NARRATIVE REVIEW

Peripheral arterial disease (PAD) in diabetics: diagnosis and management- a narrative review

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Abstract

Peripheral arterial disease (PAD) in diabetic patients is often overlooked due to associated neuropathy. The very first presentation of these patients is with an Ischaemic ulcer or toe gangrene. Diabetics have a very high amputation rate compared to non-diabetic patients due to diffuse multi-segmental disease in the calcified tibial arteries. Early detection of the condition is a challenge in these patients. Even ankle-brachial pressure index may not be reliable. Both surgical and endovascular options are effective in wound healing. Endovascular techniques include percutaneous transluminal angioplasty with and without stenting, sub-intimal angioplasty, percutaneous transluminal angioplasty with drug-coated balloons, covered stents, and use of atherectomy devices. The current narrative review was planned to discuss the essentials of diagnosing PAD in diabetic patients and its various treatment options.

Key Words: Diabetic foot, Foot ulcer, PAD, Peripheral vascular disease.

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Introduction

Diabetic foot ulcers (DFUs) and its complications represent the leading cause of hospitalisation among diabetic patients.[1] Diabetics have 5-10 times more risk of amputation compared to non-diabetics.[2] Also, 15% diabetics develop a foot ulcer over the life span. In about 85% patients with major amputations, there is a preceding history of non-healing foot ulcer.[3] DFUs can be either neuropathic (35%), ischaemic (15%), or neuroischaemic (50%).[4,5]

The incidence of peripheral arterial disease (PAD) increases with duration of diabetes. Approximately 15% patients with diabetes develop PAD 10 years after diabetes diagnosis; the number approaching 50% after 20 years. ischaemic/neuroischaemic ulcers have a much higher probability of amputation and mortality than patients with neuropathic ulcers.[6] ischaemic DFUs are due to macrovascular disease (atherosclerosis) or associated microvascular diseases.[7]

The infra-popliteal vessels are mostly involved with diffuse, multi-segmental, calcified atherosclerotic disease.[8] In more than 90% cases, more than one tibial artery is involved. Arteries at the ankle and the foot are mostly spared.

Typical presentation of diabetic patients with PAD

Neuropathy masks the symptoms of Ischaemia. Most of these do not have classic presentations of intermittent claudication and rest pain despite having severe PAD. The very first presentation can be with an Ischaemia ulcer or toe gangrene. It is important to evaluate these patients for improving blood supply to the foot before performing any minor or major amputation. In an intact foot without ulcer or gangrene, the diseased axial artery and collaterals are adequate to provide blood, but they become inadequate in case of an active foot ulcer. In the region of ankle and the foot, there are six angiosomes that emerge from the three below-the-knee (BTK) arteries. Angiosome-oriented revascularisation has gained attention and its application has resulted in higher rates of limb salvage and wound healing.[9]

Investigations to diagnose PAD and their limitations

In examining any limb for chronic limb ischaemia, one must look specifically for any hair loss, atrophy of skin and subcutaneous tissues, muscle atrophy, dry fissured skin, discolouration, dependent hyperaemia, and the presence of any ulcer or gangrene. Also, the presence and quality of pulses must be checked carefully[10].

a. Ankle brachial pressure index (ABPI)

ABPI is a useful bedside tool to diagnose and assess the severity of PAD in diabetics. Value <0.9 indicates that the ulcer is ischaemia and is least likely to heal until the vascularity is improved. Due to calcified, non-compressible arteries in most diabetics, ABPI may be falsely high.[11] In those patients, toe-brachial index (TBI) and other non-invasive tests can help to detect PAD.

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b. Toe-brachial index (TBI)

This is simple, inexpensive, quick method for detecting small vessel artery disease. It can predict healing and limb survival. It is useful to monitor efficacy of therapeutic intervention. Patients with PAD have toe pressure <55mmHg or TBI <0.7. Foot wounds have lower chance of healing at toe pressure <30mmHg.

c. Duplex ultrasound (DUS)

DUS is usually the initial investigation in patients with PAD to see the extent of the disease. It is very useful non-invasive investigation with certain limitations (Table 1). An arterial duplex scan in often sufficient to give a fair idea of the site and extent of the disease without having to resort to the use of radiation or contrast exposure[12].

d. Computed tomography angiography (CTA)

Table-1: Limitations of various investigations in diabetic patients.

