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MACROVASCULAR COMPLICATIONS IN DIABETES (VR ARODA AND A GETANEH, SECTION EDITORS)

Advances in the Management of Peripheral Artery Disease

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Abstract

Purpose of Review This paper provides a concise update on the management of peripheral artery disease (PAD).

Recent Findings PAD continues to denote a population at high risk for mortality but represents a threat for limb loss only when associated with foot ulcers, gangrene, or infections. Performing either angiogram or non-invasive testing for all patients with foot ulcers, gangrene, or foot infections will help increase the detection of PAD, and refined revascularization strategies may help optimize wound healing in this patient group. Structured exercise programs are becoming available to more patients with claudication as methods to improve adherence to community-based exercise programs will improve. Finally, ensuring more patients with PAD receive aspirin therapy and statins may improve long-term survival, while further research will help determine if adding newer antiplatelet or anticoagulant medications may reduce leg amputations in selected patients.

Summary Clinicians should have a low threshold to obtain an angiogram and to pursue revascularization in patients with foot ulcers, gangrene, or foot infections. In patients with claudication, clinicians should maximize the benefits derived from exercise therapy and medical management before offering percutaneous or surgical revascularization.

Keywords Peripheral artery disease · Foot ulcer · Claudication

Abbreviations
PAD Peripheral artery disease

Introduction

Clinicians seeing patients with diabetes are well-positioned to make a meaningful contribution to maintaining the health and well-being of this population. This is primarily due to the fact that most patients who undergo non-traumatic leg amputation in the USA have diabetes, often alongside unrecognized or untreated peripheral artery disease (PAD). New developments in the management of PAD are increasing options for maintaining mobility through limb preservation and avoiding leg amputations.

This review article will take a practical approach to update the management of PAD. We will focus on aspects of PAD management most relevant to the clinician seeing patients with diabetes, including medical management for patients with PAD, diagnostic strategies for identifying PAD, and how treatment of PAD differs in the setting of claudication versus limb-threatening foot complications such as foot ulcers or gangrene.

Medical Management of Patients with PAD

Pessimism has characterized the long-term outlook of many clinicians when managing patients with PAD. Indeed, long-term mortality among those with PAD and a foot ulcer has very consistently been 50% over 5 years (see meta-analysis [1]). Opportunities to improve long-term survival in this patient population are being identified, however. First, many patients who met indication for well-proven therapies are not receiving them [2–4]. The 2016 American Heart Association/American College of

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Cardiology Guidelines on the Management of Lower Extremity Peripheral Artery Disease suggest that all patients with PAD should receive statins, antihypertensives (preferably in the form of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers), and support for smoking cessation. Aspirin should generally be given to patients with PAD that is symptomatic or associated with an ankle-brachial index less than 0.9 [5••].

In addition to established medical therapies, newer medical options may further decrease mortality and/or leg amputation rates. An analysis from the Trial to Assess the Effects of Vorapaxar in Preventing Heart Attack and Stroke in Patients With Atherosclerosis-Thrombolysis in Myocardial Infarction 50 (TRA2°P-TIMI 50 trial) first noted significantly lower rates of acute limb ischemia, reducing both acute thrombosis of both native vessels and lower extremity interventions (i.e., thrombosis of bypass grafts and in-stent thrombosis of lower extremity stents). Since then, the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial has similarly demonstrated a lower incidence of major adverse limb events in patients with PAD or carotid disease [6] (as well as decreasing the composite endpoint of cardiovascular death, myocardial infarct, or stroke in patients with stable coronary disease [7]) in patients taking both aspirin and rivaroxaban compared to those taking either medication alone. Finally, pooled results from many trials on evaluating proprotein convertase subtilisin/kexin type 9 (PSCK9) inhibitors suggest that these promising lipid-lowering medications may also have an important role in decreasing cardiovascular morbidity and possibly improving survival [8].

