler ultrasound device and a photoplethysmograph.	To confirm diagnosis of PAD in patients with pedal artery calcification when ABI is nondiagnostic [114]. This is more commonly used in patients with diabetes [114].
Segmental limb pressures	Physiologic measurement of arterial systolic pressure in multiple limb segments compared to brachial pressure.	Useful in determining the location of arterial stenoses and/or occlusions. Generally, a pressure difference of ≥20 mmHg assessed at one cuff to the next is indicative of blockage.
Pulse volume recording	Measurement change in pulse volume of each leg segment using plethysmograph. Evaluates normalcy of waveforms.	To confirm diagnosis of PAD in patients with pedal artery calcification when ABI is nondiagnostic.
Exercise performance testing	Fixed or graded exercise test using primarily a treadmill. ABI can be performed before and immediately after the test to diagnose PAD in the presence of an equivocal ABI (0.91–0.99).	Useful for patients with high clinical suspicion of PAD but normal or borderline ABIs. Clarifies primary rate-limiter to exercise (e.g., claudication). Primary physical function test to determine effect of any clinical intervention.
Lower extremity duplex ultrasound	Noninvasive adjunct to physiologic testing. Peak systolic velocity and waveform analyses are used to quantify and localize extent of stenosis. Percentage reduction of diameter of the lumen is categorized.	Evaluation of location and severity of lower extremity arterial stenosis. Surveillance for recurrence of stenosis following endovascular or open revascularization.
Computed tomography angiogram	Noninvasive imaging study using a contrast agent to visualize lower extremity arteries. Higher risk of contrast-induced nephropathy in patients with CKD and/or diabetes.	To determine location of arterial lesions to inform planned revascularization procedures.
Magnetic resonance angiogram	Noninvasive imaging study using magnetic resonance techniques with gadolinium contrast to visualize lower extremity arteries. Higher risk of contrast-induced nephropathy in patients with CKD and/or diabetes.	Identifies the location of arterial lesions to inform planned peripheral revascularization procedures.
Digital subtraction angiogram	Invasive imaging procedure using x-ray and iodizing contrast agent to visualize lower extremity arteries. Associated with risk of hematoma and other procedural complications. Contraindicated in patients with CKD or diabetes because of the risk associated with the contrast dye, which is metabolized by the kidneys.	To determine location of arterial lesions to inform planned revascularization procedures.

ABI ankle-brachial index, *CKD* chronic kidney disease, *PAD* peripheral artery disease

Table 22.2 Summary of risk factors and therapy options for peripheral artery disease in patients with diabetes

Risk factors	Therapy options[a]	Discussion/considerations
Diabetes	Glucose control (pharmacological) 1. Sulfonylureas 2. Meglitinides 3. DPP-4 inhibitors 4. GLP-1 receptor agonists 5. SGLT2 inhibitors 6. Thiazolidinediones 7. Insulin therapy	According to the AHA, ACC, and ADA, titration of dose and schedule of glucose-lowering therapies should aim to reduce and maintain HgbA1c to 7% with more rigorous control made on an individual basis [115, 116].
Platelet aggregation	Antiplatelet agents 1. Aspirin 2. Clopidogrel	IWGDF recommendations include a low-dose aspirin or clopidogrel in patients with PAD and foot ulcers caused by diabetes [117].
Hypercholesterolemia	Statins Niacin Fibrates Bile acid resins	In a recent retrospective analysis [118], it was determined that patients with diabetes and PAD (and abdominal aortic aneurysms, carotid stenoses) had higher total and LDL cholesterol compared to patients with diabetes and CAD (152.0 ± 40.0 vs. 146.0 ± 42.0 mg·dl^{-1}, $p = 0.019$; 86.0 ± 35.0 vs. 80.0 ± 34.0 mg·dl^{-1}, $p = 0.04$). This in addition to lower statin usage compared to the latter (75% vs. 100%, $p < 0.001$).
Hypertension	Beta-adrenergic blockers Angiotensin-converting enzyme inhibitors Diuretics Calcium channel blockers	The ACC/AHA practice guidelines [35] for the management of PAD highly recommends (IA) administration of antihypertensive therapy to reduce major cardiovascular event risk.
Sedentary behavior and overall adverse risk profile	Therapeutic patient education and support Exercise therapy[b]	The ten standards within DSME and DSMS are defined by the National Standards for Diabetes Self-Management Education [119]. These standards provide guidance for ongoing support for people with diabetes by encouraging behavior change, maintaining healthy diabetes-related behaviors, and seek to address psychosocial issues. For PAD, compliance to smoking cessation and maintenance of an exercise program are key areas of focus for the patient [120]. Refer to section "Exercise Prescription in PAD and Diabetes" for more information on exercise therapy.
Smoking	Behavior modification therapy Nicotine replacement therapy Bupropion	Interestingly, diabetes is associated with femoropopliteal and tibial disease in patients with PAD, whereas smoking is related to proximal disease in the aortoiliofemoral vessels [11, 13].