US (Ultrasound)
• Operator dependent
• Difficult to visualize heavily calcified tibial vessels
• Oedema, skin ulceration and vessel calcifications may limit vision
CTA (Computed tomography angiography)
•Uses contrast
• Radiation exposure
• Calcium causes a 'blooming' artifact
• Metal implants can cause artifact
MRA (Magnetic resonance angiography)
• As calcium does not make any artifact, plaque is visualized with difficulty
• Nephrogenic Systemic Fibrosis (NSF) occurs in patients with an eGFR < 30 with an incidence of 1 in 10000.
• Contraindicated in patients with pacemakers, defibrillators cochlear implants and spinal cord stimulators
• MRI is not tolerated by approximately 10 to 15% of patients.
• Venous contamination
• Higher cost
• Long imaging time
• Invasive
Catheter Angiography
• Access related complications for transfemoral angiography in 1 in 1000 patients (0.1%)
• Contrast induced renal damage

CTA is a non-invasive and rapid method for evaluating PAD. It provides objective evidence of occlusive lesion and help in planning for any intervention. It can help in detecting lesion in the inflow arteries (iliac arteries)[13].

e. Magnetic resonance angiography (MRA)

The advantages of using MRA is that it is a non-invasive investigation with no radiation exposure. It does not cause any calcium artifact, thus visualising the lumen of even small, calcified vessels, like tibial, is easier[14].

f. Catheter angiography

In conventional angiography, images are not hindered by calcifications. It can better define disease pattern. This can be used as therapeutic purpose with some limitations. Although catheter angiography is the gold standard and gives the best imaging modality, it requires imaging in two planes. It also uses contrast that can be nephrotoxic. Pre-procedure hydration can protect the kidneys. Carbon dioxide (CO2) angiography is an alternative in patients who are at high risk for contrast-induced nephropathy, as CO2 does not affect kidney functions.[15] CO2 angiography can show reasonable quality images of large vessels up to knee, but the images may not be great in infra-popliteal arterial segments.

WIfI classification system

This system stratifies limb risk by grading three critical factors; wound, ischaemia and foot infection (WIfI). This is like the Tumour, Nodes, Metastasis (TNM) system for malignancy (Table 2). WIfI stage 1 is associated with very low amputation risk. Whereas stages 3 and 4 are more likely to require revascularisation and are at increased risk for limb loss. WIfI stage may also predict wound healing time and has been correlated with costs of care[16].

Table-2: WIfI classifications for threatened lower limbs for the assessment of amputation risk

Component	Grade	Description
Wound (W)	0	No wound
	1	Small, shallow ulcer No exposed bone, unless limited to distal phalynxNo gangrene
	2	Deeper ulcer with exposed bone joint, or tendon, not involving tissue heel.Shallow heel ulcer without calcaneal involvementGangrene limited to digits
	3	Extensive, deep ulcer involving forefoot/midfoot.Deep, full thickness heel ulcer and/or calcaneal involvement.Extensive gangrene involving forefoot/midfoot, Full thickness heel necrosis and calcaneal involvement
Ischaemia (I)	0	TP >60 mm Hg; ABI >0.8; ASP >100 mm Hg
	1	TP 40–59 mm Hg; ABI 0.6–0.79; ASP 70–100 mm Hg
	2	TP 30–39 mm Hg; ABI 0.4–0.59; ASP 50–70 mm Hg
	3	TP <30 mm Hg; ABI <0.39; ASP <50 mm Hg
Foot Infection (FI)	0	No symptoms or signs of infection
	1	Local infection involving only skin, subcutaneous tissue
	2	Local infection with erythema >2 cm, or involving structures deeper than skin, subcutaneous (eg, abscess, osteomyelitis)
	3	Local infection with signs of SIRS

WIfI: Wound, Ischaemia and foot Infection, TP: Toe pressure, ABI: Ankle -brachial index, ASP: Ankle systolic pressure, SIRS: Systemic inflammatory response syndrome.

In 2019, Global Limb Anatomic Staging System (GLASS) classification was presented.[17] In 2021, Liang P et al. evaluated this scoring system[18] and showed that a higher GLASS stage correlated well with disease recurrence and need for re-intervention.