Treatment of PAD in Patients with Claudication

Investigators who reported on the 10-year follow-up of a cohort of 1277 patients with claudication (38% of whom had diabetes) found the annual incidence of leg amputation to be < 1% [9]. More recently, clinical trial follow-up on the cohort of patients with claudication randomized to exercise therapy reported no limb loss after 7 years of follow-up (versus 4% in the group randomized to percutaneous angioplasty) [10]. Together, these findings—in addition to similar reports from other observation studies—suggest that claudication poses a very low risk for limb loss.

Randomized trials have suggested that exercise therapy is at least as effective as percutaneous interventions in improving walking distance and quality of life [11–14,10]. In exercise therapy, patients with claudication are typically guided through low-intensity, longer-duration (30–60 min) sessions of walking or cycling three or four times per week. Pain-free walking distance reliably improves despite the fact that ankle-brachial indices do not change [10]. The May 2017 decision by the Centers for Medicare and Medicaid Services to cover 36 sessions of supervised exercise therapy in a 12-week period [15] will undoubtedly increase the number of patients with claudication who receive this helpful therapy.

What about patients who, because of geography, work schedules, or other limitations, do not have access to supervised exercise programs? Home-based exercise programs (also referred to as community-based or unsupervised exercise programs) are often dismissed as being ineffective because of a concern about low adherence, but several recent studies are now suggesting that these home-based programs have good rates of adherence, improve walking distance, and improve health-related quality of life [16–18]. Cilostazol can significantly improve pain-free walking, but it is probably best to initiate this medication in suitable patients only after they have demonstrated commitment to an exercise program. Interventions such as angioplasty, stenting, endarterectomy, or bypass operations are warranted only when a significant functional limitation remains despite adherence to exercise therapy.

The next step in improving the management of claudication may therefore be developing strategies to improve adherence to home-based exercise. Trials utilizing mobile phone-based reminders [19], personal activity trackers [20], and "exer-gaming" [21] are just three examples of technologies that may have a role. Behavioral interventions such as coaching [22] providing financial incentives [23], and creating community-wide activities [24] may help as well. Our group has also done research to further improve the adoption of home-based exercise therapy, and many of our findings have direct relevance to daily clinical practice. First, many patients hold erroneous beliefs that may limit participation in exercise [25]. For example, 56% of those queried believed that exercise may harm their leg. Second, we have found that patients with claudication also have a high prevalence of osteoarthritis symptoms (99%), lower back radiculopathy symptoms (99%), and depressive symptoms (87%) [26]. Addressing these symptoms may help improve health-related quality of life overall if not also claudication symptoms in particular. Finally, patients with claudication who have successfully quit smoking cigarettes seem to more often adhere to a home-based program for exercise therapy [27]. This finding suggests that, beyond the direct health benefits from smoking cessation, patients with claudication who smoke may benefit from more intensive (i.e., guided or supervised) behavioral interventions.

Patients with Foot Ulcers or Gangrene: *Identifying* PAD

Foot infection is the most common precursor to a leg amputation. Foot infections stem from direct bacterial inoculation

of the foot through a full-thickness epithelial defect (i.e., a foot ulcer), and it is very rare for someone with an intact skin barrier to develop a foot infection. Most clinicians can recognize an epithelial defect when deeper soft tissue or bony structures are visible (e.g., dermis, tendon, bone, joint capsule or joint spaces). Ulcers covered with a gangrenous eschar and gangrenous toes, however, are also essentially "ulcers" in that they also contain epithelial defects that allow for bacterial inoculation.

In contrast to claudication, patients with PAD who present with foot ulcers or gangrene are at risk for limb loss. Along with the treatment of any superimposed infection (see below), timely revascularization is therefore a first-line component for patients with foot ulcers or gangrene who also have significant PAD. Patients with foot ulcers and PAD who undergo revascularization have much lower rates of leg amputation than those who receive wound care alone (see review [1]).