ACC American College of Cardiology, *ADA* American Diabetes Association, *AHA* American Heart Association, *CAD* coronary artery disease, *DPP-4* dipeptidyl peptidase-4, *DSME* Diabetes Self-Management Education, *DSMS* Diabetes Self-Management Support, *GLP-1* glucagon-like peptide-1, *IWGDF* International Working Group on the Diabetic Foot, *LDL* low-density lipoprotein, *mmHg* millimeters of mercury, *PAD* peripheral artery disease, *SGLT2* sodium-glucose co-transporter-2

[a]A full review of the relevant treatment options for these categories is not discussed due to the scope of this chapter.
[b]Note exercise therapy is recommended to positively impact the risk factor profile of patients with both peripheral artery disease and diabetes.

benefit in the USA for reducing leg pain and improving functional ability. Many of the initial systematic reviews examining the role of pentoxifylline to treat claudication have demonstrated lack of clinical effectiveness [39, 40]. A recent meta-analysis concluded that the role of pentoxifylline for improving walking performance endpoints remains uncertain, as the quality of trials in the analysis was low [41]. Based on this evidence, the 2016 AHA/ACC guidelines for the care of patients with lower extremity PAD have given pentoxifylline a class III, no benefit recommendation. Cilostazol is prescribed to treat claudication on a more routine basis in the USA, as it has demonstrated a modest improvement in walking and functional ability as well as quality of life [42, 43] of patients. It is generally recognized as having a greater clinical benefit but with more side effects (e.g., nausea) compared to pentoxifylline [44, 45]. Rendell et al. [46] reviewed pooled data from eight randomized controlled trials that demonstrated an improvement in peak walking distances (distance walked on a graded treadmill prior to test termination by the patient due to severe claudication pain) for patients with PAD and diabetes taking cilostazol (+51.4%) vs. placebo (+32.6%). Several studies have identified a signal of significant benefit for cilostazol in PAD and diabetes, particularly for improving claudication and ulceration prevention [47, 48]. However, other studies have shown less benefit, if any, for the drug to treat diabetes alone or the diseases when present in combination, in particular the symptom of peripheral neuropathy [49, 50]. There are other pharmacologic options available in Europe such as naftidrofuryl that show promise in PAD; however, it is still unclear if it is efficacious for treatment of PAD patients with diabetes [51].

Because the risk of limb loss is higher in patients with concomitant PAD and diabetes, revascularization therapies including lower extremity bypass or peripheral endovascular therapy are potential options for these patients. Endovascular interventions in particular have emerged as a less invasive option to open peripheral bypass procedures. The concern with endovascular revascularization is the lower patency rates over the long term when compared to open procedures, but the rates are improving with enhancements in technology [52]. The choice of treatment is largely dependent on the arterial segments that are affected, the severity and volume of lesions located in the peripheral artery anatomy, and whether the plaque is calcified. Restenosis often leads to a return of leg symptoms in PAD; thus the vascular specialist is cautioned to evaluate the risk/benefit ratio carefully before considering this as an option to treat the patient. In general, a more aggressive approach is adopted in younger active patients without comorbidities that may contribute to functional limitation and with more favorable disease anatomies (e.g., aortoiliac vs. femoropopliteal, stenosis vs. occlusion, focal vs. diffuse disease, non-calcified vs. calcified plaque). However, because of the markedly improved benefits, peripheral revascularizations using endovascular techniques are commonly used to treat PAD at all levels of symptom severity. Because of the significant risk of limb loss for patients with both diabetes and PAD, CLI should be treated aggressively using the most durable procedures in order to prevent amputation. Patients with PAD and diabetes do tend to have poorer outcomes following revascularization procedures than patients with PAD alone [53] and have a higher risk of lower extremity amputation than patients without diabetes [16, 54] as mentioned previously. One factor that may be partially responsible for the reduced effectiveness of revascularization procedures in patients with PAD and diabetes is that patients with both conditions tend to have more diffuse femoropopliteal and tibial disease, rather than focal aortoiliofemoral stenoses [55]. Regardless, it has been suggested that revascularization for the PAD patient with diabetes should be considered due to promising short-term clinical improvements in these patients [56].