PAD in diabetics is complex, involving multiple organs. A team approach can significantly improve patient outcomes with decreased amputation rate.[19]

Best medical treatment for these patients

Patients with diabetes, PAD and ulceration have overall 5-year mortality of around 50% because of markedly increased risk of cardiovascular events.[20] This survival rate is less than patients with heart failure, stroke and most cancers.[21]

Conservative measures are often the first-line treatment for patients with PAD. These include risk factor modification and exercise programme. Target is to stop smoking, treat hypertension with target BP 130/80 or less, treat hyperlipidaemia with target low-density lipoprotein (LDL) <70 mg/dl, and treat diabetes with target glycated haemoglobin (HbA1c) <7%.

Smoking is one of the most important modifiable risk factors for PAD. It is well known that smoking increases risk of PAD by three-fold. It does not only affect the development of PAD, but also clinical outcomes in patients who continue to smoke. Smokers are also more likely to progress to critical limb ischaemic amputation or vascular intervention. It also increases the mortality rate among the claudicant by a factor of 1.5-3. The United Kingdom (UK) prospective diabetes (UK-PD) study identified a strong association between HBA1c and PAD risk.[22] Each 1% increase in HBA1c was associated with a 28% increased risk of PAD.

a. **Supervised exercise therapy:** This is an integral part of this treatment. With risk factor modification and supervised exercise, 33-65% of patients improve their claudicant distance.

b. **Anti-platelets:** Either aspirin or clopidigrol is prescribed.[23] Antiplatelets do not improve claudication symptoms, but are the mainstay of secondary prevention.

c. **Cilostazol/Pentoxifylline:** Pentoxifylline acts as increasing the adenosine triphosphate (ATP) level, reducing red blood cell aggregation and fibrinogen. Cilostazol acts as a phosphodiesterase inhibitor and has an antiplatelet effect as well as increasing ATP levels in the red blood cell. There is minimal vasodilatory properties of these drugs in these patients as they are already maximally vasodilated. Naftridrofuryl is another drug used in claudication. All these drugs have been shown to improve walking distance among the claudicants.

d. **Anticoagulation:** The Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial gives clear guidance that all patients with symptomatic peripheral vascular disease had a reduction in cardiovascular events (stroke, myocardial infarction [MI], death) and not reducing major limb events.[24] A subgroup analysis in a recent trial of antiplatelets and anticoagulants suggested that combination of aspirin and the direct oral anticoagulant rivaroxaban was more effective at reducing major limb events when compared with aspirin alone in patients with PAD, but this strategy was at the expense of an increase in non-fatal events.[25]

Where surgical bypasses stand in this endovascular era ?

Critical limb ischaemia patients present with either tissue loss or rest pain. Both surgical and endovascular methods are effective in improving blood supply of the ischaemic ulcers.[26] Infra-inguinal bypasses using veins have excellent limb salvage rate with minimal perioperative morbidity and mortality.[27] These are best served for patients with good life expectancy and who are fit for anaesthesia. The bypass inflow sites may be femoral, above or below-knee popliteal, tibial, or peroneal artery. Any infra-popliteal artery can be used for outflow. Although most ischaemic limbs can be re-vascularised. Peroneal artery is the least disease vessel. Idea is to maintain an inline flow to the ankle or foot with one of the pedal arteries to improve wound healing. Non-impeded inflow and low resistance outflow is a major factor in the success of a bypass conduit. A vein with adequate size (>3mm) and of reasonable quality (without fibrosis and stenosis) is also a pre-requisite for these procedures. This can be mapped pre-operatively. Calcified and sclerotic veins are rejected. Veins can be used in reversed, non-reversed or in-situ fashion.[28] Vein harvesting can be done through long continuous incisions, through skip incisions, or endoscopically. Adequate inflow is ensured before commencing with these bypasses. Selective inflow lesions can be treated either percutaneously in advance or at the same operative sitting if needed. It is challenging to anastomose calcified arteries. Possible options to deal with calcified vessels are use of tourniquets, intraluminal balloons, glues or feeding tubes[29].