When the large benefit of revascularization in this setting is recognized, the next question should be this: what is the best strategy to identify PAD in patients with foot ulcers or gangrene? We undertook a meta-analysis and formal decision analysis with the intent of answering this question. After reviewing more than 30 studies of > 8000 patients, we found that toe pressures and skin perfusion pressures had the highest estimated sensitivity for the detection of PAD (see Table 1). Transcutaneous oximetry had comparable sensitivity but relatively lower specificity. Ankle-brachial indices had a poor sensitivity rate. The sensitivity and interrater reliability of physical exam for pedal pulses is poor. The formal decision analysis suggested two strategies were best in identifying PAD among patients with foot ulcers:

- Good strategy: Performing non-invasive testing (specifically, toe pressures or skin perfusion pressures) on the affected extremity for all patients with foot ulcers or gangrene, then proceeding to angiography for those with abnormal results (i.e., toe-brachial index < 0.7 or skin perfusion pressure < 50 mmHg; overall strategy sensitivity 82%, negative predictive value 89%). NOTE: This strategy does NOT incorporate findings from pedal pulse exam into a diagnostic strategy, as restricting non-invasive testing to those with an abnormal pulse exam decreases overall sensitivity to 44%).
- *Best* strategy: Palpating for peripheral pulses. Patients with at least one palpable pedal pulse on the affected extremity should have absence of PAD corroborated by non-invasive testing (either toe-brachial index > 0.7 or skin perfusion pressures > 50 mmHg). Those without a palpable pedal on the affected extremity should proceed directly to angiography without the need for non-invasive testing (overall strategy sensitivity 91%, negative predictive value 93%).

In brief, findings from this analysis strongly suggest that *all* patients with foot ulcers or gangrene be evaluated for the presence of significant PAD with toe pressures, skin perfusion pressures, or digital subtraction angiography. In other words, palpating of pedal pulses is NOT sufficient for ruling out PAD because of the mediocre diagnostic accuracy of this modality. Transcutaneous oximetry is being performed less often in the USA but has adequate sensitivity. Ankle-brachial indices, on the other hand, have poor sensitivity and therefore provide only limited information. Either absent/weak pedal pulses or abnormal ankle brachial indices can help rule in PAD if these other testing modalities are not available, but the presence of palpable pedal pulses and normal ABIs does *not* rule out PAD.

Digital subtraction angiography (that is, radiographic images done with a catheter inserted into an artery) currently remains the gold standard for assessing infrainguinal peripheral artery disease (the most common segment affected in patients with diabetes). Computed tomography with arterial phase contrast (CTA) imaging of the abdomen, pelvis, and lower extremities is a suboptimal modality in this clinical context for several reasons. First, the limited spatial resolution of CTA is not a limitation for aortoiliac vessel evaluation but often severely limits the ability to assess luminal stenoses in the tibial vessels—the most common arterial segment affected in patients with diabetes. Second, calcification of the media layer of the arterial wall, a process common among patients

Table 1 Pooled estimates of sensitivity and specificity (with 95% confidence intervals) for diagnostic modalities often used in the identification of PAD

Testing modality	Pooled estimate of sensitivity (95% confidence interval)	Pooled estimate of specificity (95% confidence interval)
Pedal pulse exam	53.3 (52.1–54.6)	82.6 (82.2–83.1)
Ankle-brachial index (ABI)	82.6 (82.2–83.1)	89.1 (88.6–89.6)
Skin perfusion pressure	81.7 (79.9–83.6)	79.3 (77.2–81.1)
Transcutaneous oximetry	83.0 (81.8–84.3)	62.8 (61.2–64.4)
Toe brachial index	84.0 (82.8–85.0)	77.8 (76.1–79.5)

Data from Barshes et al. [56•]

with diabetes, limits further the evaluation for luminal stenoses. Finally, the high volume of iodinated contrast (often more than 150 ml of iodinated contrast), compared to < 30 ml for an angiogram done with selective catheter placement), and the high prevalence of chronic kidney disease may predispose patients to acute kidney injury. Magnetic resonance angiography (MRA) is probably the best substitute to digital subtraction angiography, though it may overestimate somewhat luminal disease.