Exercise Prescription in PAD and Diabetes

Exercise therapy in controlled settings such as hospitals and clinics is noninvasive, cost-effective, and considered the gold standard treatment option for patients with PAD (IA practice guideline rating) [35]. Programs of walking specifically lead to incremental improvement of

physiological parameters such as peak oxygen uptake (VO_{2peak}), walking performance both in time and distance during graded exercise tests, as well as enhancement of quality of life [4]. Current guidelines do not provide classification of recommendation/level of evidence in the existence of concomitant PAD and diabetes. However, the benefits of exercise for patients with diabetes are well known [57]. Individual limitations such as disease severity, age, and other comorbidities (e.g., lung disease) guide the exercise prescription for PAD and diabetes patients. The Claudication Symptom Rating Scale [58], which ranges from 1–5 (1 = no pain; 2 = onset of claudication; 3 = mild pain; 4 = moderate pain; 5 = severe pain) is used by the patient to rate pain according to their perception of discomfort. Exercise in patients with claudication is intermittent in nature with the walking being continued until the onset of moderate leg pain [35]. Patients then rest to allow for a reduction in claudication, if not a complete resolution of pain. It is preferable for patients to sit for rest periods so that exercise can begin again as soon as possible. Recent focus group studies with PAD patients indicated barriers to continuing to exercise include a lack of seating options being readily available [59]; however, no randomized controlled trials have evaluated the effects of sitting vs. standing during training for improvement of any composite, direct, or surrogate endpoints. The total duration that includes the walk/rest ratios of time should be approximately 35–50 min. Frequency should be three times a week, and ideally the program should continue for not just a discrete period of time (3–6 months) but rather throughout the patient's lifetime. When beginning a walking exercise program for the first time, the healthcare providers should input treadmill parameters (i.e., speed and grade) at an intensity great enough to elicit moderate claudication in 3–5 min. Depending on the patient's functional level at the onset of a new program, the initial sessions should start at lower durations and progress to 50 min as tolerated. For the PAD patient who has received peripheral revascularization or has other comorbidities that limit exercise (e.g., arthritis), ratings of perceived exertion (RPE) can be used

to regulate intensity of exercise at moderate exertional levels. The most common metrics used to assess a patient's RPE include the Borg Scales and the OMNI Picture System of Perceived Exertion Scales [60, 61]. The former scales have been used successfully in PAD patients who do not experience claudication [62, 63] and thus are a valid alternative to pain scales for regulating exercise intensity.

Supervised exercise training is often not utilized despite being a highly recommended therapy for PAD. This is due to a number of problems including time constraints, habitual sedentary behavior of patients, proximity to clinics and healthcare facilities, and inadequate transportation [64–67]. Thus, unsupervised exercise programs are often provided, which consist of PAD patients being informed by their healthcare provider to walk at home or in their respective community [68–72]. There are many weaknesses to this approach that lead to the failure of these programs, including little follow-up from providers and a lack of taking into account barriers (e.g., absence of seating for rest) that may prevent the successful completion of any prescribed program. The majority of studies and subsequent results in this area support the concept that a lack of optimal training, monitoring, and coaching for the home exercise program simply does not work [73]. Thus, creating novel programs with components inclusive of those found in successful supervised programs may improve the likelihood of exercise therapy to be successful in community settings. Despite inclusion of individuals with diabetes in studies of exercise outcomes in PAD, few studies have directly compared outcomes among individuals with and without diabetes, and two recent systematic reviews on the topic have yielded conflicting findings about the role of diabetes in outcomes of exercise therapy in PAD [74, 75].

Several other modalities additional to walking have been evaluated to determine their impact on health outcomes in PAD alone, although for all modalities there has been far less research than that of supervised walking programs. Briefly, alternative modes of exercise to treat PAD include strength training, cycle and arm ergometry, pole

striding, and active pedal plantar flexion [76–80]. Strength training may offer health benefits to vascular disease patients and may consist of upper and/or lower limb movement [81]. Generally, the strength training program consists of standard guidelines utilized in healthy populations [82].