The indications for surgical bypasses or endovascular options are lifestyle limiting claudication, rest pain and

non-healing ulcers. Surgical bypasses are the most durable option for infra-inguinal revascularization of chronic atherosclerotic occlusive disease. The key to their success is the calibre and quality of the venous conduit and meticulous postoperative surveillance. They have better outcomes than complex endovascular therapy in low-to-moderate risk patient with good quality autologous conduit. Open surgery versus endovascular therapy is a subject of debate.[30] There is lack of prospective, randomised data to support one treatment over the other. Bypasses are durable. Patency rate for femoropopliteal bypass have been reported 83% and 63% at 5-year and 10-year, respectively, with limb salvage rate of 89%. Same is true for pedal bypasses who have median salvage rate of 78% at 5 years. Bypass to the tibial or pedal vessels with autogenous vein is the most predictable method of improving blood flow to the threatened limb.[31]

Endovascular interventions

Infra-inguinal bypasses are major procedures and need appropriate anaesthesia evaluation. Most patients with long-standing diabetes are high-risk cases for anaesthesia. There may also be issues with the availability of the quality vein. In those cases, endovascular therapy is a practical option which is minimal invasive and can be performed under local anaesthesia. Endovascular interventions achieved better ulcer healing in Ishchaemic diabetic foot ulcer compared with the conservative approach.[33-34] "Endovascular first approach" is the preferred approach to many interventionists.[35] Endovascular revascularisation has increased in popularity in recent years; data from the United States reveals a more than five-fold increase in endovascular interventions from 1980 to 2000.[36] In general, endovascular revascularisation is more appropriate in patients with relatively focal disease in arteries above the knee, but short-term success rates for opening long, totally occluded vessels and below-the-knee arteries are improving. Low-profile coronary devices are commonly used for these lesions with improved outcomes. Imaging is key in the success of these procedures. Mostly 0.018/ 0.014 guidewires are used. Both hydrophilic/non-hydrophilic guidewires are used to cross these lesions.[37]

Several trials, including the interm results of CRITISCH registry found no differences in long-term mortality or major amputation when comparing both strategies.[38] In Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL 1) trial, patients presenting with severe limb ischaemia due to infra-inguinal disease and who were suitable for surgery and angioplasty, a bypass-surgery-first and a balloon-angioplasty-first strategy were associated with broadly similar outcomes in terms of amputation-free survival, and in the short-term, surgery was more expensive than angioplasty.[39] The Best Endovascular versus Surgical Therapy in Patients with Critical Limb Ischaemia (BEST-CLI) trial is a promising current multicentre, randomised trial that will add evidence and further help guide treatment options for critical limb Ischaemia (CLI) patients.[40] The same is true of the BASIL 2 trial.[41]

Innovations in the endovascular treatment options

There is a myriad of endovascular techniques. They include percutaneous transluminal angioplasty (PTA) with and without stenting, subintimal angioplasty, PTA with drug-coated balloons, covered stents, cryotherapy, brachytherapy and use of atherectomy devices (Table 3).

Drug-eluting balloons and stents reduce the risk neointimal hyperplasia and re-occlusion in these vessels. Sirolimus-eluting stents have been shown to inhibit neointimal hyperplasia in the coronary vasculature.

Table-3: Recent advances in endovascular therapy (ET).

• Drug-coated balloons
• Drug-coated stents
• Re-entry devices
• Debulking devices
• Low profile systems
• Use of novel access points
• Bio-resorbable stents and scaffolds
• Bifurcated stents
• Tacking
• Robotic ET
• Paclitaxil infusion
• Angioscopic assisted ET
• Endovascular venous arterialization

Subintimal angioplasty helps in improving blood flow even in occluded arteries in which conventional intra luminal angioplasty is not effective. It helps to achieve luminal patency in totally occluded arterial segments.

The atherosclerotic segments in diabetics may be stiff and calcified and simple angioplasty may not dilate them. Atherectomy devices can debulk these lesions to facilitate angioplasty. This spares the arteries from stents and later from in-stent stenosis which is much more difficult to treat. The techniques to cross the difficult lesions have also improved. As discussed in case of failure of 'antegrade' intraluminal approach, subintimal approach is the option. Even if it fails, 'retrograde' trans-pedal arteries approach can be used to cross these lesions. Limb salvage of 80-85% have been reported using either surgical, endovascular or hybrid (combination of the two)

revascularisation techniques in these patients.

Recent advances in atherectomy and drug-coated balloon angioplasty have shown promising results. Recent advances in retrograde tibiopedal access have dramatically increased the technical success of the distal and long-segment occlusive disease, and more below-knee and pedal-loop revascularisations are providing increasing perfusion to distal tissues previously deemed non-salvageable.[42,43]

Conclusion

PAD is very common in diabetic patients and need to be detected earlier. Patients with ulceration or tissue loss should be assessed earlier to improve foot perfusion using either endovascular or surgical interventions.

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