PAD in Patients with Foot Ulcers or Gangrene: *Treating* PAD

Both surgical and endovascular techniques are commonly offered to patients with a foot ulcer and PAD. Common surgical options for patients with foot ulcers include femoral-to-tibial, femoral-to-pedal, and popliteal-to-pedal artery bypasses. Endovascular options often include tibial angioplasty with or without stent placement. Surgical techniques seem more durable, while endovascular techniques have faster recovery.

To date, the single randomized trial [28] and many risk-adjusted analyses (see Korhonen et al. [29], for example) seem to suggest that surgical and endovascular techniques produce very similar outcomes overall. That said, surgical and endovascular approaches may have relative advantages in some situations. Specifically, results from the SPINACH study, a recent large prospective observational study, is among several analyses suggesting that patients with renal failure may benefit more from endovascular therapy than open surgery [30–32]. Conversely, surgical bypass may be advantageous for patients with large wounds, significant infection, or previous toe or partial foot amputations [33]. Comorbidities should generally not preclude either surgical or endovascular revascularization [34].

For decades, the goal of revascularization for patients with foot ulcers or gangrene has been "in-line blood flow to the foot": blood flow that gets from the aorta to the foot through some relatively large caliber conduit. Such a path could be established through a purely native artery path (possibly achieved with angioplasty or other endovascular intervention) or through an arterial path augmented by a bypass graft (typically saphenous vein or PTFE). This should continue to be considered the minimum, as studies have clearly shown significantly lower leg amputation rates among those who do have this minimum versus those that do not [35–37].

Recent studies are suggesting that going beyond this minimum may provide added benefit to patients with foot ulcers or gangrene. First, efforts to establish in-line blood flow to the particular territory of the foot with the ulcer (the so-called angiosome) seem to provide better wound healing and lower leg amputation rates than revascularization not directed to the specific territory [38,39]—at least when the pedal arch is not intact [40]. Angioplasty of multiple tibial vessels may provide benefit in patients with wounds that are large or deep or in patients with advanced infection [41]. Finally, outcomes