Treatment of those with diabetes and PAD should include some special considerations. Diabetes treatment includes a comprehensive program of exercise that includes resistance training to offset the decline of atrophy of the skeletal muscle. It has also been suggested that resistance and aerobic exercise for patients with only diabetes may be more beneficial to the patient than one singular modality [57]. Although strength training targets an important component of health, it should only be prescribed as a supplement to a walking exercise regimen for PAD patients. PAD incurs a high level of detriment on the cardiovascular and microvascular systems; thus aerobic exercise is primarily recommended. This makes the decision process for the clinical care provider a difficult one, when faced with a patient who has concomitant PAD and diabetes. Determination of comorbidities and any substantial physical limitations (e.g., CLI, amputations) should be considered by the provider before prescribing the mode of exercise. For example, upper body strength training and in particular arm ergometry may be valid alternatives for patients to improve the primary limiter of claudication [79]. However, more research is still needed from large trials to establish whether these alternative modes of exercise are indeed effective.

The importance of appropriate foot care is critical in patients with PAD and diabetes. Although there is no known risk of exercise therapy to causing irreversible ischemic damage to the muscles of the lower limbs as is the case in myocardial ischemia, the vascular complications of diabetes should be assessed closely due to potential skin breakdown and infection. This can be attributed to a higher vascular permeable environment, impaired regulation of blood flow, and poor vascular tone, all of which may be present in PAD patients as well [83]. Thus, caution is advised for patients with neuropathy performing a walking exercise program, as changes in gait

may occur due to impaired sensory perception. One issue is that undue pressure could be placed on portions of the foot as the patient attempts to attenuate or avoid neurogenic pain. Abnormal friction could also go unnoticed by the patient without protective foot sensation. The presentation of peripheral symptoms from diabetes could result in pressure-induced necrosis from abnormal foot to ground contact patterns [84]. Shoes that do not fit properly or trauma as the result of poorly trimmed toenails could also cause ulcerations and potentially lead to amputation, a problem that is exponentially amplified in diabetes with PAD [56]. Footwear should consist of depth shoes that provide ample room in the toe box, and toenails should ideally be cut by an appropriate healthcare provider (e.g., podiatrist). Skin fissures and dryness should be avoided; thus lotion can be applied to the feet in the absence of non-healing wounds [84]. Regular visual inspection of skin integrity is highly recommended.

Effects of Exercise Training in PAD and Diabetes

Numerous studies have evaluated the effects of exercise training in adults with PAD. However, there is a relative dearth of trials evaluating the impact of exercise therapy programs when both diseases are present. We will discuss the available literature. Key outcomes of interventions include assessment of walking ability and functional status, objective physiological endpoints such as VO_{2peak} and endothelial dysfunction, and patient-reported outcomes via questionnaires.

Walking Performance Outcomes and Functional Ability

The most objective modality for evaluating a patient's walking ability is a treadmill walking test. This type of test has been well validated for use in patients with PAD [85, 86]. Treadmill testing can be used to establish claudication onset time or distance (time or distance of initial presentation of any claudication pain), as well as

peak walking time or distance (point at which claudication pain becomes so severe that the patient is forced to stop). Several different treadmill protocols have been used in PAD populations to test for leg pain and evaluate other potential limiting factors in response to exercise [87]. A typical exercise protocol uses a graded exercise test in which the speed is maintained at 2 mph and the grade is incrementally increased 2% every 2 min [88]. Patients are instructed to walk as long as possible until they are unable to continue. The time walked prior to the onset of pain and the total time walked are both important in the evaluation of function, and are often included in studies of exercise interventions. This type of testing has been used in patients with PAD and diabetes.

The 6-min walk test is a performance-based functional measure that requires minimal equipment or training for staff administering the test [89]. Initially developed and validated in patients with respiratory disease as well as heart failure, the test has emerged as an important tool to determine the functional ability of patients with PAD [90, 91]. To perform the 6-min walk test, the patient is instructed to walk a defined course for 6 min, covering as much ground as possible in that time period, although they are permitted to stop and rest if needed. The total distance walked, as well as the distance covered prior to the patient's first report of leg symptoms, is recorded. The 6-min walk test has been used extensively in cardiovascular and pulmonary disease research, including PAD, as a method of monitoring disease status and the effects of interventions [92, 93]. It has been found to be a valid and reliable measure of functional ability in patients with PAD [94]. A significant recent trial also used the total distance walked during the 6-min walk test as an outcome (via a post hoc analysis) in patients with both PAD and diabetes [95].

Surprisingly little data exists as to the efficacy of exercise rehabilitation among adults with PAD and diabetes, when compared to those with PAD alone. In addition, existing data are conflicting. While exercise has been shown to be an effective therapy for improving pain-free and peak walking distance among adults with PAD [96, 97], some research suggests that individuals with PAD and diabetes may experience a blunted response to exercise therapy. In one study, 40% of patients with PAD and diabetes did not respond to exercise rehabilitation, and their risk ratio for nonresponse was 4.7, when compared to adults without diabetes [98]. Similarly, another study found that maximal walking distances did not improve in patients with PAD and diabetes with a 6-month exercise program [99]. Results are not consistent; another report found that patients with diabetes improved to a similar extent compared to nondiabetes patients [100]. It is unclear why this discrepancy exists, but it has been suggested that diabetes may contribute to reduced blood volume expansion and slower oxygen kinetics in the calf muscles during exercise [101, 102], thus reducing exercise-mediated improvements typically seen in measures of claudication.

Physiological Endpoints

There are a number of objective physiological endpoints, including VO_{2peak} and endothelial dysfunction that have been evaluated as outcomes from exercise training in patients with PAD and diabetes. A recent systematic review and meta-analysis concluded that exercise training improves cardiorespiratory fitness as measured by VO_{2peak} in adults with PAD when compared to usual care, although the differences were small (0.62 ml·kg^{-1}·min^{-1}; 95% CI, 0.47–0.77) [103]. This is consistent with the lack of major change observed in markers of endothelial dysfunction among adults with both PAD and diabetes. In a study examining endothelial dysfunction as measured via brachial artery flow-mediated dilation following 3 months of structured exercise therapy, the PAD-only group demonstrated an improvement in endothelial function (+1.9%, $p < 0.05$); however there was no change in the group with both PAD and diabetes (+0.75%, $p = 0.8$) [104]. Thus, the presence of diabetes in combination with PAD appears to attenuate improvements in endothelial function and net plasma nitrite. Markers of inflammation, including intercellular adhesion molecules, vascular

cell adhesion molecules, total cholesterol, tri-glycerides, and low-density lipoprotein choles-terol, do appear to be positively influenced by exercise therapy in adults with PAD and diabetes [105].

Patient-Reported Outcomes

Functional impairment and other relevant patient-reported outcomes of exercise programs for patients with PAD can be subjectively assessed through validated questionnaires. The Medical Outcomes Study Short-Form 36-item (SF-36) questionnaire is commonly used to assess quality of life in this population [106], and results can be used to compare outcomes across patient populations. There are a number of disease-specific questionnaires that have been used to characterize PAD-related symp-toms, physical limitations, and mental, social, and emotional function. A full review of patient-reported outcome questionnaires in PAD is described elsewhere [106], but briefly, common metrics used in PAD include the Walking Impairment Questionnaire (WIQ) [107], Vascular Quality of Life Questionnaire (VascuQOL) [108], Peripheral Artery Questionnaire (PAQ) [109], Peripheral Artery Disease Quality of Life (PAD-QoL) [110], and the San Diego Claudication Questionnaire [27]. Each of these questionnaires has been used and validated in a population of adults with PAD and are frequently included as secondary out-comes of large PAD exercise trials. Studies have demonstrated improvement in self-report functional status and quality of life as a result of exercise interventions, and these improve-ments appear to be maintained long-term if individuals continue to exercise [111]; however the effect of exercise on these outcomes among patients with PAD and diabetes when compared to patients with PAD alone is unclear [99, 100]. Table 22.3 provides an overview of trials that evaluated outcomes following exercise therapy in patients with PAD and diabetes.

Conclusions and Future Directions

In conclusion, the primary aim of this chapter was to describe the role of exercise for treating symp-tomatic PAD in patients with diabetes. Importantly, relatively little is known about the interaction of the pathophysiologic effects of the two diseases in combination, although concomitant PAD and dia-betes are relatively common. Each disease has its own challenges regarding patient symptom limi-tations. It appears that those with diabetes and PAD may benefit less from exercise training with regard to ambulatory endpoints than those with PAD alone or diabetes alone. However, exercise therapy remains a key therapeutic modality given its benefits for the diabetic metabolism, and it should be aggressively pursued as a front-line option by clinicians. Optimal medical therapy especially when including exercise is important due to its low risk and high benefits. Exercise training can improve the patient-reported out-comes, functional capacity, and metabolic risk profile of these patients while also reducing healthcare costs. Revascularization is critical for improving patient symptoms in addition to poten-tially reducing morbidity (amputation) for PAD and diabetes patients.