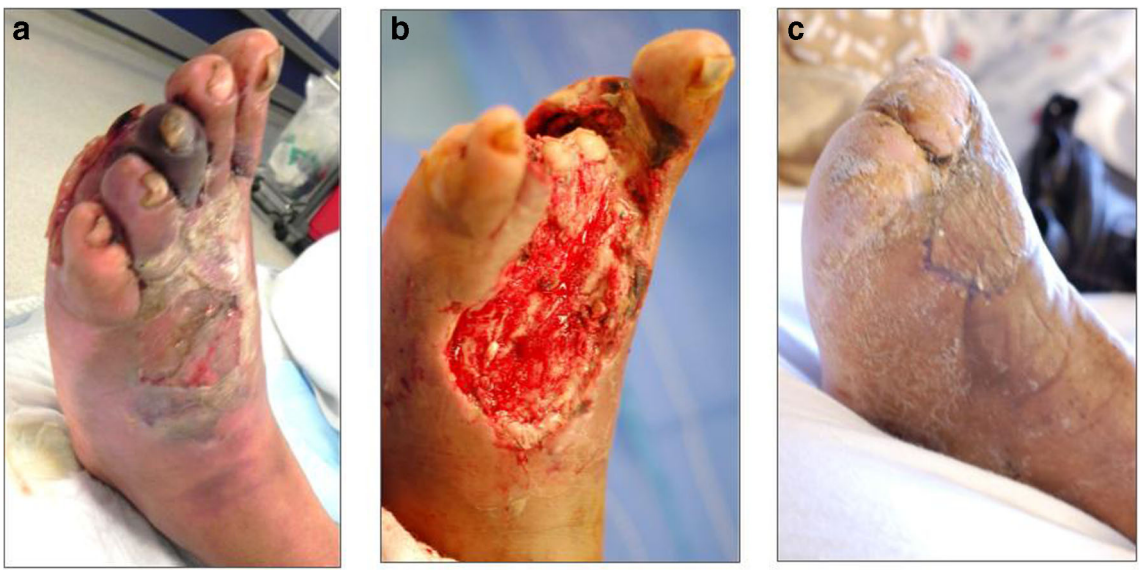

Fig. 1 Example demonstrating expedited foot wound closure in a 62-year-old man with diabetes and PAD who initially presented with a large abscess in the dorsum of the foot, cellulitis, and gangrene of the third toe (left panel) that was instigated by an ulcer overlying the third metatarsal head on the plantar aspect of the foot. Following angioplasty of the anterior tibial artery, he underwent hydrosurgical debridement (middle panel) and negative pressure wound therapy. A completion transmetatarsal amputation was used to address osteomyelitis in multiple metatarsals and to achieve closure of the majority of the foot wound. During the same operation, a split-thickness skin graft taken from the ipsilateral calf was used to reepithelialize the portion of the wound that remained on the dorsal foot. All operations were done within a span of 3 weeks. The foot was completely re-epithelialized within 6 weeks of the final operation (right panel)

reported by a few groups [42–45] suggest there may also be benefit to performing angioplasty of pedal arteries (viz. the dorsalis pedis or lateral plantar arteries) in this patient population, though larger studies with better risk-adjustment is needed to verify this.

In the end, clinicians should seek to identify PAD, then allow multidisciplinary or interdisciplinary teams of clinicians who can offer either surgical or endovascular techniques weigh arterial anatomy, patient comorbidities, patient preferences, and local factors (including expertise with various techniques) into the decision on which to pursue. The lack of consensus on the best treatment approach at this time highlights that there are many factors involved in predicting intervention success or failure; thus, the chosen approach must consider not only the intervention itself but patient functional status, symptom severity, comorbidities, vascular anatomy, and patient preference.

Treatment of the Foot After Revascularization

Infection of the foot in patients with preexisting ulcers or gangrene needs to be identified and promptly treated. Initial treatment should include empiric antibiotics and surgical drainage of any deep soft tissue infection—even if revascularization has not yet been done. Single-center series, clinical trials with < 50 participants, and guidelines abound, but little scientific progress has yet been made in the past 5–10 years on improving our understanding of how foot infections should be managed. This may change soon, however. A large multicenter randomized trial performed in the UK has compared the outcomes of oral and parenteral antibiotics for osteomyelitis, including foot osteomyelitis [46]. Results presented in abstract form have reported non-inferiority for oral antibiotics [47]. A large multicenter trial is currently underway in Veterans Healthcare Administration hospitals in the USA evaluating whether the addition of rifampin to a clinician-tailored antibiotic regimen leads to fewer amputations.

After revascularization and initiating treatment for infection, clinicians must work on achieving wound healing: an intact epithelial surface throughout the entirety of the foot. Ideally, this would follow a plan formulated at the time of initial presentation. The amount of time required for foot healing is a cost-driver after revascularization [48], and at least one series has suggested that quicker closure of the instigating foot wound can reduce leg amputation rates [49]. Delayed primary closure [50,51], negative pressure wound dressings [52], and split-thickness skin grafts [53] should be considered as adjuncts to help achieve this goal (see example in Fig. 1). Intrinsic flaps [54] and perforator flaps (free or pedicled) [55] are also offered in some centers.

Conclusions

PAD continues to denote a population at high risk for mortality but represents a threat for limb loss only when associated with foot ulcers, gangrene, or infections. The management of PAD continues to evolve. Structured exercise programs are becoming available to more patients with claudication as methods to improve adherence to community-based exercise programs will improve. Performing either angiogram or non-invasive testing for all patients with foot ulcers, gangrene, or foot infections will help increase the detection of PAD, and refined revascularization strategies may help optimize wound healing in this patient group. Finally, ensuring patients with PAD receive aspirin therapy and statins may improve long-term survival, while further research will help determine if adding newer antiplatelet or anticoagulant medications may reduce leg amputations in selected patients.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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