The current state of the healthcare system lim-its the treatment options for PAD and diabetes patients. Exercise as a method to improve health is unfortunately underused in current clinical practice. Although supervised exercise programs for PAD were recently approved for reimburse-ment by the Centers for Medicare and Medicaid, many patients are relegated to self-monitored exercise programs at home or in the community, which have been largely unsuccessful. Most of these programs that occur in the patients natural environment consist of recommendations for patients to walk as much as they can [112, 113] but without feedback or follow-up to ensure an adequate dose of exercise is performed to derive benefit. Thus, more research is needed to improve the effectiveness of these programs, particularly increasing exercise adoption and long-term adherence for those with diabetes and PAD.

Table 22.3 Results from exercise trials evaluating cohorts of only peripheral artery disease and concurrent diabetes or trials that performed subanalyses comparing those with concomitant disease vs. peripheral artery disease patients only

First author and year	Sample size[a]	Exercise intervention(s); study design (duration[b])	Results
Treat-Jacobson 2009 [79]	PAD only = 26; PAD and DM = 15	Arm ergometry, treadmill walking, combination of the two, or control; RCT (12 weeks)	PWD change scores (mean ± SD) were significantly greater for all exercise therapy groups (arm ergometry: +182.1 ± 126.7 m); treadmill walking: +294.7 ± 163.5 m; combination group: +217.2 ± 72.7 m) compared to patients randomized to the control arm (+45.3 ± 92.7 m, $p < 0.003$). Additionally, COD improved in the arm ergometry group (+89.6 ± 74.0 m) vs. controls (+4.0 ± 45.4 m, $p = 0.03$). The improvements in COD were also similar in those with and without DM.
Collins 2011 [99]	PAD and DM = 145	Home-based walking and behavioral intervention or control; RCT (6 months)	No significant difference in PWD (primary outcome) change scores between intervention and attention-control patients (+24.5 vs. +39.2 m, $p = 0.598$). However, differences were found for patients' perception of walking speed from the WIQ (+5.7 vs. −1.9%, $p = 0.034$) as well as the SF-36 mental component summary score (+3.2 vs 1.9% −2.4%, $p = 0.01$).
van Pul 2012 [100]	PAD and DM = 230; PAD only = 545	Supervised walking on a treadmill; open-label, nonrandomized design (6 months)	At 6 months, there was no difference ($p = 0.48$) in change from baseline for PWD between patients with PAD and comorbid DM (+270 m) compared to PAD patients without DM (+400 m).
Collins 2013 [105][c]	PAD and DM = 55	Home-based walking and behavioral intervention or control; RCT (6 months)	An exploratory pilot trial using liberal alpha parameters, a numerical trend ($p < 0.20$) was exhibited for improvement in specific lipid panel components (total cholesterol, triglycerides) for intervention group patients compared to those in the control arm.
Allen 2014 [104]	PAD and DM = 13; PAD only = 14	Supervised walking intervention; open-label design with PAD only patient data derived from a previous trial [121] (3 months)	Supervised walking exercise was associated with a within-group improvement ($p \leq 0.01$) in PWT for both patients with concomitant PAD and DM (+29%) and PAD only (+52%). Other exercise performance endpoints (e.g., COT, VO$_{2peak}$) and endothelial function improved in the PAD-only group; however no significant change was found among those with DM.
Gardner 2014 [98][d]	PAD and DM=25[e]; PAD only = 35[e]	Home-based and supervised walking interventions; RCT (3 months)	A sex by diabetes interaction effect was present (with total exercise strides built in as a covariate) as men with PAD and DM had a greater change in COT compared to women (mean ± SD: +273 ± 212 vs. +52 ± 155 s, $p < 0.05$). The change in COT from baseline to post-3 months was not significantly different ($p > 0.05$) between men (+189 ± 146 s) and women (+139 ± 191 s) without DM.

ABI ankle-brachial index, *COD* claudication onset distance, *COT* claudication onset time, *DM* diabetes mellitus, *FMD* flow-mediated dilation, *PAD* peripheral artery disease, *PWD* peak walking distance, *PWT* peak walking time, *RCT* randomized clinical trial, *SD* standard deviation, *SF-36* Medical Outcomes Study Short-Form 36-item Questionnaire, *VO$_{2peak}$* peak oxygen consumption, *WIQ* Walking Impairment Questionnaire

[a]Randomized patients

[b]Trial duration for the primary outcome

[c]Subanalysis of patients from previously published parent study [99]

[d]Secondary analysis from separate randomized controlled trial [122]

[e]Sample from 60 total patients who completed the trial